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Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381891
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Fax: +1-925-223-8243
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Dexmedetomidine in gastrointestinal endoscopic procedures

Somchai Amornyotin

Somchai Amornyotin, Department of Anesthesiology and Siriraj Gastrointestinal Endoscopy Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

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Correspondence to: Somchai Amornyotin, Associate Professor of Department of Anesthesiology and Siriraj Gastrointestinal Endoscopy Center, Faculty of Medicine Siriraj Hospital, Mahidol University, 2, Wanglang Rd., Siriraj, Bangkoknoi, Bangkok 10700, Thailand. somchai.amo@mahidol.ac.th
Telephone: +66-2-4197990
Fax: +66-2-4113256

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Abstract

Gastrointestinal endoscopy is the gold standard in the examination and the treatment of the diseases of gastrointestinal system, but the disadvantage of being painful process. At this point the sedative and analgesic agents may be important. Dexmedetomidine is a new sedoanalgesic agent which is alternative to

benzodiazepines and opioids. It has analgesia, amnesia, sedative and anxiolytic properties. The use of dexmedetomidine as the sole anesthetic agent and as the adjuvant analgesic agent has been published but has not been approved because of the inconsistency of efficacy and safety. The author has been collected the published papers in the literature. This article is aimed to describe the use of dexmedetomidine in various gastrointestinal endoscopic procedures.

Key words: Complication; Safety; Dexmedetomidine; Gastrointestinal endoscopy; Sedation

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Core tip: Dexmedetomidine has analgesic, amnesic, sedative and anxiolytic properties. Use of dexmedetomidine as the sole anesthetic agent and as the adjuvant anesthetic agent in various gastrointestinal endoscopic (GIE) procedures has been published. A distinct advantage of dexmedetomidine is the maintenance of respiratory force and preserved airway patency. These properties of dexmedetomidine have verified to be beneficial in high-risk patients. This article is aimed to explain the clinical use of dexmedetomidine for GIE procedures of the published papers in the literature.

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INTRODUCTION

Dexmedetomidine is an alpha-2 adrenergic receptor agonist and has an eight times higher than clonidine for alpha-2 adrenergic receptors. It has sedative, anxiolytic and analgesic properties that produce cardiorespiratory

stability at the therapeutic doses. The use of dexmedetomidine may be expanded as an intravenous drug in the medical procedures^[1,2]. Dexmedetomidine is approved by the United States Food and Drug Administration for short-term sedation (< 24 h) in adult patients in the intensive care unit (ICU). It also has been used in combination with other sedoanalgesic drugs during painful procedures. Several reports in the literature have been confirmed about its effective use in various gastrointestinal endoscopic (GIE) procedures, although further controlled studies are needed to reinforce its use. This review is aimed to define the role of dexmedetomidine in GIE procedures.

PHARMACOLOGY OF DEXMEDETOMIDINE

The alpha-2 adrenergic receptors are principally postsynaptic receptors distributed in multiple areas^[3]. Sedative and anxiolytic properties are utilized throughout alpha-2 adrenergic receptors in the locus ceruleus of pons. The analgesic effects are employed across the stimulation of alpha-2 adrenergic receptors in the dorsal horn of spinal cord. Dexmedetomidine is an alpha-2 adrenergic receptor and has an eight times higher than clonidine for alpha-2 receptors^[4]. Its distribution half-life is 6 min in adults over a dose range of 0.2-0.7 mcg/kg per hour intravenous infusion^[5]. Dexmedetomidine is rapidly distributed and has an elimination half-life of 2 h. In addition, dexmedetomidine undergoes biotransformation by cytochrome P-450 and glucuronidation. Its clearance remains unaltered in severe renal impairment. However, the clearance decreased up to 32% in severe hepatic dysfunction. Its metabolites are excreted in urine (95%) and in feces (4%).

Moreover, the activation of postsynaptic alpha-2 receptors leads to sympatholysis and results in hypotension and bradycardia. These effects of dexmedetomidine on arterial blood pressure are biphasic with an initial transient rise with a reflex fall in heart rate. This is accompanied by the reduction of arterial blood pressure and heart rate due to inhibition of central sympathetic outflow and stimulation of presynaptic alpha-2 receptors cause decreased release of nor-adrenaline leading to further fall in the blood pressure^[6]. However, these hemodynamic profiles return to the baseline fifteen minutes later. Dexmedetomidine should be contraindicated in the patients with cardiovascular compromise, severe hypovolemia and atrioventricular nodal block.

Dexmedetomidine does not have any depressant effects on respiratory function even at higher doses with no impairment of ventilation or gas exchange^[7]. The ventilatory response to hypercapnia was not affected at a dose that created a negative response to strong stimulation. Dexmedetomidine converges on a natural sleep pathway, activating pathways that promote

endogenous non-rapid eye movement sleep to exert its sedative effect^[3]. Dexmedetomidine creates a reduction in cerebral metabolic demand of oxygen and cerebral blood flow with a slight reduction in intracranial pressure. Its neuroprotective effect is not well known^[8]. It seems to employ analgesic effects at the spinal cord level and at the supraspinal sites^[9]. However, the analgesic properties of dexmedetomidine are still controversial.

DEXMEDETOMIDINE IN GASTROINTESTINAL ENDOSCOPY

Generally, propofol alone or in combination with midazolam and/or fentanyl is one of the most widely used regimens for sedation during the GIE procedures^[10-12]. However, the combination use of sedatives and/or analgesics with propofol may produce some additional risks. Dexmedetomidine offers a sedation level that facilitates natural sleep and communication and also decreases analgesic requirements. The use of dexmedetomidine for sedation during GIE interventions remains to be established. Importantly, the use of dexmedetomidine for sedation in GIE procedures gives more respiratory safety and hemodynamic stability.

Hasanin and Sira^[13] evaluated the sedative, hemodynamic, respiratory and adverse effects of dexmedetomidine and propofol during GIE procedures in the pediatric patients. Eighty pediatric patients with ASA I, II aged 1-14 years were randomized into dexmedetomidine group or propofol group. Sedation was achieved with propofol 2 mg/kg bolus then infused at a rate of 100 mcg/kg per minute or dexmedetomidine 2.5 mcg/kg over 10 min then infused at a rate of 2 mcg/kg per hour to attain a Ramsay sedation scale (RSS) P5. The HR, MAP, RR and SpO₂ were continuously monitored and analyzed. Times of induction, procedure, recovery, and adverse effects were also reported. The HR values were significantly lower in the dexmedetomidine group at induction, after insertion of endoscope, and during the procedure. There were no significant differences in MAP, RR and SpO₂ values at all time points between the two groups. Induction and recovery times were significantly longer in the dexmedetomidine group. No cases in the dexmedetomidine group presented oxygen desaturation vs six patients (15%) in the propofol group ($P = 0.026$). This study confirmed that dexmedetomidine sedation in GIE procedures was safe and efficacy as well as also provided cardiorespiratory stability^[13].

Vetsa *et al*^[14] reported a retrospective study of dexmedetomidine used for GIE procedures in three years. They aimed to evaluate the procedure completion and adverse event rates. A total of 129 procedures with dexmedetomidine were analyzed. Of these, 29% had failed, and 69% had expected difficult sedation or prolonged procedure, and 70% required narcotics during the procedure. Dexmedetomidine was administered intravenously at a bolus of 1 mcg/kg in 5 min and was maintained at the variable rates. Additionally, midazolam

and meperidine or fentanyl was also administered. The result showed the procedure completion rate was 94%. Higher dexmedetomidine maintenance rate was observed in the successfully completed cases. The most common adverse event was hypotension (37%). The interventions for adverse events were required in 86%. All these adverse events were readily managed without significant morbidity. The authors concluded that the use of dexmedetomidine with standard sedative drugs for GIE procedures was related with excellent procedure completion rate in the difficult to sedate procedures. However, the prolonged recovery period and increased adverse events were also observed^[14].

However, many anesthetic agents including dexmedetomidine reduce the lower esophageal sphincter pressure (LESP). The reduction of LESP and the gastroesophageal pressure gradient (GEPG) stimulates gastroesophageal reflux and can cause to aspiration pneumonia. Turan and coworkers compared the effects of dexmedetomidine and propofol on LESP and GEPG in the eleven healthy volunteers. The results demonstrated that no significant differences in LESP and GEPG were observed. They concluded that both dexmedetomidine and propofol had comparable effects on LESP and GEPG. Although both sedative drugs caused some decrease in LESP at high concentrations, it did not create gastroesophageal reflux during the sedation^[15].

ESOPHAGOGASTRODUODENOSCOPY

Esophagogastroduodenoscopy (EGD) is an endoscopic procedure for diagnosis and treatment of upper gastrointestinal tract problems. Generally, topical pharyngeal anesthesia is safe for the use as premedication for unsedated EGD procedure. Consequently, the unsedated EGD procedure is also well accepted^[16]. However, this procedure causes the patient discomfort and anxiety. The sedative drugs are used to relieve these symptoms and improve the endoscopic outcome.

Recently, a randomized, controlled study is conducted to evaluate the effect of dexmedetomidine and propofol on sedation for EGD procedure in outpatient cases. This study confirmed that dexmedetomidine and propofol offered an acceptable level of sedation without serious adverse effects during EGD procedure. The patients in the dexmedetomidine group demonstrated minimal respiratory-related adverse effects. More patients in the propofol group experienced a deeper level of sedation depth at the start of the procedure^[17].

Wu *et al*^[18] assessed the efficacy and safety of dexmedetomidine and midazolam for conscious sedation in patients with ASA physical status I - II who underwent elective EGD procedures. The results of the study demonstrated that patients in the dexmedetomidine group had significantly higher oxygen saturation and overall satisfaction than patients in the midazolam group. Additionally, the patients in the midazolam group experienced a significant decrease in the mean arterial blood pressure during sedation compared with

the baseline values. However, no clinically significant complications between the two groups were noted. The authors concluded that dexmedetomidine had a good safety property and was an effective sedation drug for EGD procedure^[18].

A randomized controlled study compared the efficacy and safety of dexmedetomidine and midazolam in EGD procedure. The result of the study confirmed that dexmedetomidine was suitable for endoscopic procedures of upper gastrointestinal tract. Furthermore, dexmedetomidine offered shorter recovery time and better patient's satisfaction^[19]. The study of Hashiguchi *et al*^[20] also demonstrated that dexmedetomidine for sedation during EGD procedure was as effective and safe as midazolam.

Recently, Samson *et al*^[21] evaluated and compared the sedation efficacy and hemodynamic effects of midazolam and propofol and dexmedetomidine in the patients underwent elective diagnostic EGD procedure. The 90 patients with ASA physical status I or II were randomized into three groups; Group I received midazolam infusion, Group II received propofol infusion and Group III received dexmedetomidine infusion. The study demonstrated that endoscopist satisfaction and recovery in the dexmedetomidine group was significantly better than in the midazolam and propofol groups. In addition, mean arterial blood pressure in the propofol group was significantly lesser than in the dexmedetomidine and midazolam groups^[21].

The safety and efficacy of dexmedetomidine for sedation in EGD procedure is confirmed. A prospective, randomized study investigated and compared the safety and efficacy of dexmedetomidine and midazolam for sedation in EGD procedure. A total of 50 adult patients with ASA physical status classification I and II were included. A brief questionnaire was performed to accumulate the demographic data, anxiety score, satisfaction and expected discomfort. Mean arterial blood pressure, heart rate, respiratory rate and oxygen saturation during and after the procedure were measured continuously and recorded every minute. Low levels of procedural discomfort and anxiety scores as well as high satisfaction levels were observed in these two groups. However, the endoscopist satisfaction was significant higher in the patients receiving dexmedetomidine. In addition, the adverse event rate in the midazolam group was higher than in the dexmedetomidine group. The study confirmed that dexmedetomidine was better than midazolam in term of retching, rate of adverse events and endoscopist satisfaction for sedation the patients for EGD procedures^[22].

Jiang *et al*^[23] studied the sedative effect and hemodynamic influence of dexmedetomidine on the patients undergoing EGD procedure. Forty patients were randomly assigned into two groups. In the control group (C), a single dose of 2.5 mg/kg propofol was infused. In the dexmedetomidine group (D), 0.8 mcg/kg of dexmedetomidine was infused slowly (longer than 10 min) before propofol application. The MAP, HR, SpO₂,

OAA/S, and Ramsay sedation score were recorded at four different time points, before infusion (T0), at beginning of operation (T1), when an endoscope entered the stomach (T2), after the operation was finished (T3). The total dosage of propofol, induction time and arousing time were also observed. The results showed the Ramsay sedation scores at T1, T2 and T3 of group D are statistically higher than group C and the T0 group. In addition, group D also showed the low HR and MAP of the three time points, shorter induction times and arousing times as well as less propofol dosage than group C. No patients showed signs of respiratory suppression. They suggested that the use of 0.8 mcg/kg of dexmedetomidine at periprocedural period of the EGD procedure could yield marked sedative effect, had antihypertensive effect and did not suppress respiration^[23].

Moreover, dexmedetomidine can use with the combination of other sedoanalgesic drugs. The case series of the combination use of dexmedetomidine and ketamine for EGD procedures were studied in 46 children aged 2-12 years. Dexmedetomidine 1 mcg/kg and ketamine 2 mg/kg were administered over 5 min. The alteration of mean arterial blood pressure, heart rate, and oxygen saturation was not significantly different from the baseline. In addition, no airway interventions were needed. The results of this case series showed that the combination of dexmedetomidine and ketamine not only promised to be clinically effective but also safe for EGD procedure in the pediatric patients^[24]. However, the combination dexmedetomidine and ketamine provided longer sedation times and deeper sedation level when compared to the combination etomidate and fentanyl^[25] (Table 1).

Generally, propofol has been used in combination with dexmedetomidine to offer sedation/anesthesia. The pharmacodynamic profile of this combination regimen in 24 children aged 3-10 years underwent EGD procedure was investigated^[26]. The plasma propofol concentration at which 50% of the patients presented minimal response to stimuli was evaluated. The result demonstrated that propofol in the combination with dexmedetomidine was no significant shift in the propofol concentration-response curve. The authors accomplished that a concurrent infusion of dexmedetomidine in a dose of 1 mcg/kg did not affect the propofol requirement^[26].

Sedation in the patients with obstructive sleep apnea (OSA) is very challenge. Dexmedetomidine offers sedation with minimal respiratory depression which is a desirable characteristic in the patients with OSA. An observational study assessed the safety and efficacy of dexmedetomidine/propofol anesthesia for the patients with OSA without endotracheal intubation during EGD procedure^[27]. Twenty patients with high probability of OSA undergoing EGD procedure were enrolled in the study. Dexmedetomidine 1 mcg/kg bolus was administered over 10 min followed by propofol boluses. After that, the anesthesia was maintained by

using continuous propofol infusion. The result showed transient hypoxemic events occurred in two patients during the EGD procedure. Additionally, transient hypotension was experienced in three patients during the procedure and three patients in the post-anesthesia care unit. After discharge, 16 patients complained of drowsiness, two patients informed dysphoric symptoms and one patient reported of dry mouth. The study concluded that the combination of dexmedetomidine and propofol could offer acceptable anesthesia for EGD procedure in the patients with OSA. This combination method provided a substitute to tracheal intubation in these high risk patients^[27].

Atkins *et al*^[28] presented a patient with previously undiagnosed extensive tracheomalacia who suffered airway obstruction during an elective EGD under anesthesia. In the second anesthesia, the authors used 1.5 mcg/kg of dexmedetomidine over 15 min then continuous infusion at a rate of 0.7 mcg/kg per hour and an *iv* bolus of 0.5 mg/kg of ketamine followed by infusion at a rate of 1 mcg/kg per minute. The patient was nonresponsive to the endoscope insertion and preserved normal airway tone with no episodes of any respiratory depression. This case demonstrated the potential advantages of the combination use of dexmedetomidine and ketamine for sedation the patients with achalasia underwent EGD procedure^[28].

Another case report of a nine-year-old, 45 kg child with Duchenne muscular dystrophy underwent EGD procedure by using dexmedetomidine was presented. The patient had a history of egg allergy, and the potential risk of malignant hyperthermia. The combination use of dexmedetomidine and ketamine was utilized for procedural sedation. In this case, a bolus dose of 1 mcg/kg of dexmedetomidine and a single dose of 1 mg/kg of ketamine was given and was maintained by dexmedetomidine continuous infusion at a rate of 0.5 mcg/kg per hour. This case report established that this combination regimen used for EGD procedure was successfully completed and the patient accepted the procedure^[29].

Additionally, intranasal dexmedetomidine can be used for the endoscopic procedure. Han *et al*^[30] compared the cardiorespiratory profiles between intranasal and intravenous dexmedetomidine administered 10 min before induction for the EGD procedure. A dose of 1.5-2 mg/kg of propofol was given for induction. The Mean arterial blood pressure, heart rate, respiratory rate, and oxygen saturation were monitored. The authors concluded that intranasal dexmedetomidine was an effective and safe method alternative to intravenous dexmedetomidine for EGD procedure^[30].

Cheung *et al*^[31] assessed the efficacy of intranasal dexmedetomidine combined with patient-controlled sedation (PCS) for EGD procedure. Intranasal dexmedetomidine 1.5 mcg/kg or intranasal saline was administered 1 h before the procedure. PCS with propofol and alfentanil was given for rescue sedation. The total requirement of PCS propofol and alfentanil

Table 1 The use of dexmedetomidine in a combination technique for gastrointestinal endoscopic procedures

Ref.	Type of endoscopy	No. of patients	DEX group	Non-DEX group	Summary of findings
Wu <i>et al</i> ^[17]	EGD	70	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion <i>iv</i> , FEN 1 mcg/kg <i>iv</i>	PRO 0.6 mg/kg and on demand bolus 10-20 mg <i>iv</i>	DEX showed minimal adverse effects on respiratory function. More patients in PRO created deeper sedation at start
Cheung <i>et al</i> ^[31]	EGD	50	DEX 1.5 mcg/kg <i>in</i> , PCS with PRO and Alfentanil	Normal saline <i>in</i> , PCS with PRO and Alfentanil	DEX <i>i.n.</i> with PCS PRO and alfentanil presented deeper sedation with significantly fewer use of additional sedative agents during EGD
¹ EL-Shmaa <i>et al</i> ^[25]	EGD	100	DEX 1 mcg/kg followed by 0.5-1 mcg/kg per hour infusion <i>iv</i> , KET 1 mg/kg and on demand bolus 0.5 mg/kg <i>iv</i>	ETO 0.15 mg/kg followed by 0.01-0.03 mg/kg per minute infusion <i>iv</i> , FEN 1 mcg/kg <i>iv</i>	ETO/FEN combination provides shorter sedation times and lighter sedation level compared to DEX/KET combination
Wu <i>et al</i> ^[18]	EGD	60	DEX 0.3 mcg/kg followed by 0.2-0.3 mcg/kg per hour infusion <i>iv</i> , FEN 1 mcg/kg <i>iv</i>	MDZ 0.05 mg/kg <i>iv</i> , FEN 1 mcg/kg <i>iv</i>	DEX had a good safety profile and was an effective sedation for EGD procedure
¹ Koksal <i>et al</i> ^[32]	EGD	80	DEX 0.5 mcg/kg followed by 0.2 mcg/kg per hour infusion <i>iv</i> , KET 1 mg/kg <i>iv</i>	REM 0.5 mcg/kg followed by 0.1 mcg/kg per minute infusion <i>iv</i> , KET 1 mg/kg <i>iv</i>	REM/KET combination provides faster, more sedoanalgesia and rapid recovery compared with DEX/KET combination
Hashiguchi <i>et al</i> ^[20]	EGD	40	Group D: DEX 6 mcg/kg followed by 0.6 mcg/kg per hour infusion <i>iv</i> , Butylscopolamine 20 mg <i>im</i> , Lidocaine viscous 5 mL gurgling	Group M: MDZ 0.05 mg/kg <i>iv</i> , Butylscopolamine 20 mg <i>im</i> , Lidocaine viscous 5 mL gurgling; Group L: Lidocaine viscous 5 mL gurgling	DEX is as safe and effective as MDZ. DEX significantly reduces blood pressure and heart rate
Saleh <i>et al</i> ^[36]	Esophageal dilatation	60	Group D: DEX 2 mcg/kg followed by 0.4 mcg/kg per hour infusion <i>iv</i> , MDZ 0.05 mg/kg <i>iv</i>	Group P: PRO 1 mg/kg followed by 5 mg/kg per hour infusion <i>iv</i> ; Group K: KET 2 mg/kg and on demand 0.5 mg/kg <i>iv</i> , Atropine 0.02 mg <i>iv</i>	DEX-MDZ combination and KET had more stable cardiorespiratory profiles, with adequate postprocedural analgesia
Ayazoglu <i>et al</i> ^[37]	Colonoscopy	121	DEX 0.2 mcg/kg <i>iv</i> , PRO 0.5-3 mg/kg per hour infusion <i>iv</i>	Group 1: SUF 0.1 mcg/kg <i>in</i> , PRO 0.5-3 mg/kg per hour infusion <i>iv</i> ; Group 2: MEP 0.4 mg/kg <i>iv</i> , PRO 1 mg/kg bolus followed by 0.5-3 mg/kg per hour infusion <i>iv</i> ; Group 3: MEP 0.4 mg/kg <i>iv</i> , MDZ 0.03 mg/kg <i>iv</i> , PRO 0.5-3 mg/kg per hour infusion <i>iv</i>	Sedation for colonoscopy can be safely and effectively utilized with low doses of PRO combined with DEX, <i>in</i> SUF, <i>iv</i> MEP and <i>iv</i> MEP with MDZ
Techanivate <i>et al</i> ^[36]	Colonoscopy	70	DEX 1 mcg/kg <i>iv</i> , FEN 0.5 mcg/kg <i>iv</i> , PRO 20 mg and on demand 20 mg <i>iv</i>	FEN 0.5 mcg/kg <i>iv</i> , PRO 1 mg/kg and on demand 20 mg <i>iv</i>	DEX for sedation in colonoscopy reduced hypotension incidence than PRO
Dere <i>et al</i> ^[34]	Colonoscopy	60	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion <i>iv</i> , FEN 1 mcg/kg <i>iv</i>	MDZ 0.05 mg/kg <i>iv</i> , FEN 1 mcg/kg <i>iv</i>	DEX provided more hemodynamic stability, higher sedation scores, higher satisfaction scores and lower pain scores
Abdalla <i>et al</i> ^[43]	ERCP	60	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion <i>iv</i> , PRO 5 mg/kg per hour and on demand bolus 0.5 mg/kg <i>iv</i>	KET 1 mg/kg followed by 0.5 mg/kg per hour infusion <i>iv</i> , PRO 5 mg/kg per hour and on demand bolus 0.5 mg/kg <i>iv</i>	DEX-PRO during ERCP showed better hemodynamic stability, less nausea/vomiting and shorter recovery time when compared with KET-PRO combination
¹ Ramkiran <i>et al</i> ^[54]	ERCP	72	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion <i>iv</i> , MDZ 0.05 mg/kg <i>iv</i> , Hyoscine 0.3 mg/kg <i>iv</i> , PRO 0.5-1.5 mg/kg and on demand bolus 20 mg <i>iv</i>	Group K: KET 0.25 mg/kg followed by 5 mcg/kg per minute infusion <i>iv</i> , MDZ 0.05 mg/kg <i>iv</i> , Hyoscine 0.3 mg/kg <i>iv</i> , PRO 0.5-1.5 mg/kg and on demand bolus 20 mg <i>iv</i> ; Group C: normal saline <i>iv</i> , MDZ 0.05 mg/kg <i>iv</i> , Hyoscine 0.3 mg/kg <i>iv</i> , PRO 0.5-1.5 mg/kg and on demand bolus 20 mg <i>iv</i>	Low dose KET with PRO boluses resulted in lesser PRO consumption, with earlier recovery and favorable hemodynamics compared with DEX in outpatient ERCP
Mukhopadhyay <i>et al</i> ^[46]	ERCP	45	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion <i>iv</i> , MDZ 0.5 mg/kg <i>iv</i> , Pentazocine 6 mg <i>iv</i> , KET 25 mg <i>iv</i> , PRO 0.75-1 mg/kg and on demand bolus 10-20 mg <i>iv</i>	Group 1: MDZ 1 mg/kg <i>iv</i> , PRO 0.75-1 mg/kg and on demand bolus 10-20 mg <i>iv</i> ; Group 2: MDZ 0.5 mg/kg <i>iv</i> , Pentazocine 6 mg <i>iv</i> , KET 25 mg <i>iv</i> , PRO 0.75-1 mg/kg and on demand bolus 10-20 mg <i>iv</i>	DEX increased efficacy and safety of sedate-analgesic cocktail. It reduces PRO requirement, more stable level of sedation and increases anesthetist satisfaction

Sethi <i>et al</i> ^[42]	ERCP	60	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion <i>iv</i> , FEN 1 mcg/kg <i>iv</i>	MDZ 0.04 mg/kg and on demand bolus 0.5 mg <i>iv</i> , FEN 1 mcg/kg <i>iv</i>	DEX could be a superior alternative drug to MDZ for conscious sedation in ERCP
¹ Mazanikov <i>et al</i> ^[53]	ERCP	50	DEX 1 mcg/kg followed by 0.7 mcg/kg per hour infusion <i>iv</i> , PCS with PRO and Alfentanil	Group P: Normal saline, PCS with PRO and Alfentanil	DEX alone was insufficient in alcoholics. PCS with PRO and Alfentanil could be recommended
¹ Nagaraj <i>et al</i> ^[51]	ERCP	70	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion <i>iv</i> , FEN 1 mcg/kg <i>iv</i>	PRO 0.5 mg/kg followed by 2 mg/kg per hour infusion <i>iv</i> , FEN 1 mcg/kg <i>iv</i>	PRO/FEN combination provided better overall conditions when compared to DEX/FEN combination

¹Negative result of dexmedetomidine. EGD: Esophagogastroduodenoscopy; ERCP: Endoscopic retrograde cholangiopancreatography; DEX: Dexmedetomidine; MDZ: Midazolam; PRO: Propofol; FEN: Fentanyl; MEP: Meperidine; REM: Remifentanyl; ETO: Etomidate; KET: Ketamine; SUF: Sufentanil; PCS: Patient controlled sedation.

in the dexmedetomidine group was significantly lesser than in the saline group. There were no significant differences in recovery phase, adverse events and satisfaction between the two groups. The authors concluded that intranasal dexmedetomidine with propofol and alfentanil for PCS presented deeper sedation with significantly fewer use of supplementary sedative agents during the EGD procedure^[31].

Recently, Koksai *et al*^[32] compared the effects of adding dexmedetomidine to ketamine on the safety and efficacy of anesthesia for EGD procedures. They used a loading dose of 0.5 mcg/kg of dexmedetomidine, followed by a continuous infusion of 0.2 mcg/kg per minute and a bolus dose of 1 mg/kg of ketamine compared with a loading dose of 0.5 mcg/kg of remifentanyl, followed by a continuous infusion of 0.1 mcg/kg per minute and a bolus dose of 1 mg/kg of ketamine. Additionally, a bolus dose of 0.5-1 mg/kg of propofol was supplemented if inadequate sedation occurred. The authors concluded that a combination use of dexmedetomidine and ketamine offered lesser efficacy and relatively longer recovery phase than the combination of remifentanyl and ketamine^[32]. This negative result of a combination of dexmedetomidine and ketamine could be due to relatively small dose of dexmedetomidine (Table 1).

COLONOSCOPY

Colonoscopy is the gold standard in the examination and the treatment of the disease of lower gastrointestinal tract. The ideal sedative agent for this procedure should permit a rapid adjustment of the sedation level and should not have any side effects^[33]. Currently, several studies of the use of dexmedetomidine for colonoscopy are published. A previous study compared the effects of dexmedetomidine and midazolam on hemodynamic parameters, efficacy of sedation, satisfaction and recovery scores during colonoscopy. This study confirmed that dexmedetomidine offered more hemodynamic stability, lower pain scores as well as higher sedation and satisfaction scores in colonoscopic procedure^[34].

Sula *et al*^[35] evaluated the efficacy and side effects of dexmedetomidine and propofol. They prospectively studied 231 patients with ASA class I -III underwent colonoscopy. Sedation was accomplished with propofol

1.5 mg/kg and on demand bolus dose of 0.4-0.5 mg/kg (group P) and with dexmedetomidine 1 mcg/kg (group D). Arterial blood pressure, heart rate, respiratory rate, oxygen saturation values as well as the patients' satisfaction and the endoscopists' satisfaction were compared. A decline in the systolic blood pressure occurred in 29 patients (12.5%), 17 patients (58.6%) in the group D and 12 patients (41.4%) in group P. Eleven patients (4.7%) in group P and one patient in group D had a decline in oxygen saturation. All these adverse effects were not clinically significant, and without serious effects. No severe bradycardia was noted. The satisfaction scores in both groups were comparable. The authors suggested that both regimens were safe and effective for sedation during colonoscopic procedure. The use of propofol initiated more desaturation, while the use of dexmedetomidine caused more hypotension^[35].

Another study of the hemodynamic parameters of dexmedetomidine for sedation in colonoscopy was presented. Seventy patients with ASA physical status I -III were randomized into two groups. In group P, the patients were received 0.5 mcg/kg of fentanyl over 5 min, and maintained by 1 mg/kg of propofol. In group D, the patients were received 1 mcg/kg of dexmedetomidine with 0.5 mcg/kg of fentanyl over 5 min, followed by 20 mg of propofol. The 20 mg propofol was titrated as required to achieve the target bispectral index (BIS) and sedation score. The results showed that the incidence of hypotension in group P was significantly higher than in group D. Heart rate in group P was greater than group D at 10th minute and from 25th minute throughout the period of colonoscopy. There were no significant differences in the induction time, incidence of bradycardia, patient satisfaction and postprocedural complications between the two groups. Additionally, the patients in group D recovered from sedation more quickly than in group P^[36].

Several sedation regimens are administered during colonoscopy. To date, the propofol-based sedation regimens are commonly used. The safety, efficacy and patient satisfaction of propofol combined with dexmedetomidine for conscious sedation in the colonoscopy were evaluated by Ayazoğlu *et al*^[37]. The patients in the dexmedetomidine combination with propofol group accomplished a greater degree of sedation and a rapid

recovery activity when compared with the meperidine, sufentanil and midazolam in combination with propofol groups. The authors recommended that sedation for colonoscopy could be effectively and safely done with propofol combined with dexmedetomidine and other sedoanalgesic drugs^[37].

However, the sole use of dexmedetomidine has inadequate utility for sedation during outpatient colonoscopy. For example, the study of Jalowiecki *et al*^[38] showed that dexmedetomidine sedation for colonoscopic procedure was incomplete because of its adverse effects including prolonged recovery and hemodynamic instability. The authors evaluated the capability of dexmedetomidine sedation for 64 patients underwent outpatient colonoscopic procedures. In group D, patients received 1 mcg/kg of dexmedetomidine over 15 min and maintained by an infusion of 0.2 mcg/kg per hour. Group P received 1 mg/kg of meperidine and 0.05 mg/kg of midazolam. Group F, patients received 0.1-0.2 mg of fentanyl *iv* on demand. The study was terminated because of adverse effects in group D. There was a significantly greater reduction in heart rate and arterial blood pressure in group D. In group D, additional fentanyl was needed in 47% of patients compared with 42.8% and 79.2% of patients in group P and F, respectively. Nausea/vomiting, vertigo and ventricular arrhythmia were noted only in group D. In addition, group D had the longest time to home readiness^[38]. This limited utility of dexmedetomidine for sedation during outpatient colonoscopy might be due to a relatively low dose during the procedure and inadequate analgesia (Table 2).

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Endoscopic retrograde cholangiopancreatography (ERCP) is a routinely carried out diagnostic and/or therapeutic procedure of many pancreatic and biliary diseases. It is a distressing procedure in awaked patients. These patients require sedation/anesthesia mainly to minimize their anxiety and analgesics to lessen pain and discomfort thereby enhancing patient's cooperation throughout the procedure^[39].

Kilic *et al*^[40] presented the use of dexmedetomidine for sedation during ERCP procedure. The efficacy, hemodynamic parameters and adverse effects were compared between dexmedetomidine and midazolam^[40]. Fifty patients aged 18-80 years were randomized into two groups. Group M, patients received a bolus infusion of 0.04 mg/kg of midazolam, and followed by a supplementary dose of 0.5 mg midazolam. Group D, patients received a bolus infusion of 1 mcg/kg per hour of dexmedetomidine over 10 min, and maintained by a continuous infusion of 0.2-0.7 mcg/kg per hour. All patients were sedated to target a Ramsay scale of 3-4. Heart rate in group D was significantly lesser than group M. In addition, the dexmedetomidine group also

showed higher endoscopist satisfaction scores^[40].

Furthermore, Ceylan *et al*^[41] evaluated the effects of propofol and dexmedetomidine hemodynamics, adverse effects, cognitive functions, and satisfaction during ERCP procedure. The fifty patients with ASA physical status class I and II were randomized into the two groups. Group P received propofol 75 mcg/kg per hour *iv* over 10 min, and followed by an infusion of 12.5-100.0 mcg/kg per minute. Group D received dexmedetomidine 1 mcg/kg per hour over 10 min, and maintained by an infusion of 0.2-0.7 mcg/kg per hour. All patients were sedated to attain a RSS of 3-4. The mental status examination before and after the procedure as well as pain was evaluated. The blood pressure and heart rate values in group D were significantly lesser than in group P. However, there were no significant differences in patient and endoscopist satisfaction among the two groups^[41].

Dexmedetomidine has been tried for various endoscopic procedures, and the evidence occurs to recommend its use for ERCP procedure. A randomized controlled study was planned to evaluate the hemodynamic and the recovery profiles of dexmedetomidine and midazolam. It was also to assess the grade of comfort and the procedural performance. All patients received 1 mcg/kg of fentanyl at the start of ERCP. Group M received a bolus dose of 0.04 mg/kg of midazolam and supplementary 0.5 mg doses. Group D received a bolus dose of 1 mcg/kg of dexmedetomidine at over 10 min and maintained by a continuous infusion of 0.5 mcg/kg per hour. The targeted depth of sedation was a RSS score 3-4. The heart rate, blood pressure, respiratory rate, oxygen saturation, the time to accomplish the targeted depth of sedation and pain score were evaluated and compared during and after the ERCP procedure. Heart rate and pain scores in group D were significantly lower than in group M. There were no significant differences in mean blood pressure and respiratory rate. The modified Aldrete score of 9-10 at 5 min during recovery was achieved in 27 (90%) patients in group D in contrast to 5 (17%) patients in group M ($P < 0.05$). Dexmedetomidine also showed higher patient and endoscopist satisfaction scores ($P < 0.05$)^[42].

The efficacy of dexmedetomidine for anesthesia in ERCP procedure was evaluated by Abdalla *et al*^[43]. Sixty patients with ASA physical status class II or III underwent ERCP procedures were randomly assigned into two groups. Group D, patients received a bolus dose of dexmedetomidine 1 mcg/kg and maintained by 0.5 mcg/kg per hour. Group K, patients received a loading dose of ketamine 1 mg/kg and followed by 0.5 mg/kg per hour. Propofol was used for induction of anesthesia and atracurium was utilized for endotracheal intubation. After that, anesthesia was maintained by continuous infusion of propofol. The combination of dexmedetomidine and propofol during ERCP procedure showed better hemodynamic stability, less nausea and vomiting, as well as shorter recovery time when compared with the combination of ketamine and

Table 2 The use of dexmedetomidine in a single agent technique for gastrointestinal endoscopic procedures

Ref.	Type of endoscopy	No. of patients	DEX group	Non-DEX group	Summary of findings
Samson <i>et al</i> ^[21]	EGD	90	DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion <i>iv</i>	MDZ 0.04 mg/kg followed by an additional dose of 0.5 mg <i>iv</i>	Endoscopist satisfaction and recovery in DEX group was significantly better than in MDZ and PRO groups
Jiang <i>et al</i> ^[23]	EGD	40	DEX 0.8 mcg/kg <i>iv</i>	PRO 2.5 mg/kg <i>iv</i>	DEX could yield marked sedative effect, had antihypertensive effect and did not suppress respiration
Demiraran <i>et al</i> ^[22]	EGD	50	DEX 1 mcg/kg followed by 0.2 mcg/kg per hour infusion <i>iv</i>	MDZ 0.07 mg/kg (total dose 5 mg) <i>iv</i>	DEX was superior to MDZ with regard to retching, rate of adverse events and endoscopist satisfaction for EGD sedation
Sula <i>et al</i> ^[35]	Colonoscopy	231	DEX 1 mcg/kg <i>iv</i>	PRO 1.5 mg/kg and on demand bolus 0.4-0.5 mg/kg <i>iv</i>	Both regimens were effective and safe for sedation. PRO caused more desaturation, while DEX caused more hypotension
¹ Jalowicki <i>et al</i> ^[38]	Colonoscopy	64	Group D: DEX 1 mcg/kg followed by 0.2 mcg/kg per hour infusion <i>iv</i>	Group P: 1 mg/kg of MEP with 0.05 mg/kg of MDZ <i>iv</i> , Group F: 0.1-0.2 mg of FEN <i>iv</i> on demand	There was a significantly greater decrease in heart rate and blood pressure in group D. Time to home readiness was the longest in group D
¹ Eldesuky Ali Hassan <i>et al</i> ^[48]	ERCP	50	Group D: DEX 1 mcg/kg followed by 0.5 mcg/kg per hour infusion <i>iv</i>	Group K: ketofol 1 mg/kg <i>iv</i> bolus followed by 50 mcg/kg per minute infusion <i>iv</i>	Time to achieve sedation score and total dose of rescue sedation were not significantly different. Patient and endoscopist satisfaction in group K was significantly higher than in group D
Kilic <i>et al</i> ^[40]	ERCP	50	Group D: DEX 1 mcg/kg followed by 0.2-0.7 mcg/kg per hour infusion <i>iv</i>	Group M: MDZ 0.04 mg/kg followed by an additional dose of 0.5 mg <i>iv</i>	DEX showed higher endoscopist satisfaction. Coughing, nausea and vomiting were observed in three patients in group M, but no patients in group D
Ceylan <i>et al</i> ^[41]	ERCP	50	Group D: DEX 1 mcg/kg followed by 0.2-0.7 mcg/kg per hour infusion <i>iv</i>	Group P: PRO 75 mcg/kg per hour followed by 12.5-100.0 mcg/kg per minute infusion <i>iv</i>	Blood pressure and heart rate values in group D were significantly lower than in group P. There were no significant differences in patient and endoscopist satisfaction
¹ Muller <i>et al</i> ^[52]	ERCP	26	Group D: DEX 1 mcg/kg followed by 0.2-0.5 mcg/kg per hour infusion <i>iv</i>	Group P: PRO (target plasma concentration 2-4 mcg/mL) with FEN 1 mcg/kg <i>iv</i>	DEX alone was not as effective as PRO combined with FEN. DEX was associated with greater hemodynamic instability and a prolonged recovery period
Eberl <i>et al</i> ^[55]	Esophageal intervention	64	DEX 1 mcg/kg (0.5 mcg/kg in age > 65) followed by 0.7-1 mcg/kg per hour infusion <i>iv</i>	PRO Target Controlled Infusion (OAAS scale ≤ 4)	DEX was a new representative for endoscopic sedation. The acceptance level after PRO was relatively high compared with DEX
Takimoto <i>et al</i> ^[58]	ESD	90	Group D: DEX 3 mcg/kg followed by 0.4 mcg/kg per hour infusion <i>iv</i>	Group P: PRO 5 mg bolus and 3 mg/kg per hour infusion <i>iv</i> , Group M: MDZ 0.1 mg/kg <i>iv</i>	DEX was effective and safe for patients with gastric tumors who underwent ESD

¹Negative result of dexmedetomidine. EGD: Esophagogastroduodenoscopy; ERCP: Endoscopic retrograde cholangiopancreatography; DEX: Dexmedetomidine; MDZ: Midazolam; PRO: Propofol; FEN: Fentanyl; MEP: Meperidine; REM: Remifentanyl; ETO: Etomidate; KET: Ketamine; SUF: Sufentanil; PCS: Patient controlled sedation.

propofol^[43].

Moreover, Han-wei *et al*^[44] observed the safety and feasibility of dexmedetomidine and fentanyl for conscious sedation in the ERCP procedure. Sixty patients of ASA class I - II who planned to receive ERCP were allocated into dexmedetomidine group and propofol group. The patients in the two groups were treated with anisodamine 10.0 mg and fentanyl 1.0 mcg/kg before ERCP. The patients in dexmedetomidine group were treated with dexmedetomidine 0.5 mcg/kg by injection

within 15 min, then the dexmedetomidine was infused continuously at the rate of 0.5-1.0 mcg/kg per hour to the end of operation. Patients in the propofol group were treated with propofol 1.0 mg/kg in 2 min, and followed by continuous infusion of 4.0-6.0 mg/kg per hour to the end of operation. Arterial blood pressure, heart rate and oxygen saturation were noted at the time points of before anesthesia (T0), before inserting endoscope (T1), while inserting endoscope (T2), 20 min after inserting endoscope (T3) and 10 min after the

end of examination (T4). The intubation process and cooperation of patients were scored; and the patients' satisfaction for examination was evaluated next day. In dexmedetomidine group, heart rate of patients at the time points of T1, T2, T3 and T4 was significantly lower than that at the time point of T0; but there was no significant difference in the systolic and diastolic blood pressure among the time points of T0, T1, T2, T3 and T4. There was no significant difference in the oxygen saturation all time points in the two groups. The heart rate at the time points of T1, T2, T3 and T4 in the propofol group was significantly higher than that in the dexmedetomidine group. The score of intubation process and cooperation of patients in the dexmedetomidine group was significantly higher than that in the propofol group. However, patient satisfaction in both groups was not significantly different. The authors concluded that dexmedetomidine and fentanyl for conscious sedation in ERCP procedure was safe and feasible, which could meet the test needed of sedation, and could obtain better cooperation of the patients^[44].

Generally, the combination regimens are commonly used for invasive procedures. Dexmedetomidine may employ a synergistic effect in the combination with sedoanalgesic drugs. Lee and coworkers evaluated the efficacy and adverse effects of midazolam-meperidine-dexmedetomidine (MMD) and midazolam-meperidine (MM) for ERCP procedure in 110 patients. Lower additional and total doses of midazolam were needed in group MMD. Oxygen desaturation and pain scores in group MMD were significantly lesser than in group MM. In addition, the satisfaction scores in group MMD were significantly greater than group MM. The authors recommended that the combination of dexmedetomidine, midazolam and meperidine regimen presented superior sedative efficacy and a greater safety profile during ERCP procedure compared with the combination of midazolam and meperidine regimen^[45]. Recently, Mukhopadhyay *et al*^[46] assess the safety and efficacy of dexmedetomidine as an add-on for deep sedation in prolonged ERCP procedure. The authors concluded that the addition of dexmedetomidine in sedoanalgesic cocktail increased the safety and efficacy of deep sedation^[46].

Ketofol, a combination of ketamine and propofol, is significant interest as an agent for procedural sedation. This combination regimen has several advantages in the terms of hemodynamic stability, lack of respiratory depression, post-operative analgesia and recovery^[47]. Recently, a double-blind randomized study is carried out to evaluate two techniques of moderate sedation for patients undergoing ERCP procedure, using either dexmedetomidine or ketofol as regards hemodynamic, sedation, respiratory effect, pain, recovery time, patient and endoscopist satisfaction as well as the complications. Fifty patients were randomly assigned in the two groups; dexmedetomidine received 1 mcg/kg *iv* bolus over 10 min followed by 0.5 mcg/kg per hour or ketofol received 1 mg/kg *iv* bolus and maintained by 50

mcg/kg per minute. Mean arterial pressure and heart rate in the dexmedetomidine group were significantly lesser than in the ketofol group. Additionally, time to achieve RSS score and total dose of rescue sedation in both groups were not significantly different. However, patient and endoscopist satisfaction in the ketofol group was significantly higher than in the dexmedetomidine group^[48] (Table 2). The advantage of ketofol in this study may be due to design of the study. The depth of sedation level was targeted to attain a RSS score of 4. The combination use of ketamine and propofol offered better outcome variables than the use of dexmedetomidine alone.

Several case studies also have been reported the efficacy of dexmedetomidine for procedural sedation in the difficult patients. For example, Srivastava *et al*^[49] reported a 65-year-old female presented with anorexia, vomiting and yellowish discoloration of skin for 3 mo. The patient was diagnosed as extrahepatic cholangiocarcinoma with extrahepatic biliary obstruction type 3 and was advised surgical resection of tumor. The patient had history of dyspnea on mild exertion (New York Heart Association III), left bundle branch block, and cardiomegaly. The transthoracic echocardiography demonstrated dilated left ventricle, global hypokinesia, ejection fraction 25%, moderate pulmonary artery hypertension. However, the patient refused for surgery owing to increased cardiac risk. The patient was advised endoscopic placement of stents to drain the biliary system for symptomatic relief. Monitored anesthesia care with light sedation was required for this procedure. She was induced with 1 mcg/kg of dexmedetomidine over 20 min and then continuous infusion was titrated between 0.2 and 0.5 mcg/kg per hour to keep blood pressure and HR within 10% of baseline. Mean HR during procedure was 74 ± 10 beats/min, and mean blood pressure was 80 ± 15 mmHg. The total procedure time was 40 min. The patient was oxygenated throughout the procedure until recovery from sedation by face mask. The SpO₂ was never below 98%. The recovery time was 30 min^[49].

Ko *et al*^[50] presented a 10-year-old boy, 29 kg with obstructive jaundice and a distal common bile duct stone. Five days before, ERCP sedation performed by a gastroenterologist was failed. Non-invasive blood pressure, electrocardiography, SpO₂, BIS values and Observer's Assessment of Alertness/Sedation scores were monitored. In this second sedation, a dose of 0.5 mg/kg of ketamine and 0.5 mcg/kg of fentanyl were given before the procedure. Additionally, a bolus dose of 0.7 mcg/kg of dexmedetomidine was given over 10 min followed by a continuous infusion of 0.5 mcg/kg per hour. The oxygen saturation decreased to 85% for a second. However, oxygen saturation recovered to 100% when the scope was inserted. Oxygen supplementation was administered and a child breathed spontaneously. This procedure was successfully completed with minimal decreases in blood pressure and heart rate. After the procedure, dexmedetomidine infusion was stopped.

The patient did not report of postprocedural nausea and vomiting and did not present emergence agitation or delirium^[50].

However, the negative results of the use of dexmedetomidine for ERCP procedure have been occurred (Table 2). For example, the study of Nagaraj *et al*^[51] compared the combination of dexmedetomidine and fentanyl with the combination of propofol and fentanyl for procedural sedation in ERCP procedure. In the dexmedetomidine group, patients received fentanyl 1 mcg/kg and a bolus dose of dexmedetomidine 1 mcg/kg over 10 min followed by a maintenance dose of 0.5 mcg/kg per hour intravenously. In the propofol group, the patients received fentanyl 1 mcg/kg and a loading dose of propofol infused at 0.5 mg/kg over 10 min followed by a maintenance dose of 2 mg/kg per hour intravenously. The study showed that the combination of propofol and fentanyl achieved better overall conditions for ERCP compared to the combination of dexmedetomidine and fentanyl^[51].

Generally, deep sedation is utilized for invasive GIE procedures including ERCP. A combination of two or more sedative drugs produces a synergistic effect and is commonly used for deep sedation technique. Another negative result of the use of dexmedetomidine alone was published by Muller *et al*^[52]. They conducted a randomized, double blind, study to test the hypothesis that dexmedetomidine was as effective as propofol combined with fentanyl for sedation during an ERCP procedure. Twenty-six patients with ASA physical status class I to III were randomly assigned to receive either propofol combined with fentanyl 1 mcg/kg, or dexmedetomidine 1 mcg/kg in 10 min, followed by 0.2 to 0.5 mcg/kg per minute. Supplementary sedative drugs were added if an inadequate sedation was not attained. Heart rate, blood pressure, respiratory rate and oxygen saturation were continuously monitored. The result of the study proved that dexmedetomidine alone was not as effective as a combination of propofol and fentanyl for sedation during ERCP procedure. Moreover, dexmedetomidine was related with lesser hemodynamic stability and prolonged recovery period^[52].

Similarly, the use of dexmedetomidine alone for sedation in the alcoholic patients is also inadequate (Table 1). This outcome was confirmed by the study of Mazanikov *et al*^[53]. They assessed the suitability of dexmedetomidine for sedation of the alcoholic patients during ERCP procedure. Fifty patients with chronic alcoholism underwent elective ERCP procedure were randomly assigned to receive dexmedetomidine (group D) (a bolus dose of 1 mcg/kg in 10 min, followed by continuous intravenous infusion 0.7 mcg/kg per hour) or normal saline (group P). Additionally, PCS with propofol and alfentanil was used by patients as a rescue method. Sedation was considered as successful if no intervention of an anesthesiologist was needed. Consumption of sedatives was registered, and sedation levels and vital signs were monitored. The result of the study indicated that the use of dexmedetomidine

alone was insufficient in all alcoholic patients. The mean consumption of propofol was 159 ± 72 mg in group P, and 116 ± 61 mg in group D ($P = 0.028$). Sedation was successful in 19 of 25 (76%) patients in group D and all patients in group P ($P = 0.022$). The incidence of sedation-related adverse events in both groups was comparable. However, dexmedetomidine was associated with delayed recovery. They suggested that PCS with propofol and alfentanil but not dexmedetomidine could be recommended for sedation of the alcoholic patients during ERCP procedure^[53]. Additionally, a negative result of the use of dexmedetomidine was also reported by Ramkiran *et al*^[54]. The report showed that the use of dexmedetomidine presented in greater propofol consumption, with delayed recovery and unfavorable hemodynamic profiles when compared with a combination of low dose ketamine and propofol in outpatient ERCP procedure^[54].

ESOPHAGEAL INTERVENTION

Early neoplastic lesions in esophagus could be treated by endoscopic intervention has evolved as a valid. These esophageal interventions are minimal invasive treatment options alternative to the surgical operations. The safety and effectiveness of dexmedetomidine sedation for endoscopic esophageal interventions was observed in the study of Eberl *et al*^[55]. The 64 patients were randomly allocated to the propofol and the dexmedetomidine groups. The effectiveness of sedation was the primary outcome of the study. Respiratory and hemodynamic complications were the secondary outcome variables. The authors suggested that dexmedetomidine was a new representative for endoscopic sedation. However, the sedation efficacy in the propofol group was relatively high compared with the dexmedetomidine group^[55].

To date, esophageal strictures after accidental ingestion of a corrosive substance are still clinical problems and the esophageal dilatation sessions are frequently required. The use of dexmedetomidine for these esophageal interventions in children is perceived. The combination of dexmedetomidine and the sedoanalgesic agents was used to evaluate the safety, efficacy, recovery profiles and hemodynamic parameters with those of the combination of propofol and ketamine in pediatric patients underwent endoscopic esophageal balloon dilatation^[56]. The study verified that the combination of dexmedetomidine, ketamine and midazolam had relatively more hemodynamic and respiratory stabilities, with adequate postprocedural analgesia. However, the use of ketamine alone had quicker onset and rapid recovery of sedation than the combination of dexmedetomidine and midazolam^[56].

ENDOSCOPIC SUBMUCOSAL DISSECTION

Endoscopic submucosal dissection (ESD) is an endos-

copic treatment of early gastric cancer. It has been extensively accepted. However, ESD is correlated with a longer procedure time and a higher risk of patient distress than the conventional endoscopic procedures. An acceptable and safe sedation is necessary. A combination of benzodiazepines and analgesics are usually utilized for sedation, but a new sedative agent such as dexmedetomidine is estimated to be a useful agent^[57].

Takimoto and coworkers conducted a randomized study of dexmedetomidine sedation in 90 patients with gastric tumors underwent the ESD procedure. All patients were sedated either with dexmedetomidine (a bolus of 3.0 mcg/kg per hour in 5 min followed by a continuous infusion of 0.4 mcg/kg per hour), propofol, or midazolam. The resection of gastric tumor was completed in 88 (98%) patients. No patients in the dexmedetomidine group demonstrated a significant decrease of the oxygen saturation level. This study proved that sedation with dexmedetomidine was safe and effective for patients with gastric tumors who underwent ESD procedure^[58].

Ishibashi *et al*^[59] assessed the efficacy and safety of sedation with dexmedetomidine in the intubated spontaneously breathing patients after ESD procedure for pharyngeal or esophageal cancer. The 55 patients with ASA class I or II who underwent ESD under general anesthesia and who were remained intubated until the next day in the ICU receiving sedation with dexmedetomidine. A continuous infusion of dexmedetomidine at 0.4-0.7 mcg/kg per hour was administered during procedure and continued in the ICU until extubation. Hemodynamic and respiratory parameters as well as the Richmond Agitation Sedation Scale (RASS) scores were noted. The 39 patients in group G were remained well sedated (RASS < 1). The 16 patients were poorly sedated (RASS ≥ 1 at any time-point) were in group P. Hemodynamic and respiratory variables in the ICU were not significantly different between the two groups. The requirements of rescue sedatives and analgesics in group P were significantly higher than in group G. The authors concluded that sedation with dexmedetomidine in the intubated spontaneously breathing patients after ESD was safe and effective. The higher plasma concentration of dexmedetomidine at the time of entrance into the ICU was associated with better sedation and less analgesic requirements^[59].

The combination of dexmedetomidine and propofol for the ESD procedure is also safe and effective. Forty patients with ASA physical status class I or II underwent ESD were randomized into two groups. Group A was given propofol alone. Group B was given intravenously dexmedetomidine followed by propofol. The study demonstrated that the use dexmedetomidine combined with propofol and propofol alone were no significant differences in the respiratory rate, oxygen saturation, operative time and anesthetic effect. This study confirmed that anesthetic effect of dexmedetomidine combined with propofol for patients underwent ESD procedure was satisfactory and safe^[60].

The ESD procedure of colorectal tumor is withstanding. However, this is a technical difficulty procedure. Takimoto *et al*^[61] examined the efficacy and safety of dexmedetomidine sedation for ESD procedure. The 210 patients underwent the colorectal ESD were categorized into group A (continuous infusion of dexmedetomidine at 0.2 mcg/kg per hour) and group B (no administration of dexmedetomidine). A reduced blood pressure and heart rate or a decrease of oxygen saturation was not observed. The endoscopic treatment was succeeded in 100% and 82% of the patients in group A and B, respectively. The authors suggested that the use of dexmedetomidine reduced the requirement for a rescue medication and eased an endoscopic treatment. Consequently, a combination use of dexmedetomidine might establish as an effective and safe technique for the colorectal ESD^[61].

Moreover, dexmedetomidine suppresses gastric motility. The use of dexmedetomidine during ESD procedure should be useful. The study of Kim *et al*^[62] evaluated the safety and efficacy of the combination of dexmedetomidine and remifentanyl with the combination of propofol and remifentanyl for ESD procedure. Although, the efficacy and safety of these two groups were comparable, the endoscopists favored dexmedetomidine because of its action^[62].

The patients with severe chronic obstructive pulmonary disease (COPD) have validated an increased risk for oxygen desaturation following the general anesthesia. The use of dexmedetomidine sedation is one of the appropriate methods for management of the COPD patients^[63]. Iizuka *et al*^[63] reported an anesthetic management of a 74-year-old man with severe COPD and gastric cancer underwent ESD procedure. They used dexmedetomidine under monitored anesthesia care and the patient spontaneously breathed during the procedure. The ESD procedure took 5.5 h with satisfactory analgesia, and no airway management was needed. The patient accepted the procedure and recovered well with no adverse events. Finally, the patient was discharged on the fifth postprocedural day^[63].

SMALL BOWEL ENTEROSCOPY

Currently, small bowel enteroscopy is the standard method for diagnosis and treatment of small bowel abnormalities. It is a long and invasive endoscopic procedure. Anesthesia/sedation is regularly used for this endoscopy procedure^[64]. The safety and efficacy of dexmedetomidine used in this procedure were investigated by the study of Sun *et al*^[65]. Thirty patients with ASA physical status class I or II, planned for single balloon enteroscopy were randomly assigned into two groups: Group D (intravenous perfusion of dexmedetomidine 0.6 mcg/kg), and group C (normal saline of equal volume with dexmedetomidine). Group D and group C respectively received dexmedetomidine and normal saline before induction by *iv* infusion in

10 min. Then general anesthesia was induced with propofol, fentanyl and vecuronium. The maintenance of anesthesia was used by propofol in both groups. The study summarized that the use of dexmedetomidine 0.6 mcg/kg for 10 min before induction presented more stable during the period of induction. It also reduced the doses of propofol in the period of induction and operation. Dexmedetomidine could make the patient hemodynamics more stable and the recovery more rapid and complete^[65].

To date, there is a wide variability of the efficacy of the use of dexmedetomidine in various GIE procedures. Several reports have been demonstrated the positive results. However, some studies did not confirm the benefits of dexmedetomidine for GIE procedures. The author also summarizes these in the two tables. Table 2 shows the use of dexmedetomidine in a single agent technique for GIE procedures including the positive and negative results. In addition, Table 1 lists the use of dexmedetomidine in a combination technique for GIE procedures including the positive and negative results.

CONCLUSION

Several sedative and analgesic drugs are commonly used in the GIE procedures. Their safety profile is dependent on their pharmacokinetic and pharmacodynamic profiles, the patient medical condition and the experience of the physician using them. Dexmedetomidine has analgesic, amnesic, sedative and anxiolytic properties. The use of dexmedetomidine as the sole anesthetic agent and as the adjuvant anesthetic agent in various GIE procedures has been published. A distinct advantage of dexmedetomidine is the maintenance of respiratory force and preserved airway patency even in the existence of rising sedation. These properties of dexmedetomidine have verified to be beneficial in high-risk patients such as the patients with OSA and COPD patients as well as the patients with extensive tracheomalacia. However, it can produce bradycardia and hypotension. Additionally, the negative results of dexmedetomidine for some GIE procedures have been happened. Therefore, further clinical investigations should to be done.

REFERENCES

- 1 **Chrysostomou C**, Schmitt CG. Dexmedetomidine: sedation, analgesia and beyond. *Expert Opin Drug Metab Toxicol* 2008; **4**: 619-627 [PMID: 18484919 DOI: 10.1517/17425255.4.5.619]
- 2 **Piao G**, Wu J. Systematic assessment of dexmedetomidine as an anesthetic agent: a meta-analysis of randomized controlled trials. *Arch Med Sci* 2014; **10**: 19-24 [PMID: 24701209 DOI: 10.5114/aoms.2014.40730]
- 3 **Nelson LE**, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology* 2003; **98**: 428-436 [PMID: 12552203]
- 4 **Bajwa S**, Kulshrestha A. Dexmedetomidine: an adjuvant making large inroads into clinical practice. *Ann Med Health Sci Res* 2013; **3**: 475-483 [PMID: 24379995 DOI: 10.4103/2141-9248.122044]
- 5 **Dyck JB**, Shafer SL. Dexmedetomidine pharmacokinetics and pharmacodynamics. *Anesth Pharm Rev* 1993; **1**: 238-245
- 6 **Bloor BC**, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992; **77**: 1134-1142 [PMID: 1361311]
- 7 **Venn RM**, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care* 2000; **4**: 302-308 [PMID: 11056756]
- 8 **Engelhard K**, Werner C, Kaspar S, Möllenberg O, Blobner M, Bachl M, Kochs E. Effect of the alpha2-agonist dexmedetomidine on cerebral neurotransmitter concentrations during cerebral ischemia in rats. *Anesthesiology* 2002; **96**: 450-457 [PMID: 11818781]
- 9 **Afonso J**, Reis F. Dexmedetomidine: current role in anesthesia and intensive care. *Rev Bras Anesthesiol* 2012; **62**: 118-133 [PMID: 22248773 DOI: 10.1016/S0034-7094(12)70110-1]
- 10 **Amornyotin S**. Sedative and analgesic drugs for gastrointestinal endoscopic procedure. *J Gastroenterol Hepatol Res* 2014; **3**: 1133-1144 [DOI: 10.6051/j.issn.2224-3992.2014.04.397]
- 11 **Amornyotin S**, Leelakusolvong S, Chalayonnawin W, Kongphlay S. Age-dependent safety analysis of propofol-based deep sedation for ERCP and EUS procedures at an endoscopy training center in a developing country. *Clin Exp Gastroenterol* 2012; **5**: 123-128 [PMID: 22826640 DOI: 10.2147/CEG.S31275]
- 12 **Amornyotin S**. Sedation and monitoring for gastrointestinal endoscopy. *World J Gastrointest Endosc* 2013; **5**: 47-55 [PMID: 23424050 DOI: 10.4253/wjge.v5.i2.47]
- 13 **Hasanin AS**, Sira AM. Dexmedetomidine versus propofol for sedation during gastrointestinal endoscopy in pediatric patients. *Egypt J Anesth* 2014; **30**: 21-26
- 14 **Vetsa M**, Walter MH, Olafsson S, Condon DS, Zhao YS, Lewis TD, Srikureja W. The use of dexmedetomidine for gastrointestinal endoscopic procedures in difficult to sedate cohort: a single institution experience. *Gastrointest Endosc* 2010; **71**: AB248 [DOI: 10.1016/j.gie.2010.03.537]
- 15 **Turan A**, Wo J, Kasuya Y, Govinda R, Akça O, Dalton JE, Sessler DI, Rauch S. Effects of dexmedetomidine and propofol on lower esophageal sphincter and gastroesophageal pressure gradient in healthy volunteers. *Anesthesiology* 2010; **112**: 19-24 [PMID: 20032699 DOI: 10.1097/01.anes.0000365963.97138.54]
- 16 **Amornyotin S**, Srikureja W, Chalayonnawin W, Kongphlay S, Chatchawankitkul S. Topical viscous lidocaine solution versus lidocaine spray for pharyngeal anesthesia in unsedated esophago-gastroduodenoscopy. *Endoscopy* 2009; **41**: 581-586 [PMID: 19588284 DOI: 10.1055/s-0029-1214865]
- 17 **Wu Y**, Zhang Y, Hu X, Qian C, Zhou Y, Xie J. A comparison of propofol vs. dexmedetomidine for sedation, haemodynamic control and satisfaction, during esophagogastroduodenoscopy under conscious sedation. *J Clin Pharm Ther* 2015; **40**: 419-425 [PMID: 25970229 DOI: 10.1111/jcpt.12282]
- 18 **Wu W**, Chen Q, Zhang LC, Chen WH. Dexmedetomidine versus midazolam for sedation in upper gastrointestinal endoscopy. *J Int Med Res* 2014; **42**: 516-522 [PMID: 24514431 DOI: 10.1177/0300060513515437]
- 19 **Vázquez-Reta JA**, Jiménez Ferrer MC, Colunga-Sánchez A, Pizarro-Chávez S, Vázquez-Guerrero AL, Vázquez-Guerrero AR. [Midazolam versus dexmedetomidine for sedation for upper gastrointestinal endoscopy]. *Rev Gastroenterol Mex* 2011; **76**: 13-18 [PMID: 21592898]
- 20 **Hashiguchi K**, Matsunaga H, Higuchi H, Miura S. Dexmedetomidine for sedation during upper gastrointestinal endoscopy. *Dig Endosc* 2008; **20**: 178-183 [DOI: 10.1111/j.1443-1661.2008.00803.x]
- 21 **Samson S**, George SK, Vinoth B, Khan MS, Akila B. Comparison of dexmedetomidine, midazolam, and propofol as an optimal sedative for upper gastrointestinal endoscopy: a randomized controlled trial. *J Dig Endosc* 2014; **5**: 51-57 [DOI: 10.4103/0976-5042.144826]
- 22 **Demiraran Y**, Korkut E, Tamer A, Yorulmaz I, Kocaman B, Sezen G, Akcan Y. The comparison of dexmedetomidine and midazolam used for sedation of patients during upper endoscopy: A prospective,

- randomized study. *Can J Gastroenterol* 2007; **21**: 25-29 [PMID: 17225879]
- 23 **Jiang W**, Xihong L, Haibo Z. The sedative effect and hemodynamic influence of dexmedetomidine on patients undergoing painless gastroscopy examination. *J Med Theory Pract* 2012; **18**: 009
 - 24 **Goyal R**, Singh S, Shukla RN, Patra AK, Bhargava DV. Ketodex, a combination of dexmedetomidine and ketamine for upper gastrointestinal endoscopy in children: a preliminary report. *J Anesth* 2013; **27**: 461-463 [PMID: 23223916 DOI: 10.1007/s00540-012-1538-8]
 - 25 **EL-Shmaa NS**, El-Baradei GF. The efficacy of etomidate-fentanyl versus dexmedetomidine-ketamine for procedural sedation and analgesia during upper endoscopy and biopsy: a prospective, randomized study. *J Anesth Clin Res* 2014; **5**: 480 [DOI: 10.4172/2155-6148.1000480]
 - 26 **Hammer GB**, Sam WJ, Chen MI, Golianu B, Drover DR. Determination of the pharmacodynamic interaction of propofol and dexmedetomidine during esophagogastroduodenoscopy in children. *Paediatr Anaesth* 2009; **19**: 138-144 [PMID: 19207899 DOI: 10.1111/j.1460-9592.2008.02823.x]
 - 27 **Hannallah M**, Rasmussen M, Carroll J, Charabaty A, Palese C, Haddad N. Evaluation of dexmedetomidine/propofol anesthesia during upper gastrointestinal endoscopy in patients with high probability of having obstructive sleep apnea. *Anesthesia, Pain Intens Care* 2013; **17**: 257-260
 - 28 **Atkins JH**, Mandel JE, Metz DC. Sudden Tracheal Collapse during EGD and Subsequent Anesthetic Management with Dexmedetomidine-Ketamine in a Patient with Achalasia and Tracheomalacia. *Case Rep Anesthesiol* 2011; **2011**: 281679 [PMID: 22606385 DOI: 10.1155/2011/281679]
 - 29 **Raman V**, Yacob D, Tobias JD. Dexmedetomidine-ketamine sedation during upper gastrointestinal endoscopy and biopsy in a patient with Duchenne muscular dystrophy and egg allergy. *Int J Crit Illn Inj Sci* 2012; **2**: 40-43 [PMID: 22624101 DOI: 10.4103/2229-5151.94899]
 - 30 **Han G**, Yu WW, Zhao P. A randomized study of intranasal vs. intravenous infusion of dexmedetomidine in gastroscopy. *Int J Clin Pharmacol Ther* 2014; **52**: 756-761 [PMID: 24887336 DOI: 10.5414/CP202099]
 - 31 **Cheung CW**, Qiu Q, Liu J, Chu KM, Irwin MG. Intranasal dexmedetomidine in combination with patient-controlled sedation during upper gastrointestinal endoscopy: a randomised trial. *Acta Anaesthesiol Scand* 2015; **59**: 215-223 [PMID: 25471688 DOI: 10.1111/aas.12445]
 - 32 **Koksal E**, Ustun YB, Kaya C, Torun AC, Yilmaz MZ, Atalay YO, Ozkan F. Use of remifentanyl or dexmedetomidine with ketamine for upper gastrointestinal endoscopy. *J Exp Clin Med* 2014; **31**: 221-224 [DOI: 10.5835/jcem.omu.31.04.004]
 - 33 **Amornyotin S**, Songari P, Kongphlay S. Deep sedation with propofol and pethidine versus moderate sedation with midazolam and fentanyl in colonoscopic procedure. *J Gastroenterol Hepatol Res* 2013; **2**: 885-890 [DOI: 10.6051/j.issn.2224-3992.2013.02.358]
 - 34 **Dere K**, Sucullu I, Budak ET, Yeyen S, Filiz AI, Ozkan S, Dagli G. A comparison of dexmedetomidine versus midazolam for sedation, pain and hemodynamic control, during colonoscopy under conscious sedation. *Eur J Anaesthesiol* 2010; **27**: 648-652 [PMID: 20531094 DOI: 10.1097/EJA.0b013e3283347bfe]
 - 35 **Sula H**, Domi R, Ohri I, Broqi I, Beqiri A, Gani H. Propofol versus dexmedetomidine for sedation in colonoscopy: a prospective, randomized study. *Eur J Anaesthesiol* 2012; **29**: 32
 - 36 **Techanivate A**, Verawattaganon T, Saiyuenyong C, Areeeruk P. A comparison of dexmedetomidine versus propofol on hypotension during colonoscopy under sedation. *J Anesth Clin Res* 2012; **3**: 257 [DOI: 10.4172/2155-6148.1000257]
 - 37 **Ayazoglu TA**, Polat E, Bolat C, Yasar NF, Duman U, Akbulut S, Yol S. Comparison of propofol-based sedation regimens administered during colonoscopy. *Rev Med Chil* 2013; **141**: 477-485 [PMID: 23900369 DOI: 10.4067/S0034-98872013000400009]
 - 38 **Jalowiecki P**, Rudner R, Gonciarz M, Kawecki P, Petelenz M, Dziurdzik P. Sole use of dexmedetomidine has limited utility for conscious sedation during outpatient colonoscopy. *Anesthesiology* 2005; **103**: 269-273 [PMID: 16052108]
 - 39 **Amornyotin S**, Na-pomphet S, Wongwathanyoo T, Chalayonnavin V. Anesthesia for endoscopic retrograde cholangiopancreatography (ERCP) from 1999--2003 in Siriraj Hospital: a retrospective study. *J Med Assoc Thai* 2004; **87**: 1491-1495 [PMID: 15822546]
 - 40 **Kilic N**, Sahin S, Aksu H, Yavascaoglu B, Gurbet A, Turker G, Kadioglu AG. Conscious sedation for endoscopic retrograde cholangiopancreatography: dexmedetomidine versus midazolam. *Eurasian J Med* 2011; **43**: 13-17 [PMID: 25610153 DOI: 10.5152/eajm.2011.03]
 - 41 **Ceylan G**, Yavascaoglu B, Korfali G, Kaya FN, Mogol EB, Turker G. A comparison of propofol and dexmedetomidine on the effects of hemodynamic and cognitive functions in conscious sedation during endoscopic retrograde cholangiopancreatography. *Uludag Universitesi Tip Fakultesi Dergisi* 2010; **36**: 103-110
 - 42 **Sethi P**, Mohammed S, Bhatia PK, Gupta N. Dexmedetomidine versus midazolam for conscious sedation in endoscopic retrograde cholangiopancreatography: An open-label randomised controlled trial. *Indian J Anaesth* 2014; **58**: 18-24 [PMID: 24700894 DOI: 10.4103/0019-5049.126782]
 - 43 **Abdalla MW**, El Shal SM, El Sombaty AI, Abdalla NM, Zeedan RB. Propofol dexmedetomidine versus propofol ketamine for anesthesia of endoscopic retrograde cholangiopancreatography (ERCP) (a randomized comparative study). *Egypt J Anesth* 2015; **31**: 97-105 [DOI: 10.1016/j.egja.2014.12.008]
 - 44 **Li HW**, Li YL, Liu XC, Zhou YH, Yuan J, Sun JX. Dexmedetomidine and fentanyl for conscious sedation in endoscopic retrograde cholangiopancreatography. *Xinxiang Yixueyuan Xuebao* 2013; **9**: 724-726
 - 45 **Lee BS**, Ryu J, Lee SH, Lee MG, Jang SE, Hwang JH, Ryu JK, Do SH, Kim YT. Midazolam with meperidine and dexmedetomidine vs. midazolam with meperidine for sedation during ERCP: prospective, randomized, double-blinded trial. *Endoscopy* 2014; **46**: 291-298 [PMID: 24671858 DOI: 10.1055/s-0033-1358909]
 - 46 **Mukhopadhyay S**, Niyogi M, Sarkar J, Mukhopadhyay BS, Halder SK. The dexmedetomidine augmented sedato-analgesic cocktail: an effective approach for sedation in prolonged endoscopic retrograde cholangiopancreatography. *J Anaesthesiol Clin Pharmacol* 2015; **31**: 201-206 [DOI: 10.4103/0970-9185.155149]
 - 47 **Amornyotin S**. Ketofol: a combination of ketamine and propofol. *J Anesth Crit Care* 2014; **1**: 31 [DOI: 10.15406/jaccoa.2014.01.00031]
 - 48 **Eldesuky Ali Hassan HI**. Dexmedetomidine versus ketofol for moderate sedation in endoscopic retrograde cholangiopancreatography (ERCP) comparative study. *Egypt J Anesth* 2015; **31**: 15-21 [DOI: 10.1016/j.egja.2014.11.002]
 - 49 **Srivastava D**, Solanki SL, Singh PK. Dexmedetomidine in upper gastrointestinal endoscopy of a patient with ejection fraction 25%. *Saudi J Anaesth* 2014; **8**: 571-572 [PMID: 25422626 DOI: 10.4103/1658-354X.140916]
 - 50 **Ko BJ**, Jang JH, Park JW, Lee SC, Choi SR. Procedural sedation with dexmedetomidine for pediatric endoscopic retrograde cholangiopancreatography guided stone retraction. *Korean J Anesthesiol* 2012; **63**: 567-568 [PMID: 23277822 DOI: 10.4097/kjae.2012.63.6.567]
 - 51 **Nagaraj MC**, Geetha CR, Rajavardhan R. Is dexmedetomidine a poor surrogate to propofol for procedural sedation during endoscopic retrograde cholangiopancreatography (ERCP). *J Evol Med Dent Sci* 2013; **2**: 8165-8175
 - 52 **Muller S**, Borowics SM, Fortis EA, Stefani LC, Soares G, Maguilnik I, Breyer HP, Hidalgo MP, Caumo W. Clinical efficacy of dexmedetomidine alone is less than propofol for conscious sedation during ERCP. *Gastrointest Endosc* 2008; **67**: 651-659 [PMID: 18291396 DOI: 10.1016/j.gie.2007.09.041]
 - 53 **Mazanikov M**, Udd M, Kylänpää L, Mustonen H, Lindström O, Haltunen J, Pöyhä R. Dexmedetomidine impairs success of patient-controlled sedation in alcoholics during ERCP: a randomized, double-blind, placebo-controlled study. *Surg Endosc* 2013; **27**: 2163-2168 [PMID: 23355148 DOI: 10.1007/s00464-012-2734-1]

- 54 **Ramkiran S**, Iyer SS, Dharmavaram S, Mohan CV, Balekudru A, Kunnavil R. BIS Targeted Propofol Sparing Effects of Dexmedetomidine Versus Ketamine in Outpatient ERCP: A Prospective Randomised Controlled Trial. *J Clin Diagn Res* 2015; **9**: UC07-UC12 [PMID: 26155536 DOI: 10.7860/JCDR/2015/12435.5991]
- 55 **Eberl S**, Preckel B, Bergman JJ, Hollmann MW. Safety and effectiveness using dexmedetomidine versus propofol TCI sedation during oesophagus interventions: a randomized trial. *BMC Gastroenterol* 2013; **13**: 176 [PMID: 24377675 DOI: 10.1186/1471-230X-13-176]
- 56 **Saleh EG**, Hussien GZ, Eskander AE. Comparison between dexmedetomidine-midazolam, propofol and ketamine used for children scheduled for endoscopic esophageal balloon dilatation after corrosive esophageal stricture. *Ain Shams J Anesthesiol* 2011; **4-3**: 105-115
- 57 **Sasaki T**, Tanabe S, Ishido K, Azuma M, Katada C, Higuchi K, Koizumi W. Recommended sedation and intraprocedural monitoring for gastric endoscopic submucosal dissection. *Dig Endosc* 2013; **25** Suppl 1: 79-85 [PMID: 23406354 DOI: 10.1111/den.12024]
- 58 **Takimoto K**, Ueda T, Shimamoto F, Kojima Y, Fujinaga Y, Kashiwa A, Yamauchi H, Matsuyama K, Toyonaga T, Yoshikawa T. Sedation with dexmedetomidine hydrochloride during endoscopic submucosal dissection of gastric cancer. *Dig Endosc* 2011; **23**: 176-181 [PMID: 21429025 DOI: 10.1111/j.1443-1661.2010.01080.x]
- 59 **Ishibashi C**, Fujimoto A, Minematsu K, Yamaguchi K, Hayashida M, Inada E. Safety and efficacy of dexmedetomidine in intubated, spontaneously breathing patients after endoscopic submucosal dissection for esophageal or pharyngeal cancer. *Anesth Analg* 2013; **116**: S358
- 60 **Gang X**, Ying L, Li-bing H, Su-yang C. Clinical efficacy of propofol with dexmedetomidine in endoscopic submucosal dissection. *Pract Pharm Clin Remedies* 2011; **6**: 7
- 61 **Takimoto K**, Yamauchi H, Matsuyama K, Kashiwa A, Kojima Y, Ueda T. The application of dexmedetomidine sedation to colorectal ESD. *Gastrointest Endosc* 2010; **71**: AB329
- 62 **Kim N**, Yoo YC, Lee SK, Kim H, Ju HM, Min KT. Comparison of the efficacy and safety of sedation between dexmedetomidine-remifentanyl and propofol-remifentanyl during endoscopic submucosal dissection. *World J Gastroenterol* 2015; **21**: 3671-3678 [PMID: 25834336 DOI: 10.3748/wjg.v21.i12.3671]
- 63 **Iizuka T**, Shimoyama N, Notoya A. [Dexmedetomidine for endoscopic submucosal dissection in a patient with severe chronic obstructive pulmonary disease]. *Masui* 2011; **60**: 96-99 [PMID: 21348258]
- 64 **Amornyotin S**, Kachintorn U, Kongphlay S. Anesthetic management for small bowel enteroscopy in a World Gastroenterology Organization Endoscopy Training Center. *World J Gastrointest Endosc* 2012; **4**: 189-193 [PMID: 22624071 DOI: 10.4253/wjge.v4.i5.189]
- 65 **Sun YL**, Wu WZ, Xu XC, Wu YQ. Clinical observation of dexmedetomidine applied in the diagnosis and treatment with single-balloon enteroscopy. *Modern Med J* 2013; **5**: 012

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Transcranial magnetic stimulation as a new tool to control pain perception

Emanuela Onesti, Maria Cristina Gori, Vittorio Frasca, Maurizio Inghilleri

Emanuela Onesti, Maria Cristina Gori, Vittorio Frasca, Maurizio Inghilleri, Department of Neurology and Psychiatry, University of Rome "Sapienza", 00185 Rome, Italy

Author contributions: Onesti E and Inghilleri M designed the research; Onesti E and Inghilleri M performed the research; Onesti E, Gori MC, Frasca V and Inghilleri M analyzed the data; Onesti E, Gori MC, Frasca V and Inghilleri M wrote the paper.

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Correspondence to: Maurizio Inghilleri, Professor, Department of Neurology and Psychiatry, University of Rome "Sapienza", Viale dell'Università 30, 00185 Rome, Italy. maurizio.inghilleri@uniroma1.it
Telephone: +39-06-49914120
Fax: +39-06-49914120

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Abstract

Treatment for chronic pain is frequently unsuccessful or characterized by side-effects. The high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) has been suggested in the management of refractory chronic pain. Various studies have shown that HF-

rTMS sessions of long-duration applied at primary motor cortex induce pain relief through mechanisms of plastic changes. Efficacy of rTMS mostly depends on stimulation parameters, but this aspect requires better characterization. A rationale to target other cortical areas exists. Current data are promising, but a careful analysis of stimulation settings and maintenance treatment design are needed.

Key words: Transcranial magnetic stimulation; Repetitive transcranial magnetic stimulation; Neuropathic pain; Non-neuropathic pain; Chronic pain; Neuromodulation

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Core tip: The high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) is emerging as a possible approach for pain relief. The HF-rTMS delivered to motor cortex modulates brain network implicated in pain processes, facilitating descending pain inhibitory mechanisms. Current data are promising, but a careful analysis of stimulation settings and maintenance treatment design are necessary.

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INTRODUCTION

Chronic pain can be neuropathic, non-neuropathic, mixed, or without demonstrated origin^[1]. Whilst acute pain is nociceptive secondary to chemical, mechanical and thermal stimulation of A-delta and C receptors, chronic neuropathic pain (NP) can persist after the initial injury because the nervous system is malfunctioning,

becoming the origin of the pain. Examples of NP are trigeminal neuralgia, postherpetic neuralgia, phantom limb pain, monoradiculopathies, complex regional pain syndromes and peripheral neuropathies. The prevalence of NP ranges from 7% to 8%^[2-4]. The mechanisms involved in NP are complex and engage both peripheral and central pathophysiologic events. Several NP research studies point to different causal mechanisms including neurogenic inflammation, abnormal ectopic activity in nociceptive nerves, and impaired inhibitory modulation, defining the so-called peripheral and central sensitization^[5]. Available treatments provide mainly symptomatic relief, including nonpharmacological, pharmacological, and interventional therapies^[6,7]. Unfortunately, the management of NP is not easy because the response to most drugs is not univocal^[8,9]. According to recent guidelines, less than 50% of the patients with chronic NP reach symptomatic benefits with drugs^[6,10,11].

In this setting, neurostimulation is a promising procedure in the treatment of pain^[6,12]. The techniques suggested are: Transcutaneous electrical nerve stimulation, nerve root stimulation, spinal cord stimulation, deep brain stimulation, transcranial direct current stimulation (tDCS), epidural motor cortex stimulation, and repetitive transcranial magnetic stimulation (rTMS)^[6].

Specifically, TMS was first introduced in the late 1980s^[13]. Initially, rTMS of the motor cortex was used to select patients for chronic stimulation by implanted electrodes^[14]. It is a noninvasive method of stimulating cortical motor neurons through the scalp and skull capable of inducing electrical currents and depolarizing neurons in focal brain areas with the use of rapidly changing electromagnetic fields generated by a coil placed over the scalp^[15-17]. Since then, several studies used rTMS as an investigational tool and a potential treatment for a variety of neurological and psychiatric disorders. Studies showed that rTMS provided at least partial and transient relief of chronic NP. When applied repetitively, trains of rTMS can modify cortical activity beyond the duration of the stimulation^[18]. Three main aspects influence the effect of rTMS: Frequency, intensity, and duration of stimulation. In general, bursts of high-frequency stimulation (≥ 5 Hz) lead to a facilitation of activity in the targeted brain region, whereas continuous low-frequency stimulation (about 1 Hz) provides a suppression in activity of the targeted brain region.

The rTMS produces analgesic effects activating fibres in the motor cortex and projecting to distant areas involved in pain processing^[19,20]. In 2007, the EFNS produced the first guidelines on neurostimulation therapy for NP^[6]. In recent years, new randomized controlled trials have published in various NP conditions. Therefore, we aimed to review all available evidence for TMS in neuropathic and non-NP, focusing the methods. A narrative synthesis was used to report the results.

TMS AND CHRONIC PAIN TREATMENT

A search of literature on the analgesic effect of rTMS in chronic pain published from 1991 to May 2015 was performed using PubMed and the Cochrane Library. Keywords included chronic pain and neurostimulation, chronic pain and transcranial magnetic stimulation, NP and neurostimulation, NP and transcranial magnetic stimulation. The present review included controlled studies with at least 10 subjects enrolled to ensure the quality of the studies. Moreover, we excluded observational studies, and only papers in English were included. To minimize possible bias, the study selection-process was carried out independently by two authors (EO, MI).

We identified 38 controlled studies, including sham stimulations, in patients with NP (spinal cord lesions, central post-stroke pain-CPSP-, trigeminal nerve lesions, peripheral nerve lesions, phantom pain, fibromyalgia and complex regional pain syndrome type II -CRPSII-) or non-NP (migraine, CRPS type I, low back pain, visceral and postoperative pain). Table 1 summarizes these studies. The analysis included 983 patients. Among them, 31 studies showed significant pain reduction with the high-frequency rTMS (HF-rTM) of the motor cortex (Table 1).

Unfortunately, the studies currently available have been performed on groups of patients with different kinds of NP. Evidence at medium follow-up allowing solid conclusions to be drawn is insufficient and conflicting, while evidence at long follow-up is restricted. Future studies on a large number of patients with pain due to specific diseases and the evaluation of maintenance treatment cycles should provide more certain and reproducible data.

Efficacy of rTMS in NP

Efficacy of rTMS mostly depends on stimulation parameters. When rTMS is applied in the primary motor cortex at low-frequency it is unsuccessful^[21-23], while repeated sessions of long-duration (at least 1000 pulses) stimulations at high-frequency (5-20 Hz) applied over repeated sessions induce pain relief^[1,24-27]. rTMS seems most effective when stimulation is focal (*i.e.*, figure-of-eight rather than circular coil)^[6]. The effect starts a few days later; its duration is less than a week after a single session, 2-3 wk after consecutive sessions of rTMS^[28-30]. This last aspect is the keystone for the clinical benefit^[31,32]. However, this feature requires better characterization^[6]. The TMS parameters vary in the studies, and it is complex to establish the best stimulation parameters to use^[12]. The role of coil orientation, time of train of stimulation, inter-train interval, and number of trains, is also to definite^[12].

Moreover, 22 of the 32 studies had small sample sizes, with less than 30 enrolled patients, and only 16 of 32 studies recruited homogeneous populations of patients (CRPS, spinal cord injury, diabetic polyneuropathy, poststroke pain and fibromyalgia), reducing

Table 1 Summary of the studies evaluating the effects of repetitive transcranial magnetic stimulation on chronic neuropathic pain and non-neuropathic pain

Ref.	Painful syndrome	Study design	Number of patients	Coil	Site stimulation	Frequency, intensity, <i>n</i> sessions	Outcomes	Efficacy
NP								
Lefaucheur <i>et al</i> ^[26]	Intractable neurogenic pain	Double-blind, controlled, crossover	18 (12 central NP; 6 peripheral NP)	F8	Hand M1	0.5-10 Hz 80% RMT 1	Pain intensity	Analgesic effect (only for 10 Hz)
Lefaucheur <i>et al</i> ^[116]	Pain due to thalamic stroke or trigeminal neuropathy	Double-blind, controlled, crossover	14 (7 central NP; 7 peripheral NP)	F8	Hand M1	10 Hz 80% RMT 1	VAS	Decrease in VAS
Rollnik <i>et al</i> ^[41]	Chronic refractory NP	Double-blind, controlled, crossover	12 (2 central NP; 7 peripheral NP; 2 CRPS; 1 osteomyelitis)	Double coin - Circular coin	M1	20 Hz 80% RMT 1	VAS	No effect
Lefaucheur <i>et al</i> ^[27]	Pain do to thalamic stroke, brainstem stroke, spinal cord lesion, brachial plexus lesion, or trigeminal nerve lesion	Double-blind, controlled, crossover	60 (36 central NP; 24 peripheral NP)	F8	Hand M1	10 Hz 80% RMT 1	VAS, thermal sensory thresholds	Analgesic effect mainly in trigeminal nerve lesions
Khedr <i>et al</i> ^[25]	Trigeminal neuralgia and post-stroke pain syndrome	Double-blind, controlled	48 (24 central NP; 24 trigeminal NP)	F8	Hand M1	20 Hz 80% RMT 5	VAS and the LANSS scale	Analgesic effect
André-Obadia <i>et al</i> ^[22]	Chronic refractory NP	Double-blind, controlled, crossover	14 (11 central NP; 3 peripheral NP)	F8	Hand M1	1-20 Hz 90% RMT 1	VAS	Analgesic effect (only for 20 Hz)
Hirayama <i>et al</i> ^[104]	Intractable deafferentation pain	Double-blind, controlled, crossover	20 (14 central NP; 6 peripheral NP)	F8	M1	5 Hz 90% RMT 1	VAS and SF-MPQ	Analgesic effect
Irlbacher <i>et al</i> ^[117]	Chronic NP	Double-blind, controlled	27 (13 central NP; 14 phantom p)	F8	M1	1-5 Hz 95% RMT 5	VAS	No effect
Lefaucheur <i>et al</i> ^[15]	Unilateral hand pain of various neurologic origins	Double-blind, controlled, crossover	22 (14 central NP; 8 peripheral NP)	F8	Hand M1	10 Hz 90% RMT 1	Motor threshold at rest, MEP amplitude, CSP, ICI	ICI increase
Lefaucheur <i>et al</i> ^[118]	Chronic NP	Double-blind, controlled, crossover	36	F8	Face M1	10 Hz 80% RMT 1	VAS	Analgesic effect with the stimulation applied on area adjacent to the cortical representation of the painful zone
Defrin <i>et al</i> ^[35]	Spinal cord injury	Double-blind, controlled	12	F8	Vertex	5 Hz 115% RMT 10	VAS, MPQ, pain threshold	Increased heat pain threshold
Passard <i>et al</i> ^[209]	Fibromyalgia	Double-blind, controlled	30	F8	M1	10 Hz 80% RMT 10	VAS, MPQ, quality of life (Brief Pain Inventory and the Fibromyalgia Impact Questionnaire)	Decrease in VAS and better quality of life
Saitoh <i>et al</i> ^[115]	Intractable deafferentation pain	Double-blind, controlled, crossover	13 (9 central NP; 4 peripheral NP)	F8	M1	1-5-10 Hz 90% RMT 1	VAS	Decrease in VAS (only for 5-10 Hz)
André-Obadia <i>et al</i> ^[119]	Chronic NP	Double-blind, randomized, controlled, crossover	28	F8	M1	20 Hz 90% RMT 1	Pain relief, quality of life and rescue drug intake	Analgesic effect

Lefaucheur <i>et al</i> ^[120]	Chronic refractory NP	Double-blind, controlled, crossover	46 (23 central NP; 23 peripheral NP)	F8	Hand M1	10 Hz 90% RMT 1	Thresholds for thermal and mechanical sensations	Thermal perception improvement
Carretero <i>et al</i> ^[121]	Fibromyalgia	Randomized, single-blinded	28	Butterfly coil	DLPFC	1 Hz 110% RMT 20	FibroFatigue, Likert pain, HDRS, CBI	No effect
Kang <i>et al</i> ^[36]	Spinal cord injury	Double-blind, controlled, crossover	11	F8	M1	10 Hz 80% RMT 5	NRS, BPI	No effect
Picarelli <i>et al</i> ^[33]	CRPS type 1	Double-blind, controlled	23	F8	M1	10 Hz 90% RMT 10	VAS, MPQ, the SF-36, HDRS	Analgesic effect and improved quality of life
Ahmed <i>et al</i> ^[108]	Phantom pain	Double-blind, controlled	27	F8	DLPFC	20 Hz 80% RMT 5	VAS, LANSS scale	Decrease in VAS and LANSS scale
Mhalla <i>et al</i> ^[38]	Fibromyalgia	Double-blind, controlled	40	F8	M1	10 Hz 80% RMT	Pain intensity over the last 24 h, BPI, quality of life, mood and anxiety, parameters of motor cortical excitability	Analgesic effect
Short <i>et al</i> ^[63]	Fibromyalgia	Double-blind, controlled	20	F8	M1	14 10 Hz 120% RMT	BPI, HDRS, Fibromyalgia Impact Questionnaire	Improvement of daily pain, number of tender points, HDRS and FIQ scores
Lefaucheur <i>et al</i> ^[122]	Chronic refractory NP	Controlled, crossover	14 (3 localized in the face, 4 upper limb, 3 lower limb, 4 hemibody)	F8	M1	10 10 Hz 90% RMT 3	VAS	Analgesic effect
Hosomi <i>et al</i> ^[109]	NP	Double-blind, controlled, crossover	64	F8	M1	50 Hz 90% RMT 10	VAS, SF-MPQ, PGIC, and BDI	Analgesic effect
Onesti <i>et al</i> ^[28]	Diabetic neuropathy	Double-blind, controlled, crossover	23	H-coil	Vertex	20 Hz 100% RMT 5	VAS, area and threshold of RIII nociceptive flexion reflex	Decrease in VAS and RIII area
Jetté <i>et al</i> ^[34]	Spinal cord injury	Randomized, controlled, crossover	16	F8	M1	10 Hz 90%-110% RMT 3	RIII reflex VAS, motor mapping parameters	Decrease in VAS
Boyer <i>et al</i> ^[30]	Fibromyalgia	Double-blind, randomized, controlled	38	F8	M1	10 Hz 90% RMT 14	FIQ, SF-36, brain metabolism	Improvement of quality of life
Dall'Agnol <i>et al</i> ^[123]	Myofascial pain syndrome	Double-blind, randomized, controlled	24	F8	M1	10 Hz 80% RMT 10	Pain quantitative sensory testing, conditioned pain modulation, TMS parameters, BDNF	Analgesic effect mediated by mechanisms enhancing the corticospinal inhibitory system and BDNF
Yilmaz <i>et al</i> ^[40]	Spinal cord injury	Double-blind, randomized, controlled	17	F8	Vertex	10 Hz 110% RMT 10	VAS	No effect

Hodaj <i>et al</i> ^[124]	Chronic refractory facial pain	Open-label study	55 (19 cluster headache; 21 trigeminal neuropathic pain; 15 atypical facial pain)	F8	Face M1	10 Hz 80% RMT 12	VAS, CGIC scale	Analgesic effect
Khedr <i>et al</i> ^[125]	Malignant NP	Randomized, controlled	34	F8	Hand M1	20 Hz 80% RMT 10	VDS, VAS, LANSS, HDRS	Analgesic effect
Lindholm <i>et al</i> ^[126]	Neuropathic orofacial pain	Randomized, controlled, cross-over	16	-	S1/M1, right SII	-	NRS, BPI	Analgesic effect (only for SII)
Non-NP Brighina <i>et al</i> ^[46]	Migraine	Double-blind, randomized, controlled	11	F8	DLPFC	10 Hz 90% RMT 12	Frequency of attacks, Headache index	Significant reduction of outcome measures
Pleger <i>et al</i> ^[48]	CRPS	Double-blind, controlled, crossover	10	F8	M1	10 Hz 110% RMT 1	VAS	Analgesic effect
Borckardt <i>et al</i> ^[127]	Postoperative pain	Double-blind, controlled	20	F8	Left PFC	10 Hz 100% RMT 1	VAS for mood, opioid pump use	Reduction in opioid use
Johnson <i>et al</i> ^[49]	Low back pain	Double-blind, controlled, crossover	17	F8	M1	20 Hz 95% RMT 1	Detection and pain thresholds for cold and heat sensations	Increased heat pain threshold and lowered cold detection
Fregni <i>et al</i> ^[50]	Pancreatitis	Double-blind, controlled	17	F8	SII	1 Hz 70% RMT 10 -	VAS, BDI	Analgesic effect
Conforto <i>et al</i> ^[47]	Migraine	Randomized, double-blind, parallel-group	18	-	DLPFC	-	Number of headache days	No effect
Melchior <i>et al</i> ^[51]	Irritable bowel syndrome	Double-blind, controlled, crossover	21	F8	M1	20 Hz 80% RMT 5	Pressure pain threshold, changes in maximum tolerated rectal volume, rectal compliance and average pain intensity	Maximum tolerated rectal volume and analgesic effects
Avery <i>et al</i> ^[52]	Chronic widespread pain	Double-blind, randomized, controlled	19	-	DLPFC	- 15	BIRS	No effect

NP: Neuropathic pain; BPI: Brief pain inventory; FIQ: Fibromyalgia impact questionnaire; F8: Figure of 8 coil; H: Hersed; HDRS: Hamilton depression rating scale; ICI: Intracortical inhibition; LANSS: Leeds assessment of neuropathic symptoms and signs; MPQ: McGill pain questionnaire; PFC: Prefrontal cortex; RIII: Nociceptive flexion reflex; SF-36: 36-item short-form health survey; SICI: Short intracortical inhibition; SII: Somatosensory cortex; VAS: Visual analog scale; MEP: Motor evoked potential; NRS: Numeric rating scale; PGIC: Patient global impression of change scale; BDNF: Brain-derived neurotrophic factor; VDS: Verbal descriptor scale; CGIC: Clinical global impression of change; DLPFC: Dorsolateral prefrontal cortex; BIRS: Gracely box intensity scale.

assurance about which states are more responsive to TMS^[1,28-30,33-41]. Another unsolved question concerns which site in the motor cortex gives the most effective pain relief. Stimulation is commonly delivered to the contralateral motor cortex to painful area^[1,42].

Also the left DLPFC could have a function in nociceptive control, while the left prefrontal cortex has been used in rTMS studies in patients with fibromyalgia^[39,43] (Figure 1).

Also tDCS, a technique that elicits constant weak electric currents through the scalp through two electrodes, is able to modulate excitability in cortical

tissue. Moreover, it is important to specify that tDCS does not induce action potentials in axons, but it cause polarization of neurons changing their average level of discharge. Several studies examined the tDCS applied to the motor cortex as a possible treatment of chronic pain, but a recent meta-analysis does not suggest a significant analgesic effect of this technique^[23].

The mechanisms underlying the effect of rTMS in pain are not clearly identified, but probably involve neuronal plasticity^[44,45]. Therefore it is suggested that maintenance therapy for longer intervals should prolong long-lasting effects. Unfortunately, only one study to

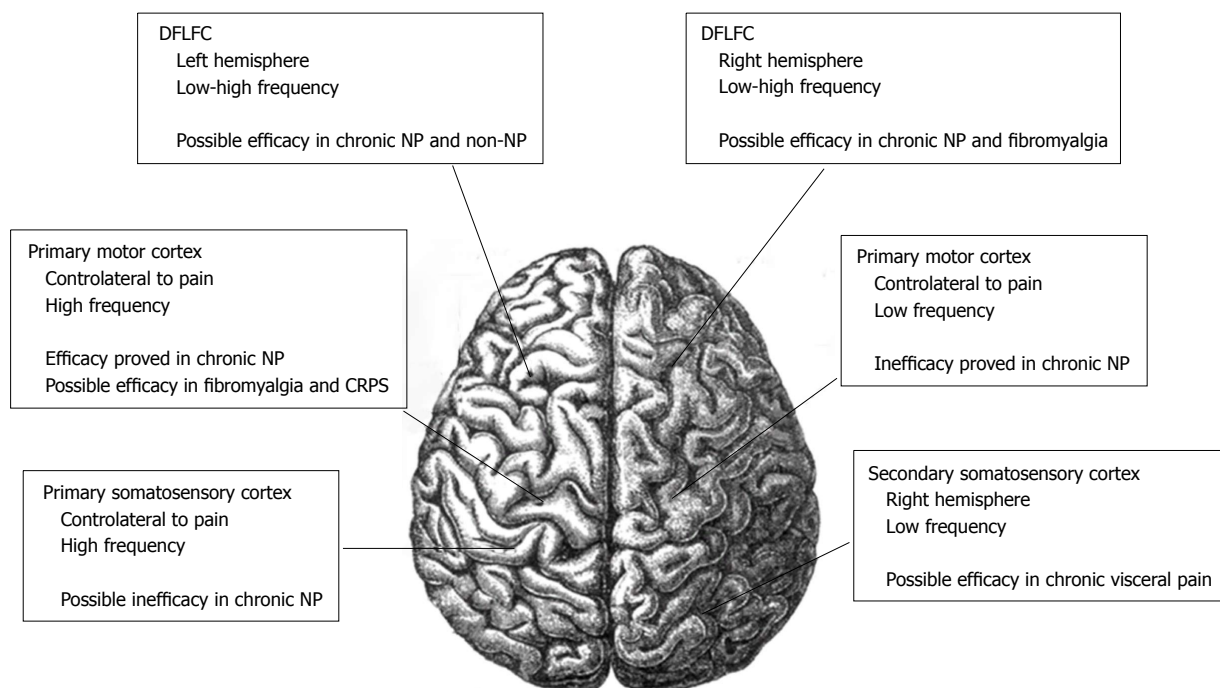


Figure 1 Analgesic efficacy of repetitive transcranial magnetic stimulation according to the cortical target. DLPFC: Dorsolateral prefrontal cortex; NP: Neuropathic pain; CRPS: Complex regional pain syndrome.

date evaluated long-term rTMS maintenance therapy^[38].

Efficacy of rTMS in non-NP

In the past ten years, the rTMS have been also evaluated in different non-NP conditions^[1] (Table 1).

Regarding application for migraine, active HF-rTMS delivered over the left DLPFC gave promising results but, in the absence of large controlled studies, no recommendation can be suggested^[1,46,47]. Also regarding to the treatment of chronic visceral pain, low back pain and CRPS type I with rTMS, literature is still limited, and no conclusion can be definitely drawn^[48-52]. Future research in this field should specifically investigate in a large number of patients the most appropriate cortical target, and the frequency of stimulation^[1]. Moreover, a specific analysis regarding to the possible effect of rTMS on other clinical aspects of these syndromes, such as affective-emotional and cognitive components is needed.

PHYSIOLOGICAL BASIS OF rTMS

Practical aspects of rTMS

In 1985 Barker *et al.*^[13] proposed the first magnetic stimulator for the transcranial stimulation of the human brain, giving the prerequisite for subsequent clinical use of TMS. A stimulating coil produces a brief magnetic field when an electrical pulse generator creates a discharge current of several thousand amperes. When the coil is placed on the skull of a subject, it induces an electrical field able to depolarize nerve cells and to stimulate neural networks^[1]. The stimulus waveform can be monophasic or biphasic^[53]. The rTMS using monophasic pulses activates an homogeneous population of

neurons, while biphasic pulses tend to generate a more complex pattern of neural activation, producing local changes but also effects at distance from the stimulus site^[1,54].

Site of stimulation

The first task for pain modulation is to locate primary motor cortex (M1), checking visually the muscle twitch inducing by TMS pulses^[12]. Commonly in clinical settings, the intensity of the TMS should be not able to induce a motor response^[12]. Specifically, TMS applied in short trains at high frequency and suprathreshold intensity over the M1 elicits a progressive increase in motor evoked potential (MEP) amplitude, demonstrating the phenomenon of MEP amplitude facilitation, through intracortical mechanisms similar to short-term synaptic plasticity^[55-59].

However, a rationale for targeting other cortical areas exists. The DLPFC could have a role in nociceptive control^[43]. In healthy subjects with pain induced by a capsaicin injection into their hand, the stimulation of the left DLPFC produced a significant pain relief. No improvement was noted when the right DLPFC was stimulated^[60]. The effect may be related to the release of endogenous opioids by the left DLPFC^[61]. Also rTMS of the cerebellum has been considered for the possible lowering in pain thresholds^[62]. Moreover, The left prefrontal cortex has been used in rTMS fibromyalgia studies, but only a small analgesic effect has been noted^[63].

Intensity of stimulation

The intensity of the stimulation is classically regulated for each patient to obtain the minimal intensity of

stimulation applied to M1 that evokes a motor response. It is measured according to the RMT, the lowest stimulation intensity able to generate a MEP small (50 mV) amplitude in 5 of 10 TMS pulses. In the clinical setting, stimulation intensity is frequently subthreshold (80%-90% of RMT)^[64]. When the RMT is identified, rTMS is performed in bursts of stimuli ("trains") with a definite frequency^[12].

Frequency of stimulation

RTMS can be carried out at low (1 Hz) or high frequencies (5 Hz). When performed at high frequencies, rTMS pulses are delivered in trains divided by specific intertrain intervals. Typically, low-frequency rTMS is considered to have inhibitory properties, whereas HF-rTMS is considered to have excitatory properties^[64]. HF-rTMS consists specifically of intermittent bursts of TMS pulses able to induce a long-term potentiation of synaptic activity, which may clarify why rTMS effects can overcome the period of stimulation^[64].

Number of sessions and total number of pulses per session

A central question is whether the analgesic effect of rTMS can be prolonged by maintenance sessions performed periodically. To date, 24 of 39 studies have performed repetitive sessions of rTMS to enhance analgesic effects of a single session of stimulation, but maintenance protocol was only tested in one study^[38]. Usually, the number of sessions applied range from 5 sessions to 30 sessions. The majority of studies have involved a total of 10 sessions. Based on more recent studies, a general trend indicates a greater number of sessions (> 10) associated with more persisting improvement in pain perception (Table 1).

The total number of pulses in each rTMS session seems related to the analgesic effect, but it is not clear whether a minimum number of pulses is required to obtain the clinical outcome. Usually this value ranges between 1000 to 2000^[1]. Moreover an important safety parameter as the intertrain interval (the time in between trains of pulsed energy when no stimulation is occurring) is usually about 10 s^[1].

Coil

Coil design and orientation are important. The "figure-of-eight" coil is able to induce a focal magnetic field stimulating only superficial cortical regions of the brain^[12]. Other novel models are the Tilted double-coil and the Heschl (H)-coil, which drop at a depth of about 6 cm^[12]. Specifically, the H-coil lets deep brain stimulation without significantly increasing induced fields in superficial cortical regions, therefore preventing the risk of adverse effects^[65,66]. rTMS with the H-coil has already proved effective as an acute treatment for major depressive disorder, bipolar depression, schizophrenia and post-traumatic stress disorder^[65,67-69]. Furthermore, there are ongoing studies of its use to

treat a very wide range of neurological, psychiatric and medical conditions, including NP^[28].

Placebo rTMS

Placebo effects need to be better reported^[25]. Theoretically, ideal placebo rTMS should be characterized by the same subjective somatic scalp sensation and the acoustic artifacts compared to active coil, and no physiological effect on the targeted cortical region^[70]. In the early research, placebo was considered a coil placed in a different area from zone stimulated in the active condition, or a coil oriented with an angle of 45-90 grades on the scalp instead of tangentially^[1]. These solutions are not the most reliable, because the stimulation site could be perceived by the subject, or the sham location could cause unexpected effects^[1,71]. In the last decades, sham coils have been projected and commercialized in order to block the magnetic field provided, and to produce auditory artifacts and scalp sensation equivalent to that of a real coil^[72,73]. Although this stimulation ideally seems a perfect placebo, the cutaneous sensation remains different in about half of the cases, especially when the stimulation intensity is high^[72,74].

CONSIDERATIONS ABOUT MECHANISMS OF ACTION OF rTMS

Although the TMS acts on the superficial cortex, the generated action potentials propagate influencing distant neural networks^[12]. The M1 contains pyramidal cells that give rise to numerous excitatory corticospinal projections. Most of These projections are oriented perpendicularly to the brain surface. rTMS applied on the M1 modulate the cortical excitability producing changes in the following physiological parameters: MT, MEP, silent period, intracortical facilitation, and intracortical inhibition^[75]. In chronic pain, the involvement of M1 projections to pain-modulating structures has been demonstrated^[23]. Moreover, a rationale for targeting other cortical areas exists. The DLPFC is a cortical target used in studies on major depression, and it is considered to have a function also in nociceptive control^[43,61,76]. HF-rTMS on the right DLPFC has shown analgesic effects similar to M1 stimulation^[46,77]. Furthermore, left DLPFC stimulation should induce an improvement of pain perception in a model of acute pain^[43,78]. The left prefrontal cortex has been used in rTMS studies in patients with fibromyalgia, but it has shown a minor analgesic effect^[63].

rTMS seems to modulate cortical plasticity, referred to as the functional reorganization of the inter neuron connections and neuronal properties. Inhibition of the gamma-aminobutyric acid (GABA) pathways produces cortical excitation, rather than a direct enhancement of motor cortex excitability^[79-82]. On the other hand, low-frequency rTMS could increase the inhibitory corticospinal control, perhaps through GABA-B

transmission, prolonging the CSP duration^[1,83-86]. The changes in synaptic plasticity brought by rTMS are explained by long term potentiation (LTP) and long term depression (LTD)^[44]. LTP is induced by high frequency stimulation and LTD by low frequency stimulation. The LTP is mediated by the post-synaptic N-methyl-D-aspartate (NMDA) receptors, that lead to calcium flux into the post-synaptic neuron when activated^[45]. Calcium activates enzymatic changes in pre- and post-synaptic neurons, increasing the synaptic activity. It also induces the expression of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on the postsynaptic neuron, increasing the cells sensitivity to glutamate^[87]. Furthermore, LTD is characterized by depression of the synaptic transmission, depending on the modulation of NMDA receptors with the reduction of calcium influx, and the internalization of AMPA^[87].

The long lasting effect of rTMS (late-LTP) is thought to be exercised by gene induction and protein synthesis^[87]. Gene expression has resulted in increased synthesis of c-fos mRNA in the thalamus and parietal cortex, and BDNF mRNA in the hippocampus and parietal cortex^[88-90]. Considerable evidence from HF-rTMS studies suggests that short-term synaptic plasticity happens at cortical rather than spinal level^[91-94]. When rTMS is delivered in human subjects, the amplitude of the MEP and the duration of the CSP increases during the train^[55,75,95-100]. The MEP facilitation also persists after the train ends, and it is probably due to the recruitment of cortical excitatory interneurons^[55,75,92,94,99]. It is influenced by the number of stimuli in the train, being greater with longer (20, 40 and 60-stimuli), suggesting mechanisms of short-term synaptic enhancement^[59,101].

rTMS has also been found to modulate the activity of brain neurotransmitters, reducing dopamine in the frontal cortex and increasing its levels in the striatum^[102]. Moreover, serotonin levels increased in the hippocampus^[102]. All these aspects may explain why different rTMS protocols are effective or not, depending on various parameters of stimulation. Further, age, and genetic features could influence the clinical effect of rTMS, with heterogeneous therapeutic responses^[1,103].

LIMITATIONS OF rTMS IN PAIN TREATMENT

The results of studies exploring the effects of rTMS on pain are positive but still inconsistent, because of small samples of patients, differences in the TMS methodologies, heterogeneous populations of patients and lack of maintenance protocols. In a Cochrane Review of 2013, a short-term effect on pain of HF-rTMS applied to M1 was confirmed^[23]. Moreover, a detailed study to determine which are the best stimulation parameters, is targeted. Studies on image-guided navigation to perform rTMS of M1 in pain patients have provided evidence that the analgesic effect of rTMS links with the integrity of the thalamocortical tract^[1,104,105].

Unfortunately, objective indicators of perceived pain, including MEP and RIII, were considered in only two studies neurophysiological^[15,28]. New extended studies should improve knowledge in this field of research.

Further rigorously designed studies, particularly of longer courses of stimulation applied on large population of patients, are required to address the issue. Future evidence may significantly confirm the current results. The main question is whether the clinical effect could indeed improve the management of patients with chronic pain in daily clinical practice.

FUTURE RESEARCH DIRECTIONS

The conclusions of our analysis, related to the actual literature data on rTMS for chronic pain, match with those suggested in previous reviews and meta-analyses^[1,6,17,23-25,32,106]. rTMS has become a promising therapeutic tool for a variety of neurological and psychiatric diseases^[107]. Different types of NP respond to rTMS, and this is producing a fast growth in researchers interested in rTMS for clinical purposes^[6,26,108-110]. Unfortunately at the current time in the lack of large studies, only careful recommendations of rTMS can be suggested^[1,6]. The efficacy of a single HF-rTMS session persists for some days, and it could extend with the repetition of sessions^[1]. Moreover, the best stimulation settings may be yet to determined.

Studies including neurophysiological evaluation of the effects of the cortex TMS in other brain regions through the use of imaging and electrophysiologic techniques (such as electroencephalography, magnetoencephalography, MRI navigated TMS) could add value at the understanding of the mechanism of action of this technique^[111]. New TMS machines have allowed the administration of pulses more focally and at higher frequencies. Moreover, frameless stereotactic systems, have been developed, permitting the identification of specific location in the desired brain target and the precise and comparable placing of the coil during different TMS sessions^[112-114].

In future, therapeutic studies need to define the correct utilization of rTMS in the clinical practice for chronic pain, above all if the long-term effect exists. Moreover, studies of rTMS in other diseases associated with chronic pain, such as osteoarthritis, bladder pain syndrome and post-stroke pain, could be of interest. Finally, if rTMS becomes a proven method for the treatment of chronic pain, the development of a home-based rTMS system will be necessary^[115].

Active research in pain is still taking place and has the potential to provide useful data (31 open studies on TMS and pain on <https://clinicaltrials.gov>). Based on this new research, novel therapeutic guidelines may be established in future. Apart from its potential clinical role, rTMS is a valuable probe of brain function that can be used to investigate the neural circuitry. This additional knowledge might help in the development of new treatments. rTMS is non-invasive and can be

applied to any patient with drug-resistant NP who could be aspirant for the insertion of a cortical stimulator. In addition, further studies using maintenance sessions of rTMS and evaluating the multiple features of chronic pain are needed to give a more solid basis for its clinical applications.

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REFERENCES

- Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Devanne H, Di Lazzaro V, Filipović SR, Hummel FC, Jääskeläinen SK, Kimiskidis VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, Poulet E, Rossi S, Rossini PM, Rothwell JC, Schönfeldt-Lecuona C, Siebner HR, Slotema CW, Stagg CJ, Valls-Sole J, Ziemann U, Paulus W, Garcia-Larrea L. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol* 2014; **125**: 2150-2206 [PMID: 25034472 DOI: 10.1016/j.clinph.2014.05.021]
- Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008; **70**: 1630-1635 [PMID: 18003941 DOI: 10.1212/01.wnl.0000282763.29778.59]
- Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 2008; **136**: 380-387 [PMID: 17888574 DOI: 10.1016/j.pain.2007.08.013]
- Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *J Pain* 2006; **7**: 281-289 [PMID: 16618472 DOI: 10.1016/j.jpain.2005.11.008]
- Truini A, Cruccu G. Pathophysiological mechanisms of neuropathic pain. *Neurol Sci* 2006; **27** Suppl 2: S179-S182 [PMID: 16688626 DOI: 10.1007/s10072-006-0597-8]
- Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, Simpson BA, Taylor RS. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol* 2007; **14**: 952-970 [PMID: 17718686 DOI: 10.1111/j.1468-1331.2007.01916.x]
- Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, Nurmikko T. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; **17**: 1113-1e88 [PMID: 20402746 DOI: 10.1111/j.1468-1331.2010.02999.x]
- Attal N, Lanteri-Minet M, Laurent B, Fermanian J, Bouhassira D. The specific disease burden of neuropathic pain: results of a French nationwide survey. *Pain* 2011; **152**: 2836-2843 [PMID: 22019149 DOI: 10.1016/j.pain.2011.09.014]
- Torrance N, Ferguson JA, Afolabi E, Bennett MI, Serpell MG, Dunn KM, Smith BH. Neuropathic pain in the community: more under-treated than refractory? *Pain* 2013; **154**: 690-699 [PMID: 23485369 DOI: 10.1016/j.pain.2012.12.022]
- Attal N, Cruccu G, Haanpää M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P; EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 2006; **13**: 1153-1169 [PMID: 17038030 DOI: 10.1111/j.1468-1331.2006.01511.x]
- Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 2005; **118**: 289-305 [PMID: 16213659 DOI: 10.1016/j.pain.2005.08.013]
- Treister R, Lang M, Klein MM, Oaklander AL. Non-invasive Transcranial Magnetic Stimulation (TMS) of the Motor Cortex for Neuropathic Pain-At the Tipping Point? *Rambam Maimonides Med J* 2013; **4**: e0023 [PMID: 24228166 DOI: 10.5041/RMMJ.10130]
- Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985; **1**: 1106-1107 [PMID: 2860322 DOI: 10.1016/S0140-6736(85)92413-4]
- Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. *Acta Neurochir Suppl (Wien)* 1991; **52**: 137-139 [PMID: 1792954 DOI: 10.1007/978-3-7091-9160-6_37]
- Lefaucheur JP, Drouot X, Ménard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. *Neurology* 2006; **67**: 1568-1574 [PMID: 17101886 DOI: 10.1212/01.wnl.0000242731.10074.3c]
- Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, Ferreira MJ, Wagner T, Fecteau S, Rigonatti SP, Riberto M, Freedman SD, Pascual-Leone A. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. *Stroke* 2006; **37**: 2115-2122 [PMID: 16809569 DOI: 10.1161/01.STR.0000231390.58967.6b]
- Leo RJ, Latif T. Repetitive transcranial magnetic stimulation (rTMS) in experimentally induced and chronic neuropathic pain: a review. *J Pain* 2007; **8**: 453-459 [PMID: 17434804 DOI: 10.1016/j.jpain.2007.01.009]
- Rothwell JC, Thompson PD, Day BL, Boyd S, Marsden CD. Stimulation of the human motor cortex through the scalp. *Exp Physiol* 1991; **76**: 159-200 [PMID: 2059424 DOI: 10.1113/expphysiol.1991.sp003485]
- Lefaucheur JP. The use of repetitive transcranial magnetic stimulation (rTMS) in chronic neuropathic pain. *Neurophysiol Clin* 2006; **36**: 117-124 [PMID: 17046606 DOI: 10.1016/j.neucli.2006.08.002]
- Gilhus NE, Barnes MR, Brainin M. European Handbook of Neurological Management. John Wiley & Sons, 2011
- Lefaucheur JP, Antal A, Ahdab R, Ciampi de Andrade D, Fregni F, Khedr EM, Nitsche M, Paulus W. The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. *Brain Stimul* 2008; **1**: 337-344 [PMID: 20633392 DOI: 10.1016/j.brs.2008.07.003]
- André-Obadia N, Peyron R, Mertens P, Mauguière F, Laurent B, Garcia-Larrea L. Transcranial magnetic stimulation for pain control. Double-blind study of different frequencies against placebo, and correlation with motor cortex stimulation efficacy. *Clin Neurophysiol* 2006; **117**: 1536-1544 [PMID: 16753335 DOI: 10.1016/j.clinph.2006.03.025]
- O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev* 2014; **4**: CD008208 [PMID: 24729198 DOI: 10.1002/14651858.CD008208.pub3]
- Leung A, Donohue M, Xu R, Lee R, Lefaucheur JP, Khedr EM, Saitoh Y, André-Obadia N, Rollnik J, Wallace M, Chen R. rTMS for suppressing neuropathic pain: a meta-analysis. *J Pain* 2009; **10**: 1205-1216 [PMID: 19464959 DOI: 10.1016/j.jpain.2009.03.010]
- Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. *J Neurol Neurosurg Psychiatry* 2005; **76**: 833-838 [PMID: 15897507 DOI: 10.1136/jnnp.2004.055806]
- Lefaucheur JP, Drouot X, Keravel Y, Nguyen JP. Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. *Neuroreport* 2001; **12**: 2963-2965 [PMID: 11588611 DOI: 10.1097/00001756-200109170-00041]
- Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Zerah F, Bendib B, Cesaro P, Keravel Y, Nguyen JP. Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. *J Neurol Neurosurg Psychiatry* 2004; **75**: 612-616 [PMID: 15026508 DOI: 10.1136/jnnp.2003.022236]
- Onesti E, Gabriele M, Cambieri C, Ceccanti M, Raccach R, Di Stefano G, Biasiotta A, Truini A, Zangen A, Inghilleri M. H-coil repetitive transcranial magnetic stimulation for pain relief in patients with diabetic neuropathy. *Eur J Pain* 2013; **17**: 1347-1356 [PMID: 23629867 DOI: 10.1002/j.1532-2149.2013.00320.x]

- 29 **Passard A**, Attal N, Benadhira R, Brasseur L, Saba G, Siche P, Perrot S, Januel D, Bouhassira D. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. *Brain* 2007; **130**: 2661-2670 [PMID: 17872930 DOI: 10.1093/brain/awm189]
- 30 **Boyer L**, Dousset A, Roussel P, Dossetto N, Cammilleri S, Piano V, Khalfa S, Mundler O, Donnet A, Guedj E. rTMS in fibromyalgia: a randomized trial evaluating QoL and its brain metabolic substrate. *Neurology* 2014; **82**: 1231-1238 [PMID: 24670891 DOI: 10.1212/WNL.0000000000000280]
- 31 **Wassermann EM**, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. *Clin Neurophysiol* 2001; **112**: 1367-1377 [PMID: 11459676 DOI: 10.1016/S1388-2457(01)00585-5]
- 32 **Galhardoni R**, Correia GS, Araujo H, Yeng LT, Fernandes DT, Kaziya HH, Marcolin MA, Bouhassira D, Teixeira MJ, de Andrade DC. Repetitive transcranial magnetic stimulation in chronic pain: a review of the literature. *Arch Phys Med Rehabil* 2015; **96**: S156-S172 [PMID: 25437106 DOI: 10.1016/j.apmr.2014.11.010]
- 33 **Picarelli H**, Teixeira MJ, de Andrade DC, Myczkowski ML, Luvisotto TB, Yeng LT, Fonoff ET, Pridmore S, Marcolin MA. Repetitive transcranial magnetic stimulation is efficacious as an add-on to pharmacological therapy in complex regional pain syndrome (CRPS) type I. *J Pain* 2010; **11**: 1203-1210 [PMID: 20430702 DOI: 10.1016/j.jpain.2010.02.006]
- 34 **Jetté F**, Côté I, Meziane HB, Mercier C. Effect of single-session repetitive transcranial magnetic stimulation applied over the hand versus leg motor area on pain after spinal cord injury. *Neurorehabil Neural Repair* 2013; **27**: 636-643 [PMID: 23579183 DOI: 10.1177/1545968313484810]
- 35 **Defrin R**, Grunhaus L, Zamir D, Zeilig G. The effect of a series of repetitive transcranial magnetic stimulations of the motor cortex on central pain after spinal cord injury. *Arch Phys Med Rehabil* 2007; **88**: 1574-1580 [PMID: 18047871 DOI: 10.1016/j.apmr.2007.07.025]
- 36 **Kang BS**, Shin HI, Bang MS. Effect of repetitive transcranial magnetic stimulation over the hand motor cortical area on central pain after spinal cord injury. *Arch Phys Med Rehabil* 2009; **90**: 1766-1771 [PMID: 19801069 DOI: 10.1016/j.apmr.2009.04.008]
- 37 **Matsumura Y**, Hirayama T, Yamamoto T. Comparison between pharmacologic evaluation and repetitive transcranial magnetic stimulation-induced analgesia in poststroke pain patients. *Neuromodulation* 2013; **16**: 349-354; discussion 354 [PMID: 23311356 DOI: 10.1111/ner.12019]
- 38 **Mhalla A**, Baudic S, Ciampi de Andrade D, Gautron M, Perrot S, Teixeira MJ, Attal N, Bouhassira D. Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. *Pain* 2011; **152**: 1478-1485 [PMID: 21397400 DOI: 10.1016/j.pain.2011.01.034]
- 39 **Lee SJ**, Kim DY, Chun MH, Kim YG. The effect of repetitive transcranial magnetic stimulation on fibromyalgia: a randomized sham-controlled trial with 1-mo follow-up. *Am J Phys Med Rehabil* 2012; **91**: 1077-1085 [PMID: 23159954 DOI: 10.1097/PHM.0b013e3182745a04]
- 40 **Yilmaz B**, Kesikburun S, Yaşar E, Tan AK. The effect of repetitive transcranial magnetic stimulation on refractory neuropathic pain in spinal cord injury. *J Spinal Cord Med* 2014; **37**: 397-400 [PMID: 24621025 DOI: 10.1179/2045772313Y.0000000172]
- 41 **Rollnik JD**, Wüstefeld S, Däuper J, Karst M, Fink M, Kossev A, Dengler R. Repetitive transcranial magnetic stimulation for the treatment of chronic pain - a pilot study. *Eur Neurol* 2002; **48**: 6-10 [PMID: 12138303 DOI: 10.1159/000064950]
- 42 **Nizard J**, Lefaucheur JP, Helbert M, de Chauvigny E, Nguyen JP. Non-invasive stimulation therapies for the treatment of refractory pain. *Discov Med* 2012; **14**: 21-31 [PMID: 22846200]
- 43 **Fierro B**, De Tommaso M, Giglia F, Giglia G, Palermo A, Brighina F. Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) during capsaicin-induced pain: modulatory effects on motor cortex excitability. *Exp Brain Res* 2010; **203**: 31-38 [PMID: 20232062 DOI: 10.1007/s00221-010-2206-6]
- 44 **Hallett M**. Transcranial magnetic stimulation: a primer. *Neuron* 2007; **55**: 187-199 [PMID: 17640522 DOI: 10.1016/j.neuron.2007.06.026]
- 45 **Cooke SF**, Bliss TV. Plasticity in the human central nervous system. *Brain* 2006; **129**: 1659-1673 [PMID: 16672292 DOI: 10.1093/brain/awl082]
- 46 **Brighina F**, Piazza A, Vitello G, Aloisio A, Palermo A, Daniele O, Fierro B. rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. *J Neurol Sci* 2004; **227**: 67-71 [PMID: 15546593 DOI: 10.1016/j.jns.2004.08.008]
- 47 **Conforto AB**, Amaro E, Gonçalves AL, Mercante JP, Guendler VZ, Ferreira JR, Kirschner CC, Peres MF. Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. *Cephalalgia* 2014; **34**: 464-472 [PMID: 24326236 DOI: 10.1177/0333102413515340]
- 48 **Pleger B**, Janssen F, Schwenkreis P, Völker B, Maier C, Tegenthoff M. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. *Neurosci Lett* 2004; **356**: 87-90 [PMID: 14746870 DOI: 10.1016/j.neulet.2003.11.037]
- 49 **Johnson S**, Summers J, Pridmore S. Changes to somatosensory detection and pain thresholds following high frequency repetitive TMS of the motor cortex in individuals suffering from chronic pain. *Pain* 2006; **123**: 187-192 [PMID: 16616419 DOI: 10.1016/j.pain.2006.02.030]
- 50 **Fregni F**, Potvin K, Dasilva D, Wang X, Lenkinski RE, Freedman SD, Pascual-Leone A. Clinical effects and brain metabolic correlates in non-invasive cortical neuromodulation for visceral pain. *Eur J Pain* 2011; **15**: 53-60 [PMID: 20822942 DOI: 10.1016/j.ejpain.2010.08.002]
- 51 **Melchior C**, Gourcerol G, Chastan N, Verin E, Menard JF, Ducrotte P, Leroi AM. Effect of transcranial magnetic stimulation on rectal sensitivity in irritable bowel syndrome: a randomized, placebo-controlled pilot study. *Colorectal Dis* 2014; **16**: O104-O111 [PMID: 24119239 DOI: 10.1111/codi.12450]
- 52 **Avery DH**, Zarkowski P, Krashin D, Rho WK, Wajdik C, Joesch JM, Haynor DR, Buchwald D, Roy-Byrne P. Transcranial magnetic stimulation in the treatment of chronic widespread pain: a randomized controlled study. *J ECT* 2015; **31**: 57-66 [PMID: 24755729 DOI: 10.1097/YCT.0000000000000125]
- 53 **Sommer M**, Alfaro A, Rummel M, Speck S, Lang N, Tings T, Paulus W. Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex. *Clin Neurophysiol* 2006; **117**: 838-844 [PMID: 16495145 DOI: 10.1016/j.clinph.2005.10.029]
- 54 **Arai N**, Okabe S, Furubayashi T, Terao Y, Yuasa K, Ugawa Y. Comparison between short train, monophasic and biphasic repetitive transcranial magnetic stimulation (rTMS) of the human motor cortex. *Clin Neurophysiol* 2005; **116**: 605-613 [PMID: 15721074 DOI: 10.1016/j.clinph.2004.09.020]
- 55 **Di Lazzaro V**, Oliviero A, Berardelli A, Mazzone P, Insola A, Pilato F, Saturno E, Dileone M, Tonali PA, Rothwell JC. Direct demonstration of the effects of repetitive transcranial magnetic stimulation on the excitability of the human motor cortex. *Exp Brain Res* 2002; **144**: 549-553 [PMID: 12037639 DOI: 10.1007/s00221-002-1106-9]
- 56 **Berardelli A**, Inghilleri M, Cruccu G, Manfredi M. Descending volley after electrical and magnetic transcranial stimulation in man. *Neurosci Lett* 1990; **112**: 54-58 [PMID: 2385364 DOI: 10.1016/0304-3940(90)90321-Y]
- 57 **Di Lazzaro V**, Oliviero A, Pilato F, Saturno E, Dileone M, Mazzone P, Insola A, Tonali PA, Rothwell JC. The physiological basis of transcranial motor cortex stimulation in conscious humans. *Clin Neurophysiol* 2004; **115**: 255-266 [PMID: 14744565 DOI: 10.1016/j.clinph.2003.10.009]
- 58 **Inghilleri M**, Berardelli A, Cruccu G, Priori A, Manfredi M. Corticospinal potentials after transcranial stimulation in humans. *J Neurol Neurosurg Psychiatry* 1989; **52**: 970-974 [PMID: 2552023 DOI: 10.1136/jnnp.52.8.970]

- 59 **Gilio F**, Conte A, Vanacore N, Frasca V, Inghilleri M, Berardelli A. Excitatory and inhibitory after-effects after repetitive magnetic transcranial stimulation (rTMS) in normal subjects. *Exp Brain Res* 2007; **176**: 588-593 [PMID: 16900360 DOI: 10.1007/s00221-006-0638-9]
- 60 **Brighina F**, De Tommaso M, Giglia F, Scalia S, Cosentino G, Puma A, Panetta M, Giglia G, Fierro B. Modulation of pain perception by transcranial magnetic stimulation of left prefrontal cortex. *J Headache Pain* 2011; **12**: 185-191 [PMID: 21350791 DOI: 10.1007/s10194-011-0322-8]
- 61 **Taylor JJ**, Borckardt JJ, George MS. Endogenous opioids mediate left dorsolateral prefrontal cortex rTMS-induced analgesia. *Pain* 2012; **153**: 1219-1225 [PMID: 22444187 DOI: 10.1016/j.pain.2012.02.030]
- 62 **Zunhammer M**, Busch V, Griesbach F, Landgrebe M, Hajak G, Langguth B. rTMS over the cerebellum modulates temperature detection and pain thresholds through peripheral mechanisms. *Brain Stimul* 2011; **4**: 210-217.e1 [PMID: 22032736 DOI: 10.1016/j.brs.2010.11.002]
- 63 **Short EB**, Borckardt JJ, Anderson BS, Frohman H, Beam W, Reeves ST, George MS. Ten sessions of adjunctive left prefrontal rTMS significantly reduces fibromyalgia pain: a randomized, controlled pilot study. *Pain* 2011; **152**: 2477-2484 [PMID: 21764215 DOI: 10.1016/j.pain.2011.05.033]
- 64 **Pascual-Leone A**, Tormos JM, Keenan J, Tarazona F, Cañete C, Catalá MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol* 1998; **15**: 333-343 [PMID: 9736467 DOI: 10.1097/00004691-199807000-00005]
- 65 **Zangen A**, Roth Y, Voller B, Hallett M. Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. *Clin Neurophysiol* 2005; **116**: 775-779 [PMID: 15792886 DOI: 10.1016/j.clinph.2004.11.008]
- 66 **Roth Y**, Amir A, Levkovitz Y, Zangen A. Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. *J Clin Neurophysiol* 2007; **24**: 31-38 [PMID: 17277575 DOI: 10.1097/WNP.0b013e31802fa393]
- 67 **Kranz G**, Shamim EA, Lin PT, Kranz GS, Hallett M. Transcranial magnetic brain stimulation modulates blepharospasm: a randomized controlled study. *Neurology* 2010; **75**: 1465-1471 [PMID: 20956792 DOI: 10.1212/WNL.0b013e3181f8814d]
- 68 **Harel EV**, Zangen A, Roth Y, Reti I, Braw Y, Levkovitz Y. H-coil repetitive transcranial magnetic stimulation for the treatment of bipolar depression: an add-on, safety and feasibility study. *World J Biol Psychiatry* 2011; **12**: 119-126 [PMID: 20854181 DOI: 10.3109/15622975.2010.510893]
- 69 **Harel EV**, Rabany L, Deutsch L, Bloch Y, Zangen A, Levkovitz Y. H-coil repetitive transcranial magnetic stimulation for treatment resistant major depressive disorder: An 18-week continuation safety and feasibility study. *World J Biol Psychiatry* 2014; **15**: 298-306 [PMID: 22313023 DOI: 10.3109/15622975.2011.639802]
- 70 **Loo CK**, Taylor JL, Gandevia SC, McDermont BN, Mitchell PB, Sachdev PS. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? *Biol Psychiatry* 2000; **47**: 325-331 [PMID: 10686267 DOI: 10.1016/S0006-3223(99)00285-1]
- 71 **Lisanby SH**, Gutman D, Lubner B, Schroeder C, Sackeim HA. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biol Psychiatry* 2001; **49**: 460-463 [PMID: 11274658 DOI: 10.1016/S0006-3223(00)01110-0]
- 72 **Rossi S**, Ferro M, Cincotta M, Ulivelli M, Bartalini S, Miniussi C, Giovannelli F, Passero S. A real electro-magnetic placebo (REMP) device for sham transcranial magnetic stimulation (TMS). *Clin Neurophysiol* 2007; **118**: 709-716 [PMID: 17188568 DOI: 10.1016/j.clinph.2006.11.005]
- 73 **Mennemeier M**, Triggs W, Chelette K, Woods A, Kimbrell T, Dornhoffer J. Sham Transcranial Magnetic Stimulation Using Electrical Stimulation of the Scalp. *Brain Stimul* 2009; **2**: 168-173 [PMID: 20160893 DOI: 10.1016/j.brs.2009.02.002]
- 74 **Arana AB**, Borckardt JJ, Ricci R, Anderson B, Li X, Linder KJ, Long J, Sackeim HA, George MS. Focal electrical stimulation as a sham control for repetitive transcranial magnetic stimulation: Does it truly mimic the cutaneous sensation and pain of active prefrontal repetitive transcranial magnetic stimulation? *Brain Stimul* 2008; **1**: 44-51 [PMID: 19424459 DOI: 10.1016/j.brs.2007.08.006]
- 75 **Pascual-Leone A**, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain* 1994; **117** (Pt4): 847-858 [PMID: 7922470 DOI: 10.1093/brain/117.4.847]
- 76 **Rumi DO**, Gattaz WF, Rigonatti SP, Rosa MA, Fregni F, Rosa MO, Mansur C, Myczkowski ML, Moreno RA, Marcolin MA. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. *Biol Psychiatry* 2005; **57**: 162-166 [PMID: 15652875 DOI: 10.1016/j.biopsych.2004.10.029]
- 77 **de Andrade DC**, Mhalla A, Adam F, Texeira MJ, Bouhassira D. Neuropharmacological basis of rTMS-induced analgesia: the role of endogenous opioids. *Pain* 2011; **152**: 320-326 [PMID: 21146300 DOI: 10.1016/j.pain.2010.10.032]
- 78 **Lorenz J**, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain* 2003; **126**: 1079-1091 [PMID: 12690048 DOI: 10.1093/brain/awg102]
- 79 **Ziemann U**, Tergau F, Wischer S, Hildebrandt J, Paulus W. Pharmacological control of facilitatory I-wave interaction in the human motor cortex. A paired transcranial magnetic stimulation study. *Electroencephalogr Clin Neurophysiol* 1998; **109**: 321-330 [PMID: 9751295 DOI: 10.1016/S0924-980X(98)00023-X]
- 80 **Wu T**, Sommer M, Tergau F, Paulus W. Lasting influence of repetitive transcranial magnetic stimulation on intracortical excitability in human subjects. *Neurosci Lett* 2000; **287**: 37-40 [PMID: 10841985 DOI: 10.1016/S0304-3940(00)01132-0]
- 81 **Di Lazzaro V**, Oliviero A, Saturno E, Pilato F, Insola A, Mazzone P, Profice P, Tonali P, Rothwell JC. The effect on corticospinal volleys of reversing the direction of current induced in the motor cortex by transcranial magnetic stimulation. *Exp Brain Res* 2001; **138**: 268-273 [PMID: 11417469 DOI: 10.1007/s002210100722]
- 82 **Ziemann U**. TMS induced plasticity in human cortex. *Rev Neurosci* 2004; **15**: 253-266 [PMID: 15526550 DOI: 10.1515/REVNEURO.2004.15.4.253]
- 83 **Cincotta M**, Borgheresi A, Gambetti C, Balestrieri F, Rossi L, Zaccara G, Ulivelli M, Rossi S, Civardi C, Cantello R. Suprathreshold 0.3 Hz repetitive TMS prolongs the cortical silent period: potential implications for therapeutic trials in epilepsy. *Clin Neurophysiol* 2003; **114**: 1827-1833 [PMID: 14499744 DOI: 10.1016/S1388-2457(03)00181-0]
- 84 **Daskalakis ZJ**, Möller B, Christensen BK, Fitzgerald PB, Gunraj C, Chen R. The effects of repetitive transcranial magnetic stimulation on cortical inhibition in healthy human subjects. *Exp Brain Res* 2006; **174**: 403-412 [PMID: 16683138 DOI: 10.1007/s00221-006-0472-0]
- 85 **Murase N**, Rothwell JC, Kaji R, Urushihara R, Nakamura K, Murayama N, Igasaki T, Sakata-Igasaki M, Mima T, Ikeda A, Shibasaki H. Subthreshold low-frequency repetitive transcranial magnetic stimulation over the premotor cortex modulates writer's cramp. *Brain* 2005; **128**: 104-115 [PMID: 15483042 DOI: 10.1093/brain/awh315]
- 86 **Filipović SR**, Rothwell JC, Bhatia K. Slow (1 Hz) repetitive transcranial magnetic stimulation (rTMS) induces a sustained change in cortical excitability in patients with Parkinson's disease. *Clin Neurophysiol* 2010; **121**: 1129-1137 [PMID: 20350836 DOI: 10.1016/j.clinph.2010.01.031]
- 87 **Malenka RC**, Bear MF. LTP and LTD: an embarrassment of riches. *Neuron* 2004; **44**: 5-21 [PMID: 15450156 DOI: 10.1016/j.neuron.2004.09.012]
- 88 **Ji RR**, Schlaepfer TE, Aizenman CD, Epstein CM, Qiu D, Huang JC, Rupp F. Repetitive transcranial magnetic stimulation activates specific regions in rat brain. *Proc Natl Acad Sci USA* 1998; **95**: 15635-15640 [PMID: 9861022 DOI: 10.1073/pnas.95.26.15635]

- 89 **Hausmann A**, Weis C, Marksteiner J, Hinterhuber H, Humpel C. Chronic repetitive transcranial magnetic stimulation enhances c-fos in the parietal cortex and hippocampus. *Brain Res Mol Brain Res* 2000; **76**: 355-362 [PMID: 10762712 DOI: 10.1016/S0169-328X(00)00024-3]
- 90 **Müller MB**, Toschi N, Kresse AE, Post A, Keck ME. Long-term repetitive transcranial magnetic stimulation increases the expression of brain-derived neurotrophic factor and cholecystokinin mRNA, but not neuropeptide tyrosine mRNA in specific areas of rat brain. *Neuropsychopharmacology* 2000; **23**: 205-215 [PMID: 10882847 DOI: 10.1016/S0893-133X(00)00099-3]
- 91 **Rothwell J**, Burke D, Hicks R, Stephen J, Woodforth I, Crawford M. Transcranial electrical stimulation of the motor cortex in man: further evidence for the site of activation. *J Physiol* 1994; **481** (Pt1): 243-250 [PMID: 7853247 DOI: 10.1113/jphysiol.1994.sp020435]
- 92 **Berardelli A**, Inghilleri M, Rothwell JC, Romeo S, Currà A, Gilio F, Modugno N, Manfredi M. Facilitation of muscle evoked responses after repetitive cortical stimulation in man. *Exp Brain Res* 1998; **122**: 79-84 [PMID: 9772114 DOI: 10.1007/s002210050493]
- 93 **Di Lazzaro V**, Oliviero A, Tonali PA, Marra C, Daniele A, Profice P, Saturno E, Pilato F, Masullo C, Rothwell JC. Noninvasive in vivo assessment of cholinergic cortical circuits in AD using transcranial magnetic stimulation. *Neurology* 2002; **59**: 392-397 [PMID: 12177373 DOI: 10.1212/WNL.59.3.392]
- 94 **Inghilleri M**, Conte A, Frasca V, Gilio F, Lorenzano C, Berardelli A. Synaptic potentiation induced by rTMS: effect of lidocaine infusion. *Exp Brain Res* 2005; **163**: 114-117 [PMID: 15940502 DOI: 10.1007/s00221-005-2225-x]
- 95 **Jennum P**, Winkel H, Fuglsang-Frederiksen A. Repetitive magnetic stimulation and motor evoked potentials. *Electroencephalogr Clin Neurophysiol* 1995; **97**: 96-101 [PMID: 7537209 DOI: 10.1016/0924-980X(94)00293-G]
- 96 **Berardelli A**, Inghilleri M, Gilio F, Romeo S, Pedace F, Currà A, Manfredi M. Effects of repetitive cortical stimulation on the silent period evoked by magnetic stimulation. *Exp Brain Res* 1999; **125**: 82-86 [PMID: 10100980 DOI: 10.1007/s002210050661]
- 97 **Chen R**. Studies of human motor physiology with transcranial magnetic stimulation. *Muscle Nerve Suppl* 2000; **9**: S26-S32 [PMID: 11135281 DOI: 10.1002/1097-4598]
- 98 **Romeo S**, Gilio F, Pedace F, Ozkaynak S, Inghilleri M, Manfredi M, Berardelli A. Changes in the cortical silent period after repetitive magnetic stimulation of cortical motor areas. *Exp Brain Res* 2000; **135**: 504-510 [PMID: 11156314 DOI: 10.1007/s002210000541]
- 99 **Modugno N**, Nakamura Y, MacKinnon CD, Filipovic SR, Bestmann S, Berardelli A, Rothwell JC. Motor cortex excitability following short trains of repetitive magnetic stimuli. *Exp Brain Res* 2001; **140**: 453-459 [PMID: 11685398 DOI: 10.1007/s002210100843]
- 100 **Lorenzano C**, Gilio F, Inghilleri M, Conte A, Fofi L, Manfredi M, Berardelli A. Spread of electrical activity at cortical level after repetitive magnetic stimulation in normal subjects. *Exp Brain Res* 2002; **147**: 186-192 [PMID: 12410333 DOI: 10.1007/s00221-002-1237-z]
- 101 **Inghilleri M**, Conte A, Frasca V, Currà A, Gilio F, Manfredi M, Berardelli A. Antiepileptic drugs and cortical excitability: a study with repetitive transcranial stimulation. *Exp Brain Res* 2004; **154**: 488-493 [PMID: 14579005 DOI: 10.1007/s00221-003-1685-0]
- 102 **Ben-Shachar D**, Belmaker RH, Grisaru N, Klein E. Transcranial magnetic stimulation induces alterations in brain monoamines. *J Neural Transm* (Vienna) 1997; **104**: 191-197 [PMID: 9203081 DOI: 10.1007/BF01273180]
- 103 **Hoogendam JM**, Ramakers GM, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimul* 2010; **3**: 95-118 [PMID: 20633438 DOI: 10.1016/j.brs.2009.10.005]
- 104 **Hirayama A**, Saitoh Y, Kishima H, Shimokawa T, Oshino S, Hirata M, Kato A, Yoshimine T. Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. *Pain* 2006; **122**: 22-27 [PMID: 16495011 DOI: 10.1016/j.pain.2005.12.001]
- 105 **Goto T**, Saitoh Y, Hashimoto N, Hirata M, Kishima H, Oshino S, Tani N, Hosomi K, Kakigi R, Yoshimine T. Diffusion tensor fiber tracking in patients with central post-stroke pain; correlation with efficacy of repetitive transcranial magnetic stimulation. *Pain* 2008; **140**: 509-518 [PMID: 19004554 DOI: 10.1016/j.pain.2008.10.009]
- 106 **Lefaucheur JP**. Use of repetitive transcranial magnetic stimulation in pain relief. *Expert Rev Neurother* 2008; **8**: 799-808 [PMID: 18457536 DOI: 10.1586/14737175.8.5.799]
- 107 **Wasserman EM**, Epstein CM, Ziemann U, Walsh V, Paus T, Lisanby SH. The Oxford Handbook of Transcranial Stimulation. Oxford: Oxford University Press, 2008
- 108 **Ahmed MA**, Mohamed SA, Sayed D. Long-term antalgic effects of repetitive transcranial magnetic stimulation of motor cortex and serum beta-endorphin in patients with phantom pain. *Neurol Res* 2011; **33**: 953-958 [PMID: 22080997 DOI: 10.1179/1743132811Y.00000000045]
- 109 **Hosomi K**, Shimokawa T, Ikoma K, Nakamura Y, Sugiyama K, Ugawa Y, Uozumi T, Yamamoto T, Saitoh Y. Daily repetitive transcranial magnetic stimulation of primary motor cortex for neuropathic pain: a randomized, multicenter, double-blind, crossover, sham-controlled trial. *Pain* 2013; **154**: 1065-1072 [PMID: 23623156 DOI: 10.1016/j.pain.2013.03.016]
- 110 **Ceccanti M**, Inghilleri M, Attilia ML, Raccach R, Fiore M, Zangen A, Ceccanti M. Deep TMS on alcoholics: effects on cortisolemia and dopamine pathway modulation. A pilot study. *Can J Physiol Pharmacol* 2015; **93**: 283-290 [PMID: 25730614 DOI: 10.1139/cjpp-2014-0188]
- 111 **Kakigi R**, Inui K, Tamura Y. Electrophysiological studies on human pain perception. *Clin Neurophysiol* 2005; **116**: 743-763 [PMID: 15792883 DOI: 10.1016/j.clinph.2004.11.016]
- 112 **Cincotta M**, Giovannelli F, Borgheresi A, Balestrieri F, Toscani L, Zaccara G, Carducci F, Viggiano MP, Rossi S. Optically tracked neuronavigation increases the stability of hand-held focal coil positioning: evidence from "transcranial" magnetic stimulation-induced electrical field measurements. *Brain Stimul* 2010; **3**: 119-123 [PMID: 20633439 DOI: 10.1016/j.brs.2010.01.001]
- 113 **Ahdab R**, Ayache SS, Brugière P, Goujon C, Lefaucheur JP. Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. *Neurophysiol Clin* 2010; **40**: 27-36 [PMID: 20230933 DOI: 10.1016/j.neucli.2010.01.001]
- 114 **Bashir S**, Edwards D, Pascual-Leone A. Neuronavigation increases the physiologic and behavioral effects of low-frequency rTMS of primary motor cortex in healthy subjects. *Brain Topogr* 2011; **24**: 54-64 [PMID: 21076861 DOI: 10.1007/s10548-010-0165-7]
- 115 **Saitoh Y**. Validation and the future of stimulation therapy of the primary motor cortex. *Neurol Med Chir* (Tokyo) 2012; **52**: 451-456 [PMID: 22850491 DOI: 10.2176/nmc.52.451]
- 116 **Lefaucheur JP**, Drouot X, Nguyen JP. Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. *Neurophysiol Clin* 2001; **31**: 247-252 [PMID: 11601430 DOI: 10.1016/S0987-7053(01)00260-X]
- 117 **Irlbacher K**, Kuhnert J, Röricht S, Meyer BU, Brandt SA. [Central and peripheral deafferent pain: therapy with repetitive transcranial magnetic stimulation]. *Nervenarzt* 2006; **77**: 1196, 1198-1203 [PMID: 16955313 DOI: 10.1007/s00115-006-2148-1]
- 118 **Lefaucheur JP**, Hatem S, Nineb A, Ménard-Lefaucheur I, Wendling S, Keravel Y, Nguyen JP. Somatotopic organization of the analgesic effects of motor cortex rTMS in neuropathic pain. *Neurology* 2006; **67**: 1998-2004 [PMID: 17159107 DOI: 10.1212/01.wnl.0000247138.85330.88]
- 119 **André-Obadia N**, Mertens P, Gueguen A, Peyron R, Garcia-Larrea L. Pain relief by rTMS: differential effect of current flow but no specific action on pain subtypes. *Neurology* 2008; **71**: 833-840 [PMID: 18779511 DOI: 10.1212/01.wnl.0000325481.61471.f0]
- 120 **Lefaucheur JP**, Drouot X, Ménard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS in chronic neuropathic pain: pain relief is associated with thermal sensory perception improvement. *J Neurol Neurosurg Psychiatry* 2008; **79**: 1044-1049 [PMID: 18457536 DOI: 10.1586/14737175.8.5.799]

- 18223016 DOI: 10.1136/jnnp.2007.135327]
- 121 **Carretero B**, Martín MJ, Juan A, Pradana ML, Martín B, Carral M, Jimeno T, Pareja A, Montoya P, Aguirre I, Salva J, Roca M, Gili M, Garcia-Toro M. Low-frequency transcranial magnetic stimulation in patients with fibromyalgia and major depression. *Pain Med* 2009; **10**: 748-753 [PMID: 19460131 DOI: 10.1111/j.1526-4637.2009.00625.x]
 - 122 **Lefaucheur JP**, Ayache SS, Sorel M, Farhat WH, Zouari HG, Ciampi de Andrade D, Ahdab R, Ménard-Lefaucheur I, Brugières P, Goujon C. Analgesic effects of repetitive transcranial magnetic stimulation of the motor cortex in neuropathic pain: influence of theta burst stimulation priming. *Eur J Pain* 2012; **16**: 1403-1413 [PMID: 22508405 DOI: 10.1002/j.1532-2149.2012.00150.x]
 - 123 **Dall'Agnol L**, Medeiros LF, Torres IL, Deitos A, Brietzke A, Laste G, de Souza A, Vieira JL, Fregni F, Caumo W. Repetitive transcranial magnetic stimulation increases the corticospinal inhibition and the brain-derived neurotrophic factor in chronic myofascial pain syndrome: an explanatory double-blinded, randomized, sham-controlled trial. *J Pain* 2014; **15**: 845-855 [PMID: 24865417 DOI: 10.1016/j.jpain.2014.05.001]
 - 124 **Hodaj H**, Alibeu JP, Payen JF, Lefaucheur JP. Treatment of Chronic Facial Pain Including Cluster Headache by Repetitive Transcranial Magnetic Stimulation of the Motor Cortex With Maintenance Sessions: A Naturalistic Study. *Brain Stimul* 2015; **8**: 801-807 [PMID: 25979838 DOI: 10.1016/j.brs.2015.01.416]
 - 125 **Khedr EM**, Kotb HI, Mostafa MG, Mohamad MF, Amr SA, Ahmed MA, Karim AA, Kamal SM. Repetitive transcranial magnetic stimulation in neuropathic pain secondary to malignancy: a randomized clinical trial. *Eur J Pain* 2015; **19**: 519-527 [PMID: 25142867 DOI: 10.1002/ejp.576]
 - 126 **Lindholm P**, Lamusuo S, Taiminen T, Pesonen U, Lahti A, Virtanen A, Forssell H, Hietala J, Hagelberg N, Pertovaara A, Parkkola R, Jääskeläinen S. Right secondary somatosensory cortex-a promising novel target for the treatment of drug-resistant neuropathic orofacial pain with repetitive transcranial magnetic stimulation. *Pain* 2015; **156**: 1276-1283 [PMID: 25830924 DOI: 10.1097/j.pain.0000000000000175]
 - 127 **Borckardt JJ**, Weinstein M, Reeves ST, Kozel FA, Nahas Z, Smith AR, Byrne TK, Morgan K, George MS. Postoperative left prefrontal repetitive transcranial magnetic stimulation reduces patient-controlled analgesia use. *Anesthesiology* 2006; **105**: 557-562 [PMID: 16931989 DOI: 10.1097/00000542-200609000-00020]

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Insight into orthodontic appliance induced pain: Mechanism, duration and management

Yasemin Kartal, Omur Polat-Ozsoy

Yasemin Kartal, Omur Polat-Ozsoy, Department of Orthodontics, Baskent University, Faculty of Dentistry, 06500 Ankara, Turkey

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Correspondence to: Omur Polat-Ozsoy, Professor, Department of Orthodontics, Baskent University, Faculty of Dentistry, 1st Street, Bahçelievler No.107, 06500 Ankara, Turkey. omurorto@yahoo.com
 Telephone: +90-31-22151336
 Fax: +90-31-22152962

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Abstract

Most of the orthodontic patients experience pain during treatment and this significantly influences their attitudes and the approach towards treatment. A number of factors that influence pain response include age, gender, personal pain threshold, mood and stress level of the person, cultural differences and types of orthodontic

treatment. Pain is a often overlooked subject by orthodontists, it is nevertheless important to understand the source and mechanism of the pain that occurs during treatment, as well as the methods for managing and controlling this pain. This review attempts to overview the mechanism, duration and current management strategies of orthodontic treatment.

Key words: Orthodontic appliance; Pain mechanism; Orthodontic treatment; Pain; Pain management

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Core tip: Pain during orthodontic treatment is an important concern for both clinicians and patients. Although it is not possible to completely eliminate pain during orthodontic treatment, it is still necessary to understand its causes and to minimize it to the greatest extent possible.

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INTRODUCTION

Pain is a commonly encountered sensation in daily human life that is usually difficult to describe or diagnose, and which often represents an important problem that must be addressed through a multidisciplinary approach encompassing all branches of medicine.

Pain during orthodontic treatment is an important concern for both clinicians and patients^[1,2]. Patient motivation and cooperation is an important factor in orthodontic treatment, while pain significantly influences

patient attitudes and the approach towards treatment. Studies indicate that 90% of orthodontic patients experience pain during treatment, and that 30% consider discontinuing or interrupting their treatment due to pain^[3,4].

The study of Abu Alhaijaa *et al.*^[5] evaluated the relationship between personal characteristics, expectation of pain, and treatment compliance, reporting that individuals who experienced less pain during treatment generally displayed a more positive attitude, and that those sufficiently informed about treatment procedures had less expectations of pain.

In another study, 95% of the patients reported that they experienced pain in different stages of their treatment, and that this inevitably affected their diet^[6].

For these reasons, although pain is a subject that is often overlooked by orthodontists, it is nevertheless important to understand the source and mechanism of the pain that occurs during treatment, as well as the methods for managing and controlling this pain.

Mechanism of pain

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Pain also has a strong motivational component, in that it not only triggers a withdrawal reflex, but also induces a highly organized avoidance and evasive behavior^[7]. The motivational aspect of pain is an essential function, without which it would be difficult - if not impossible - for the human body to protect and sustain itself^[7].

In orthodontic treatments, the force transmitted by appliances allows the movement of the teeth within the alveolar bone^[8]. However, this movement also has the effect of causing the compression and inflammation of the blood vessels and nerves within the periodontium. The perception of orthodontic pain is associated with changes in blood flow that occur due to inflammatory reactions following the application of force^[9]. Studies indicate that periodontal pain consists of a combination of pressures, ischemia, inflammation, and oedema^[10]. Davidovich and Shanfeld have reported that the application of force leads to acute inflammation, which, in turn, results in periodontal vasodilation and the sensation of pain^[11]. It is known that the development of hyperalgesic resistance is associated with the release of various chemical mediators^[12,13]. Studies have shown that the chemical mediators involved in the development of the hyperalgesic response include histamine, substance P, enkephalin, dopamine, serotonin, glycine, glutamate gamma-amino butyric acid, prostaglandins (PGs), leukotriene, and cytokines^[9,12,13]. The studies in the literature concerning the increase in the level of these mediators have also demonstrated that the hyperalgesic response occurs following the application of force^[9,14,15]. Recent studies have investigated the molecular basis of orthodontic pain by evaluating subjects such as the elevation in the level of various neuropeptides^[9].

Kato *et al.*^[16] previously investigated in rats the distribution of the neurofibrils within the PDL [such as the neurofilament protein (NFP), calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide and neuropeptides Y] following the application of force on the first molar. Three days after the application of force, they observed that the level of neurofibrils consisting of NFP and CGRP increased in both the compressed and strained sides, and that these levels returned to normal on the 14th day^[9,16].

Studies indicate that substance P - a sensory neuropeptide released from the peripheral nerve ends - and CGRP both regulate the secretion of proinflammatory cytokines released by monocytes, such as IL-1 β , IL-6, and TNF- α ^[15,17,18]. Yamaguchi *et al.*^[19] determined that the level of three major cytokines (IL-6, IL-8, and TNF- α) released from the human dental pulp cells increased significantly in the 12 h following the application of mechanical force. They also reported that major neuropeptides, such as proinflammatory cytokines, might be involved in pulpal inflammation during orthodontic teeth movement.

Duration of pain

The time of onset and duration of orthodontic pain was similar in most studies, with patients generally beginning to experience discomfort four hours after the application of orthodontic force^[20]. In a study using the Visual analogue scale (VAS) to evaluate the level of pain that developed following the placement of separators, the highest intensity of pain was observed on the second day, while the pain fully subsided by the fifth day^[21]. Nearly half of the patients evaluated during this study were compelled to change their diet habits and to use analgesics.

In a study using the VAS to evaluate pain in patients with arch wire and separators placed between their molars, Wilson *et al.*^[20] reported that pain generally began four hours after the application of force, reaching its highest level 24 h later, and almost fully disappearing by the seventh day. On the other hand, Tuncer *et al.*^[22] described that pain began two hours following the application of orthodontic elastics, reaching its highest level six hours later, and almost fully disappearing by the second day.

A previous study reported that although pain ended in most patients on the seventh day following the application of orthodontic force, 25% of the patients still continued to experience a certain level of pain^[23]. The results of the said study indicated that orthodontic pain began two to six hours following the application of orthodontic pain, reaching its maximum level within the first two days, and then gradually decreasing until it completely disappeared by the seventh day.

FACTORS AFFECTING ORTHODONTIC PAIN

Pain is a subjective finding, and different individuals may

display different pain responses to the same stimulus. There are a number of factors that are responsible for these differences in response. The main factors that influence pain response include age, gender, personal pain threshold, mood and stress level of the person, as well as cultural differences and the person's previous pain experiences^[1,4,9,24,25].

Age

As orthodontic treatments generally involve different therapeutic procedures for different age groups, making comparisons regarding the effect of age is difficult, with studies on this subject generally providing somewhat contradictory results. However, Ngan *et al.*^[26] previously reported that there were no statistically significant differences between adolescents and adults regards to pain. On the other hand, in their comprehensive and large-scale study on pre-adolescents, adolescents, and adults, Moerenhout and Brown^[27] reported that adolescents exhibited higher levels of pain.

In recent years, there is a growing consensus that the relationship between pain and age should be evaluated by also taking into account the effect of age, since this relationship appears to be particularly affected by adolescence. Sandhu and Sandhu^[28] determined in their study that girls between the ages of 14 and 17 experienced the highest levels of pain during orthodontic treatments. These authors emphasized that due to their synergistic interaction, the effects of age and gender on the level of pain during orthodontic treatment should be evaluated together rather than separately^[28].

These contradictory and conflicting results appear to stem not only from the fact that different orthodontic treatment methods are generally used for different age groups, but also from the fact pain is a multifactorial element that can be affected by gender differences, as well as the psychological and emotional state of the patients.

Gender

Similar to age, gender is another factor that is unlikely to provide accurate assessments when used independently to evaluate pain. This is because even within the same gender, factors such as age group and cultural differences can significantly affect the level of pain that is experienced. Certain studies report that while there are no statistical differences between males and females within the 11-14 age group, a significant difference begins to be observed within the 14-17 age group. This change is reported to be associated with the hormonal changes experienced by females during adolescence^[28,29]. Cultural differences similarly appear to cause significant variations in study results regarding the relationship between pain and gender. In a study evaluating the pain response of both male and female individuals, it was observed females generally found it easier to express and describe the pain they experienced compared to males^[30]. These contradictory

results indicate that the perception of pain is affected not only by physiological differences, but also by cultural factors^[31].

Although certain studies evaluating the effect of gender on orthodontic pain describe that females exhibit higher levels of pain than males^[6,32,33], most studies from the orthodontics literature have not identified a gender-related difference in the perception of pain^[34-37].

Emotional state

Dental anxiety ranks fifth among the objects and situations that are the most common sources of anxiety^[38]. A study conducted by Hamurcu^[39] compared the intensity of pain experienced with their level of anxiety, and determined that patients exhibiting higher anxiety scores also experienced more pain.

In a study comparing the level of pain experienced by patients at the beginning of orthodontic treatment with their personal characteristics, Bergius *et al.*^[40] determined that individuals with dental anxiety experienced higher intensities of pain. A similar study observed that anxiety reduced the pain threshold, causing patients to perceive even the simplest procedures as painful^[41].

THE EFFECT OF THE TYPE OF ORTHODONTIC TREATMENT ON PAIN

Orthodontic separation

Orthodontic separation is a method applied prior to the placement of an orthodontic band, and is usually associated with significant pain for the patients^[9,21,26,42]. In another study performed on 55 patients, 87% of the patients described pain following the placement of an orthodontic separator, while 72% required analgesics^[37]. In a study evaluating motor and sensory changes following the placement of a separator by using an electromyograph (EMG), Michelotti *et al.*^[43] observed a decrease in the pain threshold and motor output of the chewing muscles, and suggested that this was a protective mechanism to prevent further damage to the injured area.

Dental archwire placement and activation

The pain that develops following the initial placement of an archwire has been the subject of numerous studies. These studies generally report that most patients begin to experience pain four hours after the application of the arch, with the level of pain reaching its peak within the first 24 h, and then gradually decreasing^[6,26,32,34,42,44,45].

No statistically significant differences have been identified between the perception of pain and the intensity, prevalence, and duration of the archwire usage^[34,46,47]. In a study comparing the super-elastic nickel titanium wires with helical stainless steel wires, Sandhu *et al.*^[48] reported no statistically significant differences in the level of pain experienced with these two wires. However, they suggested that the super-elastic wire caused more pain during the hours when the level of pain reached

its peak (between the 12th and 24th h), and that was probably due to the greater force applied by this type of wire. Although the current literature indicates that the application of either strong or weak forces by the wires does not lead to a significant difference in terms of the resulting level of pain, Sandhu's study nevertheless suggests that higher forces result in higher IL-1 beta concentrations, and that this engenders a difference in the level of pain observed during the peak period^[48]. Ogura *et al*^[49] similarly performed comparisons between weak and strong forces, and determined that during the period of maximum pain levels, biting while the teeth were exposed to stronger forces lead to higher levels of pain.

Previous studies evaluating the activity of chewing muscles following arch activation by using EMG identified a decrease in the masseter muscle activity, which is believed to be responsible for the reflex mechanism for avoiding harmful stimuli^[50-52]. Murdock *et al*^[44] and Erdinç *et al*^[34] have reported that patients report greater pain in the posterior teeth than their anterior teeth during the leveling stage and chewing. In sum, most studies indicate that arch placement and activation can lead to pain, and adversely affect the daily activity and diet habits of patients^[9].

Type of appliance

The level of pain caused by different types of appliances during orthodontic treatments has been evaluated in many studies. In studies comparing fixed and removable appliances, Oliver and Knapman^[1] identified no significant differences between these two types of treatments, while Sergl *et al*^[25] and Gianelly *et al*^[53] reported that treatment with fixed appliances resulted in greater pain.

Various comparisons have been performed between fixed orthodontic treatments applied using different methods. Wu *et al*^[54] and Caniklioglu *et al*^[55] have performed comparisons between labial and lingual appliances, and reported no statistically significant difference with regards to the total level of perceived pain associated with these appliances. However, they also described greater pain on the tongue among patients who received lingual appliances, as well as greater pain on the lips and cheeks among patients who received labial appliances^[54,55]. A recent study compared the application of a fixed labial appliances with the Invisalign® and determined that Invisalign® caused less pain^[56].

Shalish *et al*^[57] have evaluated and compared the fixed lingual treatment, fixed labial treatment and Invisalign® treatment in adult patients, and determined that the most pain and general oral dysfunction occurred in the lingual apparatus group; that Invisalign® caused significant pain in the first day of treatment; and that Invisalign® was similar to conventional labial techniques in terms of general oral dysfunction^[57].

Bertl *et al*^[58] have examined self-ligating brackets and

conventional brackets with respect to pain, and determined that self-ligating brackets caused significantly more pain. In contrast to Bertl *et al*^[58], Tecco *et al*^[59] suggested that conventional brackets lead to stronger and more persistent pain, while self-ligating brackets tended to cause pain mainly during chewing and biting.

Orthopedic forces

The main purpose of craniofacial orthopedics is to bring skeletal changes by applying significant forces to the craniofacial complex. Various publications report the occurrence of pain during rapid palatal expansion applied for the transversal skeletal development of the maxilla^[60-62]. In such cases, patients generally describe a sensation of pain spreading across the craniofacial area^[9].

Headgear applications represent another treatment method used during the development stages of children to bring about skeletal and dental modification. Studies have demonstrated that patients with such appliances generally begin to experience pain approximately 24 h after initial application, with the sensation of pain and discomfort gradually decreasing after the 3rd day^[63,64].

Egolf *et al*^[65] have reported that nearly 28% of patients using orthodontic elastics and headgear discontinue to wear them due to pain. Ngan *et al*^[64] previously examined the chewing muscles of protraction headgear patients by using EMG, and determined that the pain associated with the orthopedic devices originated not from the muscle tissues, but instead from the acute inflammation caused by the accumulation of forces in the sutural areas.

Skeletal anchorage systems

Recently, skeletal anchorage systems are being used for absolute anchorage. These devices can be grouped/classified as "mini-plate" and "mini-screws". Zawawi^[66] reported that patients with mini-screw implants reported significantly less pain; that 32.5% of patients receiving mini-screw implants did not require any medication; that 59.1% of these patients only required a single-dose analgesic; and that patients generally preferred mini-screws instead of extraction.

Kuroda *et al*^[67] previously compared the level of pain experienced with mini-plate and mini-screws. No significant differences were observed in terms of perceived pain levels between mini-plates and mini-screws inserted through incisions, while a significant difference was observed when mini-plates and mini-screws were implanted without using incisions, with the mini-plates resulting in noticeably more pain^[67]. In agreement with Kuroda *et al*^[67]'s findings, Kawaguchi *et al*^[68] demonstrated that implanting mini-plates without using incisions resulted in three times greater pain than placing mini-screws without incisions. The abovementioned studies have generally suggested that the main causes of pain during the application of skeletal anchorage systems could mainly be associated

with sutures, periosteal separation, and incisions.

Debonding

Many patients also describe pain when removing their fixed appliances. Various studies have shown that applying intrusive forces during the debonding of fixed appliances reduced the level of pain experienced. These studies have therefore recommended applying finger pressure, biting a cotton roll, or using an occlusal wax layer during the removal process in order to reduce pain^[69,70].

PAIN MEASUREMENT

It is important that pain is measured by the use of standardized pain scales and by using common language due to its complex and subjective nature. Unfortunately, objective assessment methods are still developing and subjective assessment is still the commonly used method. As the pain perception varies among individuals, it is important to take the patients' own report into consideration. Ideally, a pain intensity scale must have a low rate of incorrect responses, should be easy to administer, and be sensitive with an adequate number of response categories and be statistically powerful to detect treatment effects.

VAS is considered to be superior to other pain scales in terms of reproducibility and ease of measurement. VAS is a numeric scale and consists of a horizontal or vertical 100 mm line that has "no pain" and "worst pain" labels on two endpoints; the patient is asked to mark on the line to show the degree of pain experienced. The distance between the low end of the scale and the patient's mark is used as the index of pain intensity^[8].

MANAGEMENT AND CONTROL OF ORTHODONTIC PAIN

Although it is not possible to completely eliminate pain during orthodontic treatment, it is still necessary to understand its causes and to minimize it to the greatest extent possible. It is therefore important to take into consideration and avoid overlooking the patient's complaints during the treatment process, and to inform them beforehand about the pain the treatment may cause. A study performed by Krukemeyer *et al.*^[4] determined that orthodontists tend to ignore or dismiss the pain caused by the treatment, and that they generally expect a lower level of pain and medication use than the level reported by patients. Krukemeyer *et al.*^[4] also reported a general lower-than-necessary amount of medication use. Abu Alhaijaa *et al.*^[5], on the other hand, reported that patients sufficiently informed about the treatment process had a lower medication requirements.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually the medication of choice in orthodontics to alleviate mild and moderate pain and inflammation,

although there is no standard protocol concerning the application of NSAIDs. Many drugs such as acetaminophen, ibuprofen, aspirin, and flurbiprofen have been used and determined to be effective in the management of orthodontic pain^[71-76]. However, a number of previous studies have suggested that PGs, and especially prostaglandin E2 and prostaglandin E1, can affect bone remodeling and teeth movement^[14,77-80]. Nevertheless, the general consensus in orthodontic pain management is that the application of a low-dose analgesic during the first days of treatment will not have a clinically significant effect on the movement of the teeth. Another point that needs to be taken into consideration during orthodontic treatment is the possibility that teeth movement might be affected in patients who have been regularly receiving NSAIDs for a long period of time due to a systemic condition. In such cases, acetaminophen should be preferred because it provides sufficient analgesia without affecting teeth movement^[8].

In recent times, there has been an increasing focus on preventing the development of a pain memory through preemptive drug administration. Steen Law *et al.*^[76] previously assessed the effect of ibuprofen and placebo administered one hour prior to separator application, and determined that the ibuprofen administration significantly reduced the pain experienced by the patients. Polat and Karaman^[72] similarly conducted a comprehensive study evaluating the administration of five different medication (placebo, ibuprofen, flurbiprofen, acetaminophen, naproxen sodium, and aspirin) one hour before and six hours after bracketing procedures. The lowest pain scores were observed in the naproxen sodium and aspirin groups, while the highest pain scores were observed in the acetaminophen group^[72]. In another study of the same authors, a single preoperative dose of placebo, ibuprofen and naproxen sodium was applied, and - in agreement with the findings of their previous study - lower levels of pain were reported during the first day in the naproxen sodium group. However, the authors also described that a single-dose application was not sufficient, and that additional postoperative doses were also necessary^[42].

Non-pharmacological methods used for pain management include transcutaneous electrical nerve stimulation (TENS), laser applications, vibration, and chewing apparatuses. Profitt described that the use of chewing gum or biting blocks during application would help reduce pain^[81]. This theory was investigated by Mohri *et al.*^[82] by evaluating the relationship between chewing and the serotonergic (5-HT) neurons responsible for nociceptive transmissions. Mohri *et al.*^[82] determined that the rhythmic behavior of chewing indeed suppressed the nociceptive response. Hwang *et al.*^[83] similarly determined that biting blocks reduced pain in 56% of their patients; however, they also observed that in other patients, biting blocks had the effect of increasing the experienced pain. Murdock *et al.*^[44], on the other hand, compared the effect of analgesics and

biting blocks, and determined that these apparatuses were as effective as analgesics, and that they represent a good option for adolescents.

Laser - a highly popular technological application in recent times - is also being used in the management of orthodontic pain. Fujiyama *et al.*^[84] reported that CO₂ laser applications are able to reduce orthodontic pain without affecting teeth movement. In another study, comparisons were performed between a low-energy gallium-arsenic-aluminum laser (LLLT) group, a placebo group, and a control group following the implantation of an arch wire. The study determined that the LLLT and placebo groups both experienced significantly less pain, although the difference between these two groups was not significant^[85]. Although numerous alternative, non-pharmacological methods are being used for the management of orthodontic pain, it is known that pharmacological methods still represent the most effective approach.

CONCLUSION

Although it is not possible to completely eliminate pain during orthodontic treatment, it is still necessary to understand its causes and to minimize it to the greatest extent possible. It is therefore important to take into consideration and avoid overlooking the patient's complaints during the treatment process, and to inform them beforehand about the pain the treatment may cause. During pain management, medication that ensures the maximum reduction of pain with the minimum side effects should be administered by employing the most effective methods. In particular, the decision regarding the choice of medication or approach for reducing pain should not be left to the patient's relatives. Although there are no controlled studies supporting low-energy laser and TENS applications, further studies and growing interest on these techniques might eventually bring a new dimension to orthodontic pain management.

REFERENCES

- 1 Oliver RG, Knapman YM. Attitudes to orthodontic treatment. *Br J Orthod* 1985; **12**: 179-188 [PMID: 3863673 DOI: 10.1179/bjo.12.4.179]
- 2 Kluemper GT, Hiser DG, Rayens MK, Jay MJ. Efficacy of a wax containing benzocaine in the relief of oral mucosal pain caused by orthodontic appliances. *Am J Orthod Dentofacial Orthop* 2002; **122**: 359-365 [PMID: 12411880 DOI: 10.1067/mod.2002.126405]
- 3 Otasevic M, Naini FB, Gill DS, Lee RT. Prospective randomized clinical trial comparing the effects of a masticatory bite wafer and avoidance of hard food on pain associated with initial orthodontic tooth movement. *Am J Orthod Dentofacial Orthop* 2006; **130**: 6.e9-6.e15 [PMID: 16849064 DOI: 10.1016/j.jado.2005.11.033]
- 4 Krukemeyer AM, Arruda AO, Inglehart MR. Pain and orthodontic treatment. *Angle Orthod* 2009; **79**: 1175-1181 [PMID: 19852612 DOI: 10.2319/121308-632R.1]
- 5 Abu Alhaija ES, Aldaikki A, Al-Omairi MK, Al-Khateeb SN. The relationship between personality traits, pain perception and attitude toward orthodontic treatment. *Angle Orthod* 2010; **80**: 1141-1149 [PMID: 20677967 DOI: 10.2319/012710-59.1]
- 6 Scheurer PA, Firestone AR, Bürgin WB. Perception of pain as a result of orthodontic treatment with fixed appliances. *Eur J Orthod* 1996; **18**: 349-357 [PMID: 8921656 DOI: 10.1093/ejo/18.4.349]
- 7 McNeil C, Dubner R, Woda A. What is pain and how do we classify orofacial pain? In: Sessle BJ, Lavigne GJ, Lund JP, Dubner R. Orofacial Pain. From Basic Science to Clinical Management. Second Edition. Quintessence Publishing Co, 2008: 3-11
- 8 Polat O. Pain and discomfort after orthodontic appointments. *Semin Orthod* 2007; **13**: 292-300 [DOI: 10.1053/j.sodo.2007.08.010]
- 9 Krishnan V. Orthodontic pain: from causes to management--a review. *Eur J Orthod* 2007; **29**: 170-179 [PMID: 17488999 DOI: 10.1093/ejo/cjl081]
- 10 Furstman L, Bernick S. Clinical considerations of the periodontium. *Am J Orthod* 1972; **61**: 138-155 [PMID: 4500502 DOI: 10.1016/002-9416(72)90092-9]
- 11 Stanfeld J, Jones J, Laster L, Davidovitch Z. Biochemical aspects of orthodontic tooth movement. I. Cyclic nucleotide and prostaglandin concentrations in tissues surrounding orthodontically treated teeth in vivo. *Am J Orthod Dentofacial Orthop* 1986; **90**: 139-148 [PMID: 3017094 DOI: 10.1016/0889-5406(86)90046-6]
- 12 Erdine S. Ağrı mekanizmaları giriş. İçinde: Özcan İ (Ed). Ağrı: Baş-Boyun ve orofasiyal ağrılar. İstanbul: Nobel Tıp Kitabevleri, 2000; 17-32
- 13 Aldemir T. Akut Ağrı Fizyopatolojisi. In: Özcan İ. Ağrı Bas-Boyun ve Orofasiyal Ağrılar. 2nd ed İstanbul, Nobel Tıp Kitabevleri, 2006: 43-48
- 14 Yamasaki K, Shibata Y, Imai S, Tani Y, Shibasaki Y, Fukuhara T. Clinical application of prostaglandin E1 (PGE1) upon orthodontic tooth movement. *Am J Orthod* 1984; **85**: 508-518 [PMID: 6587784 DOI: 10.1016/0002-9416(84)90091-5]
- 15 Alhashimi N, Frithiof L, Brudvik P, Bakhiet M. Orthodontic tooth movement and de novo synthesis of proinflammatory cytokines. *Am J Orthod Dentofacial Orthop* 2001; **119**: 307-312 [PMID: 11244425 DOI: 10.1067/mod.2001.110809]
- 16 Kato J, Wakisaka S, Kurisu K. Immunohistochemical changes in the distribution of nerve fibers in the periodontal ligament during an experimental tooth movement of the rat molar. *Acta Anat (Basel)* 1996; **157**: 53-62 [PMID: 9096742 DOI: 10.1159/000147866]
- 17 Nicolay OF, Davidovitch Z, Shanfeld JL, Alley K. Substance P immunoreactivity in periodontal tissues during orthodontic tooth movement. *Bone Miner* 1990; **11**: 19-29 [PMID: 1702686 DOI: 10.1016/0169-6009(90)90012-5]
- 18 Norevall LI, Forsgren S, Matsson L. Expression of neuropeptides (CGRP, substance P) during and after orthodontic tooth movement in the rat. *Eur J Orthod* 1995; **17**: 311-325 [PMID: 8521925 DOI: 10.1093/ejo/17.4.311]
- 19 Yamaguchi M, Kojima T, Kanekawa M, Aihara N, Nogimura A, Kasai K. Neuropeptides stimulate production of interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha in human dental pulp cells. *Inflamm Res* 2004; **53**: 199-204 [PMID: 15105969 DOI: 10.1007/s00011-003-1243-z]
- 20 Wilson S, Ngan P, Kess B. Time course of the discomfort in young patients undergoing orthodontic treatment. *Pediatr Dent* 1989; **11**: 107-110 [PMID: 2762180]
- 21 Bondemark L, Fredriksson K, Ilros S. Separation effect and perception of pain and discomfort from two types of orthodontic separators. *World J Orthod* 2004; **5**: 172-176 [PMID: 15615136]
- 22 Tuncer Z, Ozsoy FS, Polat-Ozsoy O. Self-reported pain associated with the use of intermaxillary elastics compared to pain experienced after initial archwire placement. *Angle Orthod* 2011; **81**: 807-811 [PMID: 21446869 DOI: 10.2319/092110-550.1]
- 23 Tuncer Z. The evaluation of the effects of the preoperative and postoperative non-steroidal antiinflammatory analgesics on the pain induced by orthodontic tooth movement and inflammatory mediator levels. Phd's thesis. University of Baskent, 2011
- 24 O'Connor PJ. Patients' perceptions before, during, and after orthodontic treatment. *J Clin Orthod* 2000; **34**: 591-592 [PMID: 11314173]
- 25 Sergrl HG, Klages U, Zentner A. Pain and discomfort during orthodontic treatment: causative factors and effects on compliance. *Am J Orthod Dentofacial Orthop* 1998; **114**: 684-691 [PMID: 9844209 DOI: 10.1016/S0889-5406(98)70201-X]

- 26 **Ngan P**, Kess B, Wilson S. Perception of discomfort by patients undergoing orthodontic treatment. *Am J Orthod Dentofacial Orthop* 1989; **96**: 47-53 [PMID: 2750720 DOI: 10.1016/0889-5406(89)90228-X]
- 27 **Brown DF**, Moerenhout RG. The pain experience and psychological adjustment to orthodontic treatment of preadolescents, adolescents, and adults. *Am J Orthod Dentofacial Orthop* 1991; **100**: 349-356 [PMID: 1927986 DOI: 10.1016/0889-5406(91)70073-6]
- 28 **Sandhu SS**, Sandhu J. Orthodontic pain: an interaction between age and sex in early and middle adolescence. *Angle Orthod* 2013; **83**: 966-972 [PMID: 23705940 DOI: 10.2319/030113-174.1]
- 29 **Greydanus DE**, Bashe P. American Academy of Pediatrics. Caring for Your Teenager: The Complete and Authoritative Guide. New York, NY: Bantam Books, 2003
- 30 **Hobara M**. Beliefs about appropriate pain behavior: cross-cultural and sex differences between Japanese and Euro-Americans. *Eur J Pain* 2005; **9**: 389-393 [PMID: 15979019 DOI: 10.1016/j.ejpain.2004.09.006]
- 31 **Bergius M**, Kiliaridis S, Berggren U. Pain in orthodontics. A review and discussion of the literature. *J Orofac Orthop* 2000; **61**: 125-137 [PMID: 10783564 DOI: 10.1007/BF01300354]
- 32 **Firestone AR**, Scheurer PA, Bürgin WB. Patients' anticipation of pain and pain-related side effects, and their perception of pain as a result of orthodontic treatment with fixed appliances. *Eur J Orthod* 1999; **21**: 387-396 [PMID: 10502901 DOI: 10.1093/ejo/21.4.387]
- 33 **Kvam E**, Bondevik O, Gjerdet NR. Traumatic ulcers and pain in adults during orthodontic treatment. *Community Dent Oral Epidemiol* 1989; **17**: 154-157 [PMID: 2736897 DOI: 10.1111/j.1600-0528.1989.tb00012.x]
- 34 **Erdinç AM**, Dinçer B. Perception of pain during orthodontic treatment with fixed appliances. *Eur J Orthod* 2004; **26**: 79-85 [PMID: 14994886 DOI: 10.1093/ejo/26.1.79]
- 35 **Riley JL**, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. *Pain* 1998; **74**: 181-187 [PMID: 9520232 DOI: 10.1016/S0304-3959(97)00199-1]
- 36 **Jones M**, Chan C. The pain and discomfort experienced during orthodontic treatment: a randomized controlled clinical trial of two initial aligning arch wires. *Am J Orthod Dentofacial Orthop* 1992; **102**: 373-381 [PMID: 1456222 DOI: 10.1016/0889-5406(92)70054-E]
- 37 **Bergius M**, Berggren U, Kiliaridis S. Experience of pain during an orthodontic procedure. *Eur J Oral Sci* 2002; **110**: 92-98 [PMID: 12013568 DOI: 10.1034/j.1600-0722.2002.11193.x]
- 38 **Akarslan Z**, Erten H. Dis Hekimligi Korkusu ve Kaygısı. *Hacettepe Dis Hekimligi Fakültesi Dergisi* 2009; **1**: 62-68
- 39 **Hamurcu KN**. The Evaluation of the Relationship between Dental Anxiety and Coping Strategies of the Patients who Referred to Oral and Maxillofacial Surgery Clinic with Pain Complaints and their Pain Perception. Phd's thesis. University of Gazi, 2014. Available from: URL: <http://www.acikarsiv.gazi.edu.tr/index.php?menu=2&secim=10&YayinBIK=10715>
- 40 **Bergius M**, Broberg AG, Hakeberg M, Berggren U. Prediction of prolonged pain experiences during orthodontic treatment. *Am J Orthod Dentofacial Orthop* 2008; **133**: 339.e1-339.e8 [PMID: 18331926 DOI: 10.1016/j.ajodo.2007.09.013]
- 41 **Litt MD**. A model of pain and anxiety associated with acute stressors: distress in dental procedures. *Behav Res Ther* 1996; **34**: 459-476 [PMID: 8687368 DOI: 10.1016/0005-7967(96)00015-0]
- 42 **Polat O**, Karaman AI, Durmus E. Effects of preoperative ibuprofen and naproxen sodium on orthodontic pain. *Angle Orthod* 2005; **75**: 791-796 [PMID: 16279825]
- 43 **Michelotti A**, Farella M, Martina R. Sensory and motor changes of the human jaw muscles during induced orthodontic pain. *Eur J Orthod* 1999; **21**: 397-404 [PMID: 10502902 DOI: 10.1093/ejo/21.4.397]
- 44 **Murdock S**, Phillips C, Khondker Z, Hershey HG. Treatment of pain after initial archwire placement: a noninferiority randomized clinical trial comparing over-the-counter analgesics and bite-wafer use. *Am J Orthod Dentofacial Orthop* 2010; **137**: 316-323 [PMID: 20197167 DOI: 10.1016/j.ajodo.2008.12.021]
- 45 **Shetty N**, Patil AK, Ganeshkar SV, Hegde S. Comparison of the effects of ibuprofen and acetaminophen on PGE2 levels in the GCF during orthodontic tooth movement: a human study. *Prog Orthod* 2013; **14**: 6 [PMID: 24325834 DOI: 10.1186/2196-1042-14-6]
- 46 **Jones ML**, Richmond S. Initial tooth movement: force application and pain--a relationship? *Am J Orthod* 1985; **88**: 111-116 [PMID: 3861096 DOI: 10.1016/0002-9416(85)90234-9]
- 47 **Fernandes LM**, Ogaard B, Skoglund L. Pain and discomfort experienced after placement of a conventional or a superelastic NiTi aligning archwire. A randomized clinical trial. *J Orofac Orthop* 1998; **59**: 331-339 [PMID: 9857602 DOI: 10.1007/BF01299769]
- 48 **Sandhu SS**, Sandhu J. A randomized clinical trial investigating pain associated with superelastic nickel-titanium and multistranded stainless steel archwires during the initial leveling and aligning phase of orthodontic treatment. *J Orthod* 2013; **40**: 276-285 [PMID: 24297959 DOI: 10.1179/1465313313Y.0000000072]
- 49 **Ogura M**, Kamimura H, Al-Kalaly A, Nagayama K, Taira K, Nagata J, Miyawaki S. Pain intensity during the first 7 days following the application of light and heavy continuous forces. *Eur J Orthod* 2009; **31**: 314-319 [PMID: 19088059 DOI: 10.1093/ejo/cjn072]
- 50 **Smith BR**, Flanary CM, Hurst LL, Rugh JD. Effects of orthodontic archwire changes on masseter muscle activity. *J Dent Res* 1984; **63**: 258 (abstract)
- 51 **Goldreich H**, Gazit E, Lieberman MA, Rugh JD. The effect of pain from orthodontic arch wire adjustment on masseter muscle electromyographic activity. *Am J Orthod Dentofacial Orthop* 1994; **106**: 365-370 [PMID: 7942651 DOI: 10.1016/S0889-5406(94)70057-5]
- 52 **Lund JP**, Lamarre Y, Lavigne G, Duquet G. Human jaw reflexes. In Desmedt J E (ed.) Motor control mechanisms in health and disease. Raven Press, New York, 1983: 739-755
- 53 **Gianelly AA**, Goldman HM. Tooth movement. Biological basis of orthodontics. Lea and Febiger, Philadelphia, 1971: 116-204
- 54 **Wu AK**, McGrath C, Wong RW, Wiechmann D, Rabie AB. A comparison of pain experienced by patients treated with labial and lingual orthodontic appliances. *Eur J Orthod* 2010; **32**: 403-407 [PMID: 20018798 DOI: 10.1093/ejo/cjp117]
- 55 **Caniklioglu C**, Öztürk Y. Patient discomfort: a comparison between lingual and labial fixed appliances. *Angle Orthod* 2005; **75**: 86-91 [PMID: 15747820]
- 56 **Miller KB**, McGorray SP, Womack R, Quintero JC, Perelmutter M, Gibson J, Dolan TA, Wheeler TT. A comparison of treatment impacts between Invisalign aligner and fixed appliance therapy during the first week of treatment. *Am J Orthod Dentofacial Orthop* 2007; **131**: 302.e1-302.e9 [PMID: 17346581 DOI: 10.1016/j.ajodo.2006.05.031]
- 57 **Shalish M**, Cooper-Kazar R, Ivgi I, Canetti L, Tsur B, Bachar E, Chaushu S. Adult patients' adjustability to orthodontic appliances. Part I: a comparison between Labial, Lingual, and Invisalign™. *Eur J Orthod* 2012; **34**: 724-730 [PMID: 21750242 DOI: 10.1093/ejo/cjr0862]
- 58 **Bertl MH**, Onodera K, Čelar AG. A prospective randomized split-mouth study on pain experience during chairside archwire manipulation in self-ligating and conventional brackets. *Angle Orthod* 2013; **83**: 292-297 [PMID: 22827479 DOI: 10.2319/042312-338.1]
- 59 **Tecco S**, D'Attilio M, Tetè S, Festa F. Prevalence and type of pain during conventional and self-ligating orthodontic treatment. *Eur J Orthod* 2009; **31**: 380-384 [PMID: 19465738 DOI: 10.1093/ejo/cjp003]
- 60 **Handelman CS**. Nonsurgical rapid maxillary alveolar expansion in adults: a clinical evaluation. *Angle Orthod* 1997; **67**: 291-305; discussion 306-308 [PMID: 9267578]
- 61 **Needleman HL**, Hoang CD, Allred E, Hertzberg J, Berde C. Reports of pain by children undergoing rapid palatal expansion. *Pediatr Dent* 2000; **22**: 221-226 [PMID: 10846733]
- 62 **Schuster G**, Borel-Scherf I, Schopf PM. Frequency of and complications in the use of RPE appliances--results of a survey in the Federal State of Hesse, Germany. *J Orofac Orthop* 2005; **66**:

- 148-161 [PMID: 15827702 DOI: 10.1007/s00056-005-0431-6]
- 63 **Cureton SL**. Headgear and pain. *J Clin Orthod* 1994; **28**: 525-530 [PMID: 8617835]
 - 64 **Ngan PW**, Yiu C, Hagg U, Wei SH, Bowley J. Masticatory muscle pain before, during, and after treatment with orthopedic protraction headgear: a pilot study. *Angle Orthod* 1997; **67**: 433-437 [PMID: 9428961]
 - 65 **Egolf RJ**, BeGole EA, Upshaw HS. Factors associated with orthodontic patient compliance with intraoral elastic and headgear wear. *Am J Orthod Dentofacial Orthop* 1990; **97**: 336-348 [PMID: 2321602 DOI: 10.1016/0889-5406(90)70106-M]
 - 66 **Zawawi KH**. Acceptance of orthodontic miniscrews as temporary anchorage devices. *Patient Prefer Adherence* 2014; **8**: 933-937 [PMID: 25061281 DOI: 10.2147/PPA.S66133]
 - 67 **Kuroda S**, Sugawara Y, Deguchi T, Kyung HM, Takano-Yamamoto T. Clinical use of miniscrew implants as orthodontic anchorage: success rates and postoperative discomfort. *Am J Orthod Dentofacial Orthop* 2007; **131**: 9-15 [PMID: 17208101 DOI: 10.1016/j.ajodo.2005.02.032]
 - 68 **Kawaguchi M**, Miyazawa K, Tabuchi M, Fuyamada M, Goto S. Questionnaire survey on pain and discomfort after insertion of orthodontic buccal miniscrews, palatal miniscrews and, orthodontic miniplates. *Orthodontic Waves* 2014; **73**: 1-7 [DOI: 10.1016/j.odw.2013.09.001]
 - 69 **Williams OL**, Bishara SE. Patient discomfort levels at the time of debonding: a pilot study. *Am J Orthod Dentofacial Orthop* 1992; **101**: 313-317 [PMID: 1558060 DOI: 10.1016/S0889-5406(05)80324-5]
 - 70 **Rinchuse DJ**. Pain-free debonding with occlusal rim wax. *J Clin Orthod* 1994; **28**: 587-588 [PMID: 8617816]
 - 71 **Bernhardt MK**, Southard KA, Batterson KD, Logan HL, Baker KA, Jakobsen JR. The effect of preemptive and/or postoperative ibuprofen therapy for orthodontic pain. *Am J Orthod Dentofacial Orthop* 2001; **120**: 20-27 [PMID: 11455373 DOI: 10.1067/mod.2001.115616]
 - 72 **Polat O**, Karaman AI. Pain control during fixed orthodontic appliance therapy. *Angle Orthod* 2005; **75**: 214-219 [PMID: 15825785]
 - 73 **Chumbley AB**, Tuncay OC. The effect of indomethacin (an aspirin-like drug) on the rate of orthodontic tooth movement. *Am J Orthod* 1986; **89**: 312-314 [PMID: 3083687 DOI: 10.1016/0002-9416(86)90053-9]
 - 74 **Kehoe MJ**, Cohen SM, Zarrinnia K, Cowan A. The effect of acetaminophen, ibuprofen, and misoprostol on prostaglandin E2 synthesis and the degree and rate of orthodontic tooth movement. *Angle Orthod* 1996; **66**: 339-349 [PMID: 8893104]
 - 75 **Roche JJ**, Cisneros GJ, Acs G. The effect of acetaminophen on tooth movement in rabbits. *Angle Orthod* 1997; **67**: 231-236 [PMID: 9188968]
 - 76 **Steen Law SL**, Southard KA, Law AS, Logan HL, Jakobsen JR. An evaluation of preoperative ibuprofen for treatment of pain associated with orthodontic separator placement. *Am J Orthod Dentofacial Orthop* 2000; **118**: 629-635 [PMID: 11113797 DOI: 10.1067/mod.2000.110638]
 - 77 **Lee WC**. Experimental study of the effect of prostaglandin administration on tooth movement--with particular emphasis on the relationship to the method of PGE1 administration. *Am J Orthod Dentofacial Orthop* 1990; **98**: 231-241 [PMID: 2403075 DOI: 10.1016/S0889-5406(05)81600-2]
 - 78 **Klein DC**, Raisz LG. Prostaglandins: stimulation of bone resorption in tissue culture. *Endocrinology* 1970; **86**: 1436-1440 [PMID: 4315103]
 - 79 **Leiker BJ**, Nanda RS, Currier GF, Howes RI, Sinha PK. The effects of exogenous prostaglandins on orthodontic tooth movement in rats. *Am J Orthod Dentofacial Orthop* 1995; **108**: 380-388 [PMID: 7572849 DOI: 10.1016/S0889-5406(95)70035-8]
 - 80 **Yamasaki K**, Shibata Y, Fukuhara T. The effect of prostaglandins on experimental tooth movement in monkeys (*Macaca fuscata*). *J Dent Res* 1982; **61**: 1444-1446 [PMID: 6960050]
 - 81 **Proffit WR**. Contemporary Orthodontics, 3rd Edn. The C V Mosby Company, St Louis, 2000
 - 82 **Mohri Y**, Fumoto M, Sato-Suzuki I, Umino M, Arita H. Prolonged rhythmic gum chewing suppresses nociceptive response via serotonergic descending inhibitory pathway in humans. *Pain* 2005; **118**: 35-42 [PMID: 16202533 DOI: 10.1016/j.pain.2005.07.009]
 - 83 **Hwang JY**, Tee CH, Huang AT, Taft L. Effectiveness of thera-bite wafers in reducing pain. *J Clin Orthod* 1994; **28**: 291-292 [PMID: 8613507]
 - 84 **Fujiyama K**, Deguchi T, Murakami T, Fujii A, Kushima K, Takano-Yamamoto T. Clinical effect of CO(2) laser in reducing pain in orthodontics. *Angle Orthod* 2008; **78**: 299-303 [PMID: 18251609 DOI: 10.2319/033007-153.1]
 - 85 **Tortamano A**, Lenzi DC, Haddad AC, Bottino MC, Dominguez GC, Vigorito JW. Low-level laser therapy for pain caused by placement of the first orthodontic archwire: a randomized clinical trial. *Am J Orthod Dentofacial Orthop* 2009; **136**: 662-667 [PMID: 19892282 DOI: 10.1016/j.ajodo.2008.06.028]

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Improvised technique for measuring tracheal tube cuff pressure

René Agustín Flores-Franco

René Agustín Flores-Franco, Intensive Critical Care Unit, Regional General Hospital of Zone 1, Mexican Institute of Social Security, Chihuahua PC 3000, México

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Correspondence to: René Agustín Flores-Franco, MD, Intensive Critical Care Unit, Regional General Hospital of Zone 1, Mexican Institute of Social Security, García Conde St and University Ave, Chihuahua PC 3000, México. rflores99@prontomail.com
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Abstract

We agree with the editorial published by Feng *et al* concerning the insufficient routine monitoring of tracheal tube cuff pressure (TTCP) by anesthesiologists, and propose an improvised technique that can facilitate and promote such routine monitoring by intensive care staff who attend to patients receiving mechanical ventilation. Insufficient monitoring of tracheal cuff pressure has

also been documented for intensive care unit nurses. Measurements of cuff pressure are beneficial when used in management of air leakage around an endotracheal tube, and can be easily obtained with the aid of a personalized and simple technique performed using materials that are readily available in all hospitals. Other investigators have previously demonstrated the usefulness of employing an improvised technique. We considered that possible disadvantages are similar to those encountered when using standardized equipment. With our improvised technique, we seek to promote among the nursing staff the determination of the TTCP in intubated patients to reduce the risk of related medical complications.

Key words: Endotracheal tube; Mechanical ventilation; Cuff pressure; Improvised devices; Nursing practice

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Core tip: This letter to the editor supports an opinion expressed in an article recently published in the *World Journal of Anesthesiology*. In that article, Feng *et al* mentioned that despite evidence suggesting its benefits, anesthesiologists often do not measure a patient's endotracheal tube cuff pressure. We suggest an improvised and personalized technique that can be employed to facilitate taking such measurements on a routine basis in the setting of an intensive care unit with limited resources.

Flores-Franco RA. Improvised technique for measuring tracheal tube cuff pressure. *World J Anesthesiol* 2016; 5(1): 36-37 Available from: <http://www.wjgnet.com/2218-6182/full/v5/i1/36.htm> DOI: <http://dx.doi.org/10.5313/wja.v5.i1.36>

TO THE EDITOR

We read with great interest the editorial written by Feng



Figure 1 Simple and practical technique used for determining endotracheal tube cuff pressure at our institution.

et al^[1], which stated that despite evidence supporting the benefits of monitoring tracheal tube cuff pressure (TTCP), such monitoring is not routinely performed in clinical practice. We support the point of view expressed by those authors, and believe it would be also applicable when monitoring patients in intensive care units (ICUs). Surveys performed in other centers have revealed that approximately 50% of nurses working in adult ICUs do not routinely determine TTCP, even when an audible air leak is detected^[2]. Unlike air leakage resulting from structural damage, air leakage accompanied by normal or elevated TTCP can result from partial tracheal extubation, inadvertent intratracheal placement of the gastric tube, high mean airway pressure or a discrepancy between diameters of the endotracheal tube and trachea^[3].

The high cost and limited availability of equipment specifically designed to measure cuff pressure makes such measurements difficult to perform on a routine basis in our ICUs. To overcome this problem, we have designed a simple technique for measuring cuff pressure that can be performed with readily available materials. When using this technique, a 1 mL syringe is interposed between a blood pressure manometer and the pilot balloon of the endotracheal tube (Figure 1). Optionally, a 3-way stopcock can also be interposed to add or remove air, and achieve the desired pressure level.

An additional advantage of this technique is that

the required materials can be easily disposed of after their use, and thus the risk of transmitting an infection is minimized. On the other hand, one possible disadvantage is that a small loss of air volume may occur while handling the pilot balloon; however, this can also occur when using more expensive equipment.

The effectiveness of using an improvised technique to determine TTCP has previously been demonstrated by other authors, who reported results comparable with those achieved when using standard equipment, and even better results than those achieved using the pilot balloon palpitation technique^[4]. Thus, we believe that our simple and practical method may strengthen protocols which call for measurements of TTCP in hospitals with limited resources.

REFERENCES

- 1 **Feng TR**, Ye Y, Doyle DJ. Clinical importance of tracheal tube cuff pressure management. *World J Anesthesiol* 2015; **4**: 10-12 [DOI: 10.5313/wja.v4.i2.10]
- 2 **Jordan P**, van Rooyen D, Venter D. Endotracheal tube cuff pressure management in adult critical care units. *S Afr J Crit Care* 2012; **28**: 13-16 [DOI: 10.7196/SAJCC.129]
- 3 **El-Orbany M**, Salem MR. Endotracheal tube cuff leaks: causes, consequences, and management. *Anesth Analg* 2013; **117**: 428-434 [PMID: 23744958 DOI: 10.1213/ANE.0b013e318292ee21]
- 4 **Goyal MR**, Kumar LCG, Waghray MGMR. Endotracheal tube cuff pressure monitoring in peripheral hospitals. *MJAFI* 2006; **62**: 243-245 [DOI: 10.1016/S0377-1237(06)80011-0]

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Interventional pain therapy in cervical post-surgery syndrome

Stephan Klessinger

Stephan Klessinger, Department of Neurosurgery, Nova Clinic, 88400 Biberach, Germany

Stephan Klessinger, Department of Neurosurgery, University of Ulm, 89081 Ulm, Germany

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Correspondence to: Dr. Stephan Klessinger, PD, MD, Department of Neurosurgery, Nova Clinic, Eichendorffweg 5, 88400 Biberach, Germany. klessinger@nova-clinic.de
 Telephone: +49-7351-44030
 Fax: +49-7351-440311

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Abstract

Fifteen percent to forty percent of patients present with persistent disabling neck pain or radicular pain after cervical spine surgery. Persistent pain after cervical surgery is called cervical post-surgery syndrome (CPSS). This

review investigates the literature about interventional pain therapy for these patients. Because different interventions with different anatomical targets exist, it is important to find the possible pain source. There has to be a distinction between radicular symptoms (radicular pain or radiculopathy) or axial pain (neck pain) and between persistent pain and a new onset of pain after surgery. In the case of radicular symptoms, inadequate decompression or nerve root adherence because of perineural scarring are possible pain causes. Multiple structures in the cervical spine are able to cause neck pain. Hereby, the type of surgery and also the number of segments treated is relevant. After fusion surgery, the so-called adjacent level syndrome is a possible pain source. After arthroplasty, the load of the facet joints in the index segment increases and can cause pain. Further, degenerative alterations progress. In general, two fundamentally different therapeutic approaches for interventional pain therapy for the cervical spine exist: Treatment of facet joint pain with radiofrequency denervation or facet nerve blocks, and epidural injections either *via* a transforaminal or *via* an interlaminar approach. The literature about interventions in CPSS is limited to single studies with a small number of patients. However, some evidence exists for these procedures. Interventional pain therapies are eligible as a target-specific therapy option. However, the risk of these procedures (especially transforaminal epidural injections) must be weighed against the benefit.

Key words: Post-surgery syndrome; Neck pain; Cervical epidural injections; Cervical interlaminar injections; Cervical transforaminal injections; Cervical facet joint pain; Cervical radiofrequency neurotomy; Facet joint nerve block; Epidural steroids; Local anesthetics

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Core tip: This review investigates the evidence for interventional pain therapy treatments for patients with

cervical post-surgery syndrome. Persistent pain after cervical surgery is a common problem. Interventional therapies are specific therapy options which are well investigated for patients with neck pain and radicular symptoms. Unfortunately, only single studies for patients with post-surgery syndrome exist. These studies, the different approaches (radiofrequency, facet joint nerve blocks, transforaminal and interlaminar epidural injections), and pain sources for patients after cervical surgery are discussed.

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INTRODUCTION

The indications for cervical spine surgery for degenerative findings are relatively well described as radiculopathy or myelopathy with compression of the nerve roots or spinal cord, or instability^[1,2]. The most common surgical interventions are intersomatic decompressions and fusion with a cage with or without additional anterior instrumentation^[2-7]. However, some patients who undergo spinal surgery continue to suffer pain. Persistent pain after cervical surgery is called cervical post-surgery syndrome (CPSS), and can incur increased costs to the healthcare system^[8]. CPSS occurs irrespective of the type of surgery and despite the best endeavors of the surgeon^[9]. CPSS is a cluster of clinical findings. The result fails to achieve the expected outcome of the surgery by both the patient and the surgeon^[8].

To develop therapeutic strategies for the patient with CPSS and for a specific treatment, it is important to define the source of postsurgical pain^[8,10,11]. Whether conservative management, interventional pain therapy or revision surgery are adequate depends on the cause of the pain. The rate of reoperations after the treatment of degenerative cervical spine disorders is 13.4%^[2]. Indications for revision surgery are pseudarthrosis, adjacent segment degeneration, inadequate decompression, instability, and deformity^[1,3]. If there is no indication for revision surgery or if there is a need to avoid surgery, interventional therapies are an option. Interventional pain therapy is a specific treatment for an expected pain source. Two different therapeutic approaches exist: (1) facet joint pain (the facet joints are the pain source) can be treated with medial branch blocks (MBBs) and radiofrequency (RF) neurotomy^[12-15]; (2) epidural injections are used to treat radicular pain and chronic neck pain of discogenic origin (a disc is the pain source). They are performed either by interlaminar or transforaminal approaches^[16].

While several studies about the prevalence and therapy modalities for the failed back surgery syndrome of the lumbar spine exist^[17,18], the literature about CPSS is

sparse. This review provides an overview of the available literature about interventional pain therapy for CPSS.

Prevalence

Fifteen percent to forty percent of patients after cervical spine surgery present with persistent disabling neck pain. Only two studies have revealed the prevalence of persistent neck pain in CPSS. In a study with 251 patients with persistent neck pain (45 post-surgery vs 206 nonsurgical), the prevalence of cervical facet joint pain was calculated after controlled, comparative blocks with local anesthetics with 80% pain relief as the threshold for a positive response. The positive response rate was 36%^[8]. This retrospective evaluation demonstrated a similar prevalence of facet joint pain in postsurgical and non-surgical patients. Another study of 242 patients with persistent neck pain after cervical spine surgery demonstrated a 13% prevalence of facet joint pain^[10], using a criterion of 80% pain relief after controlled MBBs as the criterion. The extent of surgery and a higher number of levels treated are risk factors for facet joint pain after surgery^[2,10].

The main indications for primary cervical spine surgery are nerve root or spinal cord compression or instability^[1]. Excellent results can be achieved for this indications^[1]. However, if the indication for surgery is expanded to axial neck pain, the number of good to excellent results for fusion decrease to only 70%^[1,3]. Thus, cervical spine surgery for axial neck pain will fail more often. Most patients with CPSS will suffer from neck pain.

Pain sources

In cases of intra-operative complications, the problem, and therefore, the pain source is often known. Possible causes are dislocation of the cage or failure of the implant, inadequate decompression or iatrogenic instability or deformities (incorrect alignment, kyphosis)^[1]. These etiologies are the most frequent reasons for revision surgery^[1]. It is necessary to distinguish between complications and patients with complaints despite optimal surgery. Often, it is challenging to discover the pain sources in patients after unremarkable surgery.

To detect the etiology of the persistent or new pain after surgery, it is important to determine whether the pain differs from the preoperative pain or if the complaints are exactly the same as before surgery. It is also necessary to elucidate whether the patient experienced a pain-free interval after surgery or if the pain was persistent. The difference between radicular symptoms and axial pain, which are distinct entities^[19], is very important.

If there is persistent radicular pain after surgery, an inadequate decompression of the nerve root or nerve root adherence because of perineural scarring are possible causes^[1,3,8]. A recurrent disc herniation after complete removal of the disc and interbody fusion is not typical; however, retention of disc material or ligament and, of course, disc herniation in an adjacent level are

conceivable. In particular, in cases with radiculopathy (sensory loss or motor weakness) further diagnostics including magnetic resonance imaging are necessary. This also applies to the new onset of radicular symptoms or the new onset of a radiculopathy.

A common situation is excellent relief of the radicular symptoms but new or persistent axial pain. Multiple structures are able to cause neck pain, including the intervertebral disc, facet joints, ligaments, fascia, and muscles, which are capable of transmitting pain^[8,16]. The type of surgery and the number of segments treated are relevant. In a review of 900 patients, anterior decompression with fusion and anterior instrumentation in one or two levels showed the lowest revision rate (11%) compared with a 32% revision rate after multi-level corpectomy with posterior instrumentation^[2]. The influence of the fusion length on the revision rate was high^[2]. Similarly, the prevalence of facet joint pain in patients with CPSS was significantly higher after double level fusions compared to single level surgery^[10].

The anterior approach is most common^[1-7]. An alternative to an interbody fusion with or without anterior instrumentation is the implantation of a disc prosthesis. After interbody fusion, the so-called "adjacent level syndrome" (the pain source is located not in the level of surgery, but in the adjacent level above or below) is a possible pain source^[1,8,10]. There is no range of motion in the index level after fusion, which has to be compensated by an increase in motion at the adjacent segments^[20]. Therefore, the incidence of disc degeneration in adjacent levels is increased^[21-23], and changes in the load on the facet joints occur^[21]. Especially during extension the force in the adjacent joints increases significantly, for which reason the joint capsules are stretched whereby pain can be provoked^[24,25]. In contrast, after arthroplasty with implantation of a disc prosthesis, the range of motion in the index segment increases (most prosthesis use a ball-socket joint). The continuing movement in the index segment protects the adjacent segments from overload; however, the forces on the facet joints increase in the index level, especially if the center of rotation of the prosthesis is not in the ideal position^[10,26]. Many of these etiologies are interrelated and arise from biomechanical derangement at the facet joints^[8], potentiated by inflammation^[3].

Furthermore, degenerative alterations of the spine can often not be changed by surgery. Particularly, the degeneration of adjacent levels can remain a painful condition as the underlying degenerative disease progresses^[10]. Another reason for CPSS is poor decision making or an inadequate indication for surgery^[1].

INTERVENTIONAL THERAPY

Generally, two fundamentally different therapeutic approaches in interventional pain therapy for the cervical spine exist: Treatment of facet joint pain (MBBs and RF neurotomy) and epidural injections (transforaminal and interlaminar).

The rationale of cervical medial branch thermal RF neurotomy is to achieve pain relief by coagulating the medial branch, which conducts the pain, and, thereby, interrupting the nociceptive pathways^[10,27]. The only prerequisite is that the pain is mediated by a cervical medial branch. Therefore, the indication for RF neurotomy is analgesic response to comparative (or controlled) diagnostic MBBs^[12,27]. MBBs are a diagnostic procedure to test whether the pain is mediated by one or more of the medial branches^[28]. The nerve is anesthetized with a small volume of local anesthetic under fluoroscopic control. Sometimes, MBBs are used in a therapeutic intention; steroids are added to the local anesthetic to treat inflammatory processes^[10-12,29-31]. Cervical epidural injections are used to treat radicular pain from a herniated disc or a spinal canal stenosis, but also to treat chronic neck pain of discogenic origin^[3,10,32]. Either transforaminal or interlaminar approaches are used.

The recent literature about cervical interventions in patients with CPSS provides some evidence, but is limited to single studies with a small number of patients (Table 1).

Thermal RF neurotomy and MBBs

Different forms of RF for spinal pain exist and can be confused with medial branch thermal RF neurotomy. Some techniques are not anatomically valid and do not produce effective thermal lesions, others use different techniques like pulsed-RF^[15]. A recent review about cervical thermal RF lesions^[15] has taken these differences into account; comprising only the indication and technique as described in the guidelines of the International Spine Intervention Society^[27,28]. Earlier studies validated the technique and became the basis for the guidelines^[33-35]. Thermal medial branch neurotomy is only done if the facet joint pain is diagnosed definitively by comparative MBBs. The face validity, construct validity and predictive validity has been demonstrated^[36-38] for comparative MBBs. Engel *et al*^[15] included six observational studies^[14,33-35,39,40] and two explanatory studies^[41,42]. Evidence shows that 63% of patients are pain-free 6 mo after RF and 38% are pain-free at one year. This effectiveness is dependent on the type of RF procedure and cannot be generalized for different techniques^[15].

Only one study (Table 1) exists evaluating the effectiveness of thermal RF neurotomy in patients with CPSS^[10]; overall, 32 patients were treated. Facet joint pain was diagnosed with single MBBs and 80% pain relief as a positive response. Here, 59% of the treated patients achieved at least 50% pain relief and 25% of the patients complete pain relief with a mean follow-up time of 15 mo. It has to be taken into account that patients might have different pain sources at the same time after surgery. Therefore, 59% satisfying pain relief is important for patients with a diagnosis for which there are few specific therapy options^[10].

Although MBBs are actually a diagnostic tool, facet joint nerve blocks are sometimes used in a therapeutic intention^[10-12,29-31], because some studies show en-

Table 1 Studies of patients with cervical post-surgery syndrome treated with interventional therapies

Ref.	Interventions	Outcome measures	Number of patients	Follow-up period	Positive results
Klessinger ^[10]	Thermal radiofrequency neurotomy	Pain relief $\geq$ 50%	32	15 mo	59% of patients $\geq$ 50% pain relief
Klessinger ^[11]	Facet joint nerve block	Pain relief $\geq$ 80% or satisfied patient	104	6 mo	53% satisfying result
Manchikanti <i>et al</i> ^[3]	Interlaminar, epidural	Pain relief $\geq$ 50% Improvement in functional status	56	1 yr	71% of patients local anesthetic 64% of patients local anesthetic with steroid

couraging results^[29,30]. A recent study^[31] reveals Level II evidence for the long-term effectiveness of facet joint nerve blocks in managing cervical facet joint pain. In a single study (Table 1) of 104 patients with CPSS, 53% of the patients treated with facet joint nerve blocks, using local anesthetic and a steroid, reported a satisfying result after single injection^[11].

Epidural injections

The evidence for cervical epidural injections is a subject of debate and depends on, whether an interlaminar or a transforaminal approach was chosen. For the interlaminar approach, a recent review^[43] including eight randomized controlled studies^[3,44-50] was performed. The evidence for the management of a cervical disc herniation, discogenic pain, or spinal canal stenosis is Level II (evidence from at least one relevant high quality randomized controlled trial or multiple relevant moderate or low quality randomized trials)^[43]. For the transforaminal approach, the review of Engel *et al*^[51] found six primary papers^[52-57] presenting the effectiveness of transforaminal injections. The evidence was found to be of low quality^[51]. The outcome in the different studies shows moderate effectiveness. However, the number of reports of severe complications (spinal cord infarction, cerebral ischemia, quadriplegia, seizures) increases^[51]. Therefore, cervical transforaminal injections are not strongly recommended. When comparing the interlaminar and the transforaminal approach, better evidence and less reports of severe complications make the interlaminar approach superior^[43,51]. The main advantage of the transforaminal approach is the selection of a single nerve root which. Therefore, the result after transforaminal injection can be helpful for the decision, which level is eligible for surgery.

Patients with CPSS are sporadically included in studies about the effectiveness of epidural injections^[35,47,48,58]. Only one trial (Table 1) evaluated the effect of interlaminar epidural injections explicitly in patients after surgery^[3]. The randomized, double-blind study with a one-year follow-up of 56 patients with CPSS demonstrated a minimum pain relief of 50% and improvement in functional status in 71% of patients receiving local anesthetic only and in 64% of patients receiving steroids and local anesthetic. The average duration of pain relief was 12 to 15 wk after two initial injections. The evidence for CPSS is assessed as Level III (evidence from one nonrandomized trial with multiple observational studies)^[43].

CONCLUSION

Persistent pain after cervical spine surgery is a frequent problem. Interventional pain therapies are eligible as a target-specific therapy option. Both, facet joint interventions and epidural injections are used. Some evidence exists for these procedures. However, the risk of these procedures (especially transforaminal epidural injections) must be weighed against the benefit. Patients with CPSS are sporadically included in evaluations about the effectiveness of cervical injections. In addition, regarding thermal RF neurotomy, therapeutic MBBs, and interlaminar epidural injections only single studies exist that specifically follow-up CPPS patients. Further studies focusing on CPPS patients are necessary.

REFERENCES

- 1 Helgeson MD, Albert TJ. Surgery for failed cervical spine reconstruction. *Spine* (Phila Pa 1976) 2012; **37**: E323-E327 [PMID: 22076644 DOI: 10.1097/BRS.0b013e31823ec9d2]
- 2 Greiner-Perth R, Allam Y, El-Saghir H, Röhl F, Franke J, Böhm H. Analysis of reoperations after surgical treatment of degenerative cervical spine disorders: a report on 900 cases. *Cent Eur Neurosurg* 2009; **70**: 3-8 [PMID: 19191203 DOI: 10.1055/s-0028-1082061]
- 3 Manchikanti L, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic cervical interlaminar epidural injections in managing chronic pain of cervical postsurgery syndrome: preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; **15**: 13-25 [PMID: 22270734]
- 4 Wang MC, Chan L, Maiman DJ, Kreuter W, Deyo RA. Complications and mortality associated with cervical spine surgery for degenerative disease in the United States. *Spine* (Phila Pa 1976) 2007; **32**: 342-347 [PMID: 17268266 DOI: 10.1097/01.brs.0000254120.25411.ae]
- 5 Patil PG, Turner DA, Pietrobon R. National trends in surgical procedures for degenerative cervical spine disease: 1990-2000. *Neurosurgery* 2005; **57**: 753-758; discussion 753-758 [PMID: 16239888 DOI: 10.1227/01.NEU.0000175729.79119.1d]
- 6 Irwin ZN, Hilibrand A, Gustavel M, McLain R, Shaffer W, Myers M, Glaser J, Hart RA. Variation in surgical decision making for degenerative spinal disorders. Part II: cervical spine. *Spine* (Phila Pa 1976) 2005; **30**: 2214-2219 [PMID: 16205349 DOI: 10.1097/01.brs.0000181056.76595.f7]
- 7 Shamji MF, Cook C, Pietrobon R, Tackett S, Brown C, Isaacs RE. Impact of surgical approach on complications and resource utilization of cervical spine fusion: a nationwide perspective to the surgical treatment of diffuse cervical spondylosis. *Spine J* 2009; **9**: 31-38 [PMID: 18790678 DOI: 10.1016/j.spinee.2008.07.005]
- 8 Manchikanti L, Manchikanti KN, Pampati V, Brandon DE, Giordano J. The prevalence of facet-joint-related chronic neck pain in postsurgical and nonpostsurgical patients: a comparative evaluation. *Pain Pract* 2008; **8**: 5-10 [PMID: 18211589 DOI: 10.1111/j.1533-2500.2007.00169.x]

- 9 **Klessinger S.** Zygapophysial joint pain in post lumbar surgery syndrome. The efficacy of medial branch blocks and radiofrequency neurotomy. *Pain Med* 2013; **14**: 374-377 [PMID: 23241083 DOI: 10.1111/pme.12012]
- 10 **Klessinger S.** Radiofrequency neurotomy for the treatment of therapy-resistant neck pain after ventral cervical operations. *Pain Med* 2010; **11**: 1504-1510 [PMID: 20807342 DOI: 10.1111/j.1526-4637.2010.00942.x]
- 11 **Klessinger S.** The benefit of therapeutic medial branch blocks after cervical operations. *Pain Physician* 2010; **13**: 527-534 [PMID: 21102965]
- 12 **Falco FJ,** Erhart S, Wargo BW, Bryce DA, Atluri S, Datta S, Hayek SM. Systematic review of diagnostic utility and therapeutic effectiveness of cervical facet joint interventions. *Pain Physician* 2008; **12**: 323-344 [PMID: 19305483]
- 13 **Kirpalani D,** Mitra R. Cervical facet joint dysfunction: a review. *Arch Phys Med Rehabil* 2008; **89**: 770-774 [PMID: 18374011 DOI: 10.1016/j.apmr.2007.11.028]
- 14 **MacVicar J,** Borowczyk JM, MacVicar AM, Loughnan BM, Bogduk N. Cervical medial branch radiofrequency neurotomy in New Zealand. *Pain Med* 2012; **13**: 647-654 [PMID: 22458772 DOI: 10.1111/j.1526-4637.2012.01351.x]
- 15 **Engel A,** Rappard G, King W, Kennedy DJ; Standards Division of the International Spine Intervention Society. The Effectiveness and Risks of Fluoroscopically-Guided Cervical Medial Branch Thermal Radiofrequency Neurotomy: A Systematic Review with Comprehensive Analysis of the Published Data. *Pain Med* 2015 [PMID: 26359589 DOI: 10.1111/pme.12928]
- 16 **Diwan S,** Manchikanti L, Benyamin RM, Bryce DA, Geffert S, Hameed H, Sharma ML, Abdi S, Falco FJ. Effectiveness of cervical epidural injections in the management of chronic neck and upper extremity pain. *Pain Physician* 2012; **15**: E405-E434 [PMID: 22828692]
- 17 **Bordoni B,** Marelli F. Failed back surgery syndrome: review and new hypotheses. *J Pain Res* 2016; **9**: 17-22 [PMID: 26834497 DOI: 10.2147/JPR.S96754]
- 18 **Chan CW,** Peng P. Failed back surgery syndrome. *Pain Med* 2011; **12**: 577-606 [PMID: 21463472 DOI: 10.1111/j.1526-4637.2011.01089.x]
- 19 **Bogduk N.** The anatomy and pathophysiology of neck pain. *Phys Med Rehabil Clin N Am* 2011; **22**: 367-382, vii [PMID: 21824580 DOI: 10.1016/j.pmr.2011.03.008]
- 20 **Chang UK,** Kim DH, Lee MC, Willenberg R, Kim SH, Lim J. Range of motion change after cervical arthroplasty with ProDisc-C and prestige artificial discs compared with anterior cervical discectomy and fusion. *J Neurosurg Spine* 2007; **7**: 40-46 [PMID: 17633486 DOI: 10.3171/SPI-07/07/040]
- 21 **Chang UK,** Kim DH, Lee MC, Willenberg R, Kim SH, Lim J. Changes in adjacent-level disc pressure and facet joint force after cervical arthroplasty compared with cervical discectomy and fusion. *J Neurosurg Spine* 2007; **7**: 33-39 [PMID: 17633485 DOI: 10.3171/SPI-07/07/033]
- 22 **Bohlman HH,** Emery SE, Goodfellow DB, Jones PK. Robinson anterior cervical discectomy and arthrodesis for cervical radiculopathy. Long-term follow-up of one hundred and twenty-two patients. *J Bone Joint Surg Am* 1993; **75**: 1298-1307 [PMID: 8408151]
- 23 **Hilibrand AS,** Carlson GD, Palumbo MA, Jones PK, Bohlman HH. Radiculopathy and myelopathy at segments adjacent to the site of a previous anterior cervical arthrodesis. *J Bone Joint Surg Am* 1999; **81**: 519-528 [PMID: 10225797]
- 24 **Yang KH,** King AI. Mechanism of facet load transmission as a hypothesis for low-back pain. *Spine (Phila Pa 1976)* 1984; **9**: 557-565 [PMID: 6238423 DOI: 10.1097/00007632-198409000-00005]
- 25 **Cavanaugh JM,** Ozaktay AC, Yamashita HT, King AI. Lumbar facet pain: biomechanics, neuroanatomy and neurophysiology. *J Biomech* 1996; **29**: 1117-1129 [PMID: 8872268 DOI: 10.1016/0021-9290(96)00023-1]
- 26 **Pickett GE,** Rouleau JP, Duggal N. Kinematic analysis of the cervical spine following implantation of an artificial cervical disc. *Spine (Phila Pa 1976)* 2005; **30**: 1949-1954 [PMID: 16135984 DOI: 10.1097/01.brs.0000176320.82079.ce]
- 27 **International Spine Intervention Society.** Cervical Medial Branch Thermal Radiofrequency Neurotomy. In: Bogduk N (ed). Practice Guidelines for Spinal Diagnostic and Treatment Procedures, 2nd edn. International Spine Intervention Society, San Francisco, 2013, 165-209
- 28 **International Spine Intervention Society.** Cervical Medial Branch Blocks. In: Bogduk N (ed). Practice Guidelines for Spinal Diagnostic and Treatment Procedures, 2nd edn. International Spine Intervention Society, San Francisco, 2013, 101-140
- 29 **Boswell MV,** Colson JD, Sehgal N, Dunbar EE, Epter R. A systematic review of therapeutic facet joint interventions in chronic spinal pain. *Pain Physician* 2007; **10**: 229-253 [PMID: 17256032]
- 30 **Manchikanti L,** Damron K, Cash K, Manchukonda R, Pampati V. Therapeutic cervical medial branch blocks in managing chronic neck pain: a preliminary report of a randomized, double-blind, controlled trial: clinical trial NCT0033272. *Pain Physician* 2006; **9**: 333-346 [PMID: 17066118]
- 31 **Manchikanti L,** Hirsch JA, Kaye AD, Boswell MV. Cervical zygapophysial (facet) joint pain: effectiveness of interventional management strategies. *Postgrad Med* 2016; **128**: 54-68 [PMID: 26653406 DOI: 10.1080/00325481.2016.1105092]
- 32 **Manchikanti L,** Falco FJ, Diwan S, Hirsch JA, Smith HS. Cervical radicular pain: the role of interlaminar and transforaminal epidural injections. *Curr Pain Headache Rep* 2014; **18**: 389 [PMID: 24338702 DOI: 10.1007/s11916-013-0389-9]
- 33 **Govind J,** King W, Bailey B, Bogduk N. Radiofrequency neurotomy for the treatment of third occipital headache. *J Neurol Neurosurg Psychiatry* 2003; **74**: 88-93 [PMID: 12486273 DOI: 10.1136/jnnp.74.1.88]
- 34 **Lord SM,** McDonald GJ, Bogduk N. Percutaneous radiofrequency neurotomy of the cervical medial branches: A validated treatment for cervical zygapophysial joint pain. *Neurosurg Q* 1988; **8**: 288-308 [DOI: 10.1097/00013414-199812000-00004]
- 35 **McDonald GJ,** Lord SM, Bogduk N. Long-term follow-up of patients treated with cervical radiofrequency neurotomy for chronic neck pain. *Neurosurgery* 1999; **45**: 61-67; discussion 67-68 [PMID: 10414567 DOI: 10.1097/00006123-199907000-00015]
- 36 **Barnsley L,** Bogduk N. Medial branch blocks are specific for the diagnosis of cervical zygapophyseal joint pain. *Reg Anesth* 1993; **18**: 343-350 [PMID: 8117629]
- 37 **Barnsley L,** Lord S, Wallis B, Bogduk N. False-positive rates of cervical zygapophysial joint blocks. *Clin J Pain* 1993; **9**: 124-130 [PMID: 8358135 DOI: 10.1097/00002508-199306000-00007]
- 38 **Barnsley L,** Lord S, Bogduk N. Comparative local anaesthetic blocks in the diagnosis of cervical zygapophysial joint pain. *Pain* 1993; **55**: 99-106 [PMID: 8278215 DOI: 10.1016/0304-3959(93)90189-V]
- 39 **Lord SM,** Barnsley L, Bogduk N. Percutaneous radiofrequency neurotomy in the treatment of cervical zygapophysial joint pain: a caution. *Neurosurgery* 1995; **36**: 732-739 [PMID: 7596504 DOI: 10.1227/00006123-199504000-00014]
- 40 **Barnsley L.** Percutaneous radiofrequency neurotomy for chronic neck pain: outcomes in a series of consecutive patients. *Pain Med* 2005; **6**: 282-286 [PMID: 16083457 DOI: 10.1111/j.1526-4637.2005.00047.x]
- 41 **Lord SM,** Barnsley L, Wallis BJ, McDonald GJ, Bogduk N. Percutaneous radio-frequency neurotomy for chronic cervical zygapophyseal-joint pain. *N Engl J Med* 1996; **335**: 1721-1726 [PMID: 8929263 DOI: 10.1056/NEJM199612053352302]
- 42 **Wallis BJ,** Lord SM, Bogduk N. Resolution of psychological distress of whiplash patients following treatment by radiofrequency neurotomy: a randomised, double-blind, placebo-controlled trial. *Pain* 1997; **73**: 15-22 [PMID: 9414052 DOI: 10.1016/S0304-3959(97)00060-2]
- 43 **Kaye AD,** Manchikanti L, Abdi S, Atluri S, Bakshi S, Benyamin R, Boswell MV, Buenaventura R, Candido KD, Cordner HJ, Datta S, Doulatram G, Gharibo CG, Grami V, Gupta S, Jha S, Kaplan ED, Malla Y, Mann DP, Nampiaparampil DE, Racz G, Raj P, Rana MV,

- Sharma ML, Singh V, Soin A, Staats PS, Vallejo R, Wargo BW, Hirsch JA. Efficacy of Epidural Injections in Managing Chronic Spinal Pain: A Best Evidence Synthesis. *Pain Physician* 2015; **18**: E939-1004 [PMID: 26606031]
- 44 **Manchikanti L**, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic epidural injections in cervical spinal stenosis: preliminary results of a randomized, double-blind, active control trial. *Pain Physician* 2012; **15**: E59-E70 [PMID: 22270749]
- 45 **Manchikanti L**, Cash KA, Pampati V, Malla Y. Two-year follow-up results of fluoroscopic cervical epidural injections in chronic axial or discogenic neck pain: a randomized, double-blind, controlled trial. *Int J Med Sci* 2014; **11**: 309-320 [PMID: 24578607 DOI: 10.7150/ijms.8069]
- 46 **Manchikanti L**, Cash KA, Pampati V, Wargo BW, Malla Y. A randomized, double-blind, active control trial of fluoroscopic cervical interlaminar epidural injections in chronic pain of cervical disc herniation: results of a 2-year follow-up. *Pain Physician* 2013; **16**: 465-478 [PMID: 24077193]
- 47 **Castagnera L**, Maurette P, Pointillart V, Vital JM, Erny P, S  n  gas J. Long-term results of cervical epidural steroid injection with and without morphine in chronic cervical radicular pain. *Pain* 1994; **58**: 239-243 [PMID: 7816491 DOI: 10.1016/0304-3959(94)90204-6]
- 48 **Stav A**, Ovadia L, Sternberg A, Kaadan M, Weksler N. Cervical epidural steroid injection for cervicobrachialgia. *Acta Anaesthesiol Scand* 1993; **37**: 562-566 [PMID: 8213020 DOI: 10.1111/j.1399-6576.1993.tb03765.x]
- 49 **Pasqualucci A**, Varrassi G, Braschi A, Peduto VA, Brunelli A, Marinangeli F, Gori F, Col   F, Paladini A, Mojoli F. Epidural local anesthetic plus corticosteroid for the treatment of cervical brachial radicular pain: single injection versus continuous infusion. *Clin J Pain* 2007; **23**: 551-557 [PMID: 17710003 DOI: 10.1097/AJP.0b013e318074c95c]
- 50 **Cohen SP**, Hayek S, Semenov Y, Pasquina PF, White RL, Veizi E, Huang JH, Kurihara C, Zhao Z, Guthmiller KB, Griffith SR, Verdun AV, Giampetro DM, Vorobeychik Y. Epidural steroid injections, conservative treatment, or combination treatment for cervical radicular pain: a multicenter, randomized, comparative-effectiveness study. *Anesthesiology* 2014; **121**: 1045-1055 [PMID: 25335172 DOI: 10.1097/ALN.0000000000000409]
- 51 **Engel A**, King W, MacVicar J. The effectiveness and risks of fluoroscopically guided cervical transforaminal injections of steroids: a systematic review with comprehensive analysis of the published data. *Pain Med* 2014; **15**: 386-402 [PMID: 24308846 DOI: 10.1111/pme.12304]
- 52 **Vall  e JN**, Feydy A, Carlier RY, Mutschler C, Mompont D, Vall  e CA. Chronic cervical radiculopathy: lateral-approach periradicular corticosteroid injection. *Radiology* 2001; **218**: 886-892 [PMID: 11230671 DOI: 10.1148/radiology.218.3.r01mr17886]
- 53 **Kolstad F**, Leivseth G, Nygaard OP. Transforaminal steroid injections in the treatment of cervical radiculopathy. A prospective outcome study. *Acta Neurochir (Wien)* 2005; **147**: 1065-1070; discussion 1070 [PMID: 15924210 DOI: 10.1007/s00701-005-0542-2]
- 54 **Dreyfuss P**, Baker R, Bogduk N. Comparative effectiveness of cervical transforaminal injections with particulate and nonparticulate corticosteroid preparations for cervical radicular pain. *Pain Med* 2006; **7**: 237-242 [PMID: 16712623 DOI: 10.1111/j.1526-4637.2006.00162.x]
- 55 **Razzaq AA**, O'Brien D, Mathew B, Bartlett R, Taylor D. Efficacy and durability of fluoroscopically guided cervical nerve root block. *Br J Neurosurg* 2007; **21**: 365-369 [PMID: 17676456 DOI: 10.1080/02688690701434634]
- 56 **Lee JH**, Lee SH. Comparison of clinical effectiveness of cervical transforaminal steroid injection according to different radiological guidances (C-arm fluoroscopy vs. computed tomography fluoroscopy). *Spine J* 2011; **11**: 416-423 [PMID: 21558036 DOI: 10.1016/j.spinee.2011.04.004]
- 57 **Persson L**, Anderberg L. Repetitive transforaminal steroid injections in cervical radiculopathy: a prospective outcome study including 140 patients. *Evid Based Spine Care J* 2012; **3**: 13-20 [PMID: 23531493]
- 58 **Benyamin RM**, Singh V, Parr AT, Conn A, Diwan S, Abdi S. Systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain. *Pain Physician* 2009; **12**: 137-157 [PMID: 19165300]

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Anaesthesia for patients with arrhythmogenic right ventricular dysplasia

Ivett Blaskovics, Kamen Valchanov

Ivett Blaskovics, Kamen Valchanov, Department of Anaesthesia and Intensive Care, Papworth Hospital, Cambridge CB23 3RE, United Kingdom

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Correspondence to: Kamen Valchanov, MD, FRCA, FFICM, Department of Anaesthesia and Intensive Care, Papworth Hospital, Papworth Everard, Cambridge CB23 3RE, United Kingdom. kamen.valchanov@papworth.nhs.uk
Telephone: +44-1480-364406
Fax: +44-1480-364936

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Abstract

Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited heart muscle disease. Myocyte apoptosis and fibro-fatty scar tissue predisposes patients to malignant ventricular arrhythmias. Patients may present to variety of surgical procedures with diagnosed ARVD. Surgical insult, catecholamine surge and physiological

disturbance can be hazardous on the vulnerable myocardium and may result in life-threatening ventricular tachycardia or sudden cardiac death in the perioperative period. Anaesthetists have particular role in perioperative management of this patient population, meticulous perioperative planning, close haemodynamic monitoring and maintenance of physiological stability throughout helps to avoid devastating perioperative loss.

Key words: Arrhythmogenic right ventricular dysplasia; Arrhythmogenic cardiomyopathy; Anaesthesia

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Core tip: Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited disease of the cardiac muscle, characterised by progressive myocyte death and scarring of the myocardium associated with ventricular tachycardia and sudden cardiac death. Electrical instability is exacerbated by physiological changes induced by surgical insult and may lead to unexpected perioperative death. Careful anaesthetic management can minimise stress response and reduce the incidence of malignant ventricular arrhythmias in the perioperative period. In this article we discuss the available literature with the aim to provide some guidance for the clinical anaesthetist encountering patient with ARVD.

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INTRODUCTION

Arrhythmogenic right ventricular dysplasia (ARVD) is inherited cardiomyopathy characterised by progressive

death of the myocytes most commonly in the right ventricle. Fibro-fatty replacement of the myocardium forms scar tissue causes malignant ventricular arrhythmias, sudden cardiac death (SCD), or cardiac failure. In the late stages it affects both left and right ventricles. Early diagnosis could offer control over progress of the disease and prevention of malignant arrhythmias and cardiac arrest. Once arrhythmia control is achieved ARVD could become a stable condition^[1,2].

Patients with ARVD undergo variety of surgical procedures in their life span. This is why the condition is of a particular interest for anaesthetists and perioperative physicians. Physiological changes and medication in the perioperative period may have proarrhythmic effect. Surgical insult activates stress response with catecholamine surge while adverse effects of anaesthetic agents induce significant cardiovascular instability.

ARVD have autosomal dominant inheritance pattern with an estimated prevalence rate of 1:5000 that may be underestimated. Forensic autopsy following unexpected perioperative death in young individuals proved ARVD in eighteen out of fifty patients^[3]. It is common enough for most anaesthetists to encounter a patient with ARVD at some point in their career either: (1) In the subclinical stage, leading to sudden perioperative death in seemingly healthy patients undergoing low-risk surgical intervention. In such cases post mortem examination could confirm the diagnosis of ARVD; or (2) in patients with established diagnosis of ARVD presenting for elective or emergency surgical procedure. Disease may be in the early or advanced stage at the time of presentation, symptoms may be well or poorly controlled.

Literature on the management of ARVD in the anaesthetic practice is based on a small number of individual case reports describing anaesthetic technique used in patients with subclinical or diagnosed ARVD. Straightforward link between anaesthetic agents and perioperative mortality is difficult to establish. Previously uneventful general or regional anaesthesia does not exclude ARVD. It could be that perioperative death is associated with physiological instability, rather than administration individual anaesthetic agent. Majority of the recommendations on perioperative management of these patients are based on case reports when many things have gone wrong, and it is difficult to untangle whether a particular medication was a culprit. Not many anaesthetists have had frequent exposure to ARVD patients to be able to scientifically approach the management. In this review we will discuss the literature on presentation and perioperative management of these patients, and add some of the experience of our centre where there is an unusually high concentration of ends stage cardiac failure ARVD patients.

PATHOGENESIS AND GENETICS

ARVD in an heritable cardiac muscle disease, most

commonly follows autosomal dominant inheritance with variable penetrance in families and wide spectrum of disease severity^[4]. ARVD does not present at birth. Symptoms develop in adolescence, and diagnosis is commonly made in the second and third decade of life. ARVD affects young men three times more frequently than women and an important cause of SCD in young adults and athletes^[5-7].

ARVD incidence remains unclear, prevalence is estimated between 1 in 2000-5000 showing high variability between geographical regions. Positive family history presents in up to 50% of the cases. High incidence was observed in Vento region of Italy where forensic autopsy proved ARVD behind SCD in 20% of the cases^[8,9]. Autosomal recessive forms are less common, Naxos disease is associated with palmoplantar keratosis and severe cardiac features^[10].

ARVD develops due to desmosomal and non-desmosomal gene mutation. Gene mutation alters protein synthesis. Desmosomes (also called macula densa) are the structural and functional units of the heart muscle cell, connecting cells in the intercalate discs and mediating intracellular signal conduction. Disrupted desmosomal structure cannot withstand physical activity and shear forces and induces cardiomyocyte death. Apoptotic cells are replaced with fibro-fatty tissue causing increased excitability and structural abnormality. Initially focal process becomes generalised leaving extensive scar tissue with scattered residual myocytes within the thin ventricular wall. Gene mutation alters the structure of the following five desmosomal proteins: Plakoglobin, Desmoplakin, Plakophilin, Desmoglein and Desmocollin.

Non-desmosomal gene mutations are also found to be linked to ARVD. Ryanodine receptor-2 mutation causes ryanodine receptor dysfunction and alter intracellular calcium release from the sarcoplasmic reticulum. Transforming growth factor-B3 gene mutation may have a role in myocardial fibrosis whilst *TMEM43* gene mutation may cause dysregulation in adipogenic pathway and induces fibro-fatty replacement of the cardiomyocytes^[2,11,12].

DIAGNOSIS

ARVD is difficult to diagnose when asymptomatic. First presentation is cardiac arrest in up to 50% of the clinical cases. Post mortem examination confirms fibro-fatty histology. Screening of family members is important to identify and risk stratify genetically affected relatives to prevent SCD.

Diagnostic test specific for ARVD has not been invented. In 1994, the International Task Force proposed the first diagnostic criteria system and combined multiple diagnostic information (structural, histological, arrhythmic, echocardiographic, genetic and familial features). This system highly specific but failed to identify early, asymptomatic and familial cases. International Task Force Criteria has been modified in 2010. Diagnosis was based on the combination of major and

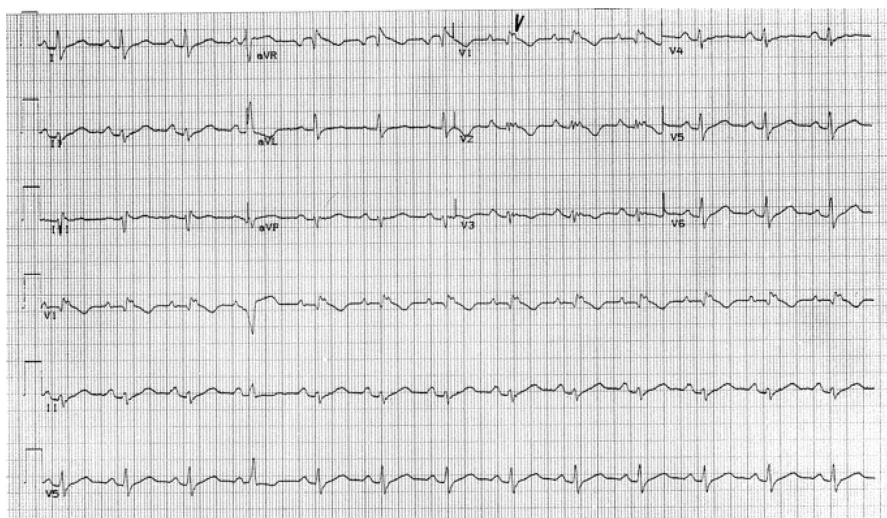


Figure 1 Twelve-lead electrocardiogram leads with regular sinus rhythm and an epsilon waves (arrow) in leads V1-V3.

minor criteria^[13].

Electrocardiogram (ECG) abnormalities observed include T-wave inversion in anterior precordial leads, left axis deviation, wide QRS complexes and epsilon waves. Ventricular tachy-arrhythmias may present in a wide spectrum on resting ECG from premature ventricular extrasystoles, non-sustained ventricular tachycardia and monomorphic ventricular tachyarrhythmia with left bundle branch block.

Echocardiography may detect regional or global dysfunction, predominantly affecting the RV. RV wall thinning and dilation with tricuspid regurgitation are the features of advanced right heart failure.

Cardiac magnetic resonance imaging (MRI) is a non-specific diagnostic modality, however allows reliable quantification of the right ventricle volume however may fail to detect the ventricular adipose tissue and wall thinning accurately.

Right ventricular angiogram is considered a reliable invasive method for evaluating regional right ventricular wall motional abnormality. Cardiac MRI and 3D Echocardiography are non-invasive and preferred over right ventricular angiography for assessing morphology and functional abnormalities of the right ventricle^[14].

Ventricular biopsy may confirm the suspected diagnosis of ARVD however negative biopsy should be interpreted with caution. Myocardial sample may be unreliable as ARVD often does not involve the subendocardium whilst the myocardium exhibits patchy involvement. Negative biopsy does not exclude the diagnosis of ARVD^[15]. Involvement of a specialist pathologist experienced in this condition is important.

Immunohistochemical analysis: Reference diagnostic test highly sensitive and specific to ARVD would provide accurate early diagnosis in asymptomatic cases. Immunohistochemical analysis of plakoglobin in the intercalate discs found reduced signal level in patients with ARVD and may be of value in diagnosing ARVD^[16,17] (Figure 1).

TREATMENT

Current data suggest that asymptomatic patients with established ARVD do not benefit from prophylactic therapeutic interventions.

Once the clinical diagnosis of ARVD is established, treatment modalities target three main goals.

Life-style modification

Clinical evidence suggests the strenuous physical exercise accelerates myocyte apoptosis and increase the risk of SDC in competitive athletes. Physical exercise may also be responsible for "hot disease phase" when myocyte atrophy accelerates. This phase is characterised by increased excitability^[18,19]. Restriction from strenuous exercise and competitive sports is thought to be slow down myocardial cell death.

Prevention or effective termination of recurrent arrhythmias

Ventricular arrhythmias manifest in a wide spectrum. Sporadic premature ventricular extrasystole may progress to non-sustained or sustained ventricular tachycardia and VF. VF leads to sudden cardiac arrest. Long term arrhythmia control may be achieved with implantable cardioverter defibrillator (ICD) alone or in combination with antiarrhythmic drugs.

The effect of β -blockers or Amiodarone in treatment of sustained VT has been proven. Sotalol provides the most effective arrhythmia control. Amiodarone is usually preserved for advance heart failure. In combination with B-blocker its efficacy is comparable to Sotalol^[20,21].

ICD is considered for primary prevention in high risk cases and proved to be successful when cardiac dysfunction occurs. However ICD for ARVD treatment will require long term follow up and may be complicated with adverse effects associated with procedures. When cardiac failure is a problem the ICD can be also used as a biventricular re-synchronisation therapy too^[22].

Catheter ablation: Developing fibro-fatty scar tissue with scattered myocytes increases the risk of re-entrant tachycardia. Catheter ablation is reserved for patients with recurrent ventricular arrhythmia not responsive to pharmacological treatment as it only offers short-term success, long-term efficacy remained debatable^[23].

Cardiac failure

Symptomatic heart failure is rare and occurs predominantly in advanced stage. Cardiac failure should be treated in conjunction with conventional heart failure guidelines, most commonly with angiotensin-converting enzyme inhibitors, diuretics, digoxin and anticoagulants. In the rare occasions, when heart failure is unresponsive to medical management, heart transplantation may be necessary.

ANAESTHETIC CONSIDERATIONS

Given a prevalence rate of 1:5000, most anaesthetists will encounter a patient with ARVD during their practice. SDC during general anaesthesia is unresponsive to cardiopulmonary resuscitation. Disease awareness, understanding pathophysiology and hazardous conditions help improve safety in these patients. Perioperative management is divided in two groups: For patients with already diagnosed ARVD, and for patients who present with malignant arrhythmias and SDC.

Preoperative management

Preoperative evaluation of patients with ARVD should include collecting medical history, documenting physical findings and obtaining specialized diagnostic tests. All elective patients must be consulted with a cardiologist with experience with the disease. History of provoked arrhythmias and safe medication is essential.

Subclinical stage of ARVD is symptomless or characterised by non-specific clinical symptoms such as palpitation, chest pain and syncope. Linking these features to a rare cardiac muscle disease may be difficult. Previous uneventful general or regional anaesthesia does not exclude ARVD^[24]. ECG is not used for routine assessment in young and healthy patients.

Patient with confirmed diagnosis of ARVD should undergo regular follow up to evaluate efficacy of arrhythmia control and cardiac function. Review of case notes and discussion with a cardiologist would enable the anaesthetist to gain information about the course of the disease. Physical examination carries limited significance in early stages, signs and symptoms of systemic or pulmonary congestion become apparent in advanced stage. Twenty-four hour holter-monitor is a reliable non-invasive method to discover sustained and non-sustained ventricular tachycardia. Echocardiography is available in most institutions to offer a quick insight to cardiac function. Preoperative optimisation carries high impact on perioperative mortality. Multidisciplinary team approach including cardiologist, anaesthetist and operating surgeon facilitate safe perioperative planning.

Elective procedure should be postponed until ventricular arrhythmia controlled and heart failure is optimised. Regular anti-arrhythmic drugs should be continued until surgery. Patient with ICD should undergo device check to assess optimal function and number of appropriate ICD discharges. Electrical safety may warrant inactivation of the device in the immediate preoperative period^[25].

Intraoperative management

Maintaining haemodynamic state near to the normal physiological conditions is likely to offer best arrhythmia protection. Close haemodynamic monitoring is essential for early recognition of physiological instability and assessment cardiovascular response to intervention. Routine monitoring with ECG, oxygen saturation probe, non-invasive blood pressure cuff and capnography may be supplemented with invasive arterial blood pressure cannula even in case of minor surgical procedures. Invasive arterial pressure monitoring will allow for blood pressure monitoring even in the face of arrhythmia, when NIBP could be unreliable. Major interventions warrant more invasive monitoring. Central venous pressure provides information about right heart function and filling status. The role of pulmonary artery catheters may be controversial outside specialised cardiothoracic institutions due to induction of malignant ventricular arrhythmia and ventricular perforation during placement. However, intraoperative transoesophageal echocardiography offers superior diagnostic and avoids risks of arrhythmia. Less invasive forms of continuous cardiac output monitoring allow assessment of contractility, ventricular filling.

Malignant ventricular arrhythmia and SCD could occur at induction of general anaesthesia, during the surgical procedure or in the immediate postoperative stage. Therefore, appropriate post-operative monitoring and care locations must be chosen according to institutional organisation.

Safe anaesthetic management is facilitated by the following two principles

Understanding the pharmacokinetics and adverse effects of the anaesthetic agents: Hemodynamic variation during anaesthesia is related to specific effects of the anaesthetic agents on the sympathetic nervous system. Patient with extensive sympathetic blockade are prone to develop reduced systemic vascular resistance, reduced cardiac output and severe arterial hypotension.

Midazolam causes little direct myocardial depression and was reported to be safe for sedation in conjunction with opioid analgesics or for induction of general anaesthesia in combination with a different induction agent^[26]. However in two case reports administration of Midazolam was associated with perioperative death^[27,28]. Propofol is known to induce significant arterial hypotension and myocardial suppression. Judicious dosing or slow infusion for induction may help to overcome these

unfavourable pharmacological properties making it one of the commonly used induction agent. Maintenance of general anaesthesia using Propofol gains increasing popularity. Case reports describe Propofol as a safe agent for induction^[27] and maintenance of general anaesthesia^[26]. Ketamine has a stable haemodynamic profile however anticholinergic effect can result in sinus tachycardia.

Opioid analgesia should be selected carefully. Perioperative death in patients with diagnosed ARVD was reported after administration of Sufentanyl^[28]. Fentanyl is considered to be safe^[28,29]. High dose of Fentanyl was used in a cardiothoracic patient population^[26].

Volatile anaesthetic agents should be administered cautiously to patients with ARVD as these are known to induce dose-dependent myocardial depression, tachycardia and arterial hypertension. Isoflurane was associated with intraoperative SCD but paradoxically, uneventful anaesthesia was also described^[27-31].

Muscle relaxants have several unfavourable side effects on the circulation. Careful selection helps to avoid haemodynamic instability. Perioperative death was observed in a patient receiving Suxamethonium and Atracurium^[32]. This had been explained by histamine release followed haemodynamic instability. Cisatracurium has minimal effect on the cardiovascular system and was associated with positive patient outcome^[31]. Pancuronium is likely to induce sinus tachycardia due to its vagolytic effect and thought to be contraindicated in patients with ARVD. However Pancuronium was the muscle relaxant of choice in successful case series of intraoperative management of patients with advance cardiac failure ARVD patients undergoing orthotopic cardiac transplantation. There were no deleterious effects reported^[26,33].

Anticipating and promptly responding physiological disturbance. These are the principles of balanced anaesthesia for all operations. However, there are no more important in any other group of patients other than ARVD.

Arterial perfusion pressure

Hypertension increase afterload on the diseased ventricle. Hypertension may be treated with deepening the plane of anaesthesia. Intravenous Nicardipine has been described as a safe choice. Although there is lack of experience, it is possible that other systemic blood pressure lowering agents are safe too.

Hypotension could diminish coronary perfusion and oxygen delivery. Although direct vasoactive drugs can provoke arrhythmias, these may need to be used to maintain haemodynamic parameters. Vasopressor infusions have been previously described. Dopamine is known to increase the incidence arrhythmias whilst used to treat arterial hypotension^[34], however safe administration in patients with ARVD was reported in the literature^[26].

Heart rate and rhythm

Tachycardia increases the incidence of premature ventricular complexes and ventricular extrasystole predisposing to malignant arrhythmias. During general anaesthesia tachycardia may be explained by for several factors. Pain control, adequate depth of anaesthesia and muscle relaxation should be maintained at all time. Agents with positive dromotropic and batmotropic effects have to be avoided where possible. Controlling electrolyte levels of potassium and magnesium can offer some protection. Persistent tachycardia may be treated with short acting intravenous β -blocker (Esmolol). When premature ventricular extrasystole increases in number, Amiodarone infusion should be commenced.

Volume status

Excessive intravenous fluid administration is hazardous in case of ventricular dysfunction as it can distend the heart. Hypovolaemia secondary to dehydration or large fluid shift during complex abdominal and thoracic procedures should be treated intravenous crystalloid. Anticipating and promptly responding to haemorrhage helps to avoid decompensated blood. Compensatory tachycardia to maintain cardiac out and oxygen delivery predisposes to malignant tachyarrhythmia.

Normoxia and normocapnia

Controlled ventilation maintains normal arterial carbon-dioxide partial pressure (pCO_2). Tachycardia may be the first manifestation of increased pCO_2 . Muscle relaxation in major surgical cases could offer also reduction of oxygen demand due to reduced striated muscle oxygen demand.

Normothermia

Hypothermia increases the risk of shivering and increased oxygen consumption and predispose to tachyarrhythmia.

Electrolyte and acid-base balance

Calcium, magnesium and potassium play important role in regulation of cardiac function and vessel tone. Deranged plasma level can precipitate haemodynamic instability. Metabolic acidosis has deleterious effect on cardiac contractility and reduces sensitivity to endogenous and exogenous catecholamines.

Postoperative care

Postoperative care plays an important role, malignant arrhythmia in the postoperative phase must be anticipated and predisposing factors prevented or promptly eliminated. ARVD may present exclusion criteria for day surgery even following low risk surgical interventions. Patient with ARVD should be cared for in a clinical area where close monitoring can be maintained.

Maintaining physiological parameters near to the normal values decreases the incidence of malignant arrhythmias and SDC.

Table 1 Anaesthetic management of patients with arrhythmogenic right ventricular dysplasia

Preoperative management	
History	Symptomatic arrhythmia, cardiac drug history, cardiology follow-up
Physical findings	Signs of systemic and pulmonary congestion
Specific diagnostic tests	ECG, Holter monitor, Echocardiography
Preoperative optimisation	Multidisciplinary approach involving cardiologist, surgeons, anaesthetists and intensivists
Intraoperative management	
Monitoring	Minor surgical intervention: ECG, non-invasive blood pressure monitoring, SpO ₂ , capnography Major surgical interventions: Central venous pressure, pulmonary artery catheter and cardiac output monitoring, temperature monitoring, intraoperative transoesophageal echocardiography
Haemodynamic stability	Maintaining adequate depth of anaesthesia and analgesia Adequate arterial perfusion pressure Avoiding tachycardia, bradycardia and arrhythmias Avoiding blood loss, hypovolaemia and fluid overload Maintaining adequate gas exchange Temperature control Electrolyte balance Acid-base balance
Choice of anaesthetic agents and vasoactive drugs	Understanding pharmacokinetics and side effects of the individual anaesthetic agents and anticipating cardiovascular effects
Postoperative management	Cardiovascular stability: Avoiding hypo- and hypertension, tachycardia, bradycardia and arrhythmias Prompt recognition of blood loss and hypovolaemia Normoxia and normocapnia Temperature control Adequate pain control Early treatment of postoperative nausea and vomiting Electrolyte and acid-base balance

ECG: Electrocardiogram.

Adequate arterial perfusion pressure is essential to maintain coronary perfusion pressure, myocardial oxygen supply and end-organ perfusion. Perioperative clinicians should have low threshold to treat bradycardia and tachycardia. Close monitoring of fluid balance and early recognition of significant aim to maintain haemodynamic stability.

Supplemental oxygen may help to avoid arrhythmias induced by hypoxia, however, importance of adequate carbon-dioxide removal must not be overlooked.

Adequate pain control reduces anxiety, maintains autonomic stability and prevents further catecholamine surge. Multimodal approach with non-opioid analgesic drugs may be appropriate choice after minor surgical interventions. Opioids analgesics have significant side effects on the cardiovascular and respiratory systems and their use is reserved to treat severe postoperative pain after. Regional and neuroaxial blockade may be useful after major surgical interventions.

Satisfactory treatment of postoperative nausea and vomiting eliminates vagotonic effect. Electrolyte balance maintains electrical stability of the diseased myocardium.

When malignant supraventricular or ventricular arrhythmia occurs, pharmacological treatment or electrical cardioversion should not be delayed. Prompt consideration of reversible causes and electrolyte abnormalities may help to restore cardiovascular stability. Early involvement of experienced cardiologist should be thought. Management of cardiovascular collapse follows Adult Life Support (ALS) guidelines

(Table 1).

SPECIAL FIELDS OF ANAESTHESIA

Obstetric anaesthesia

In pregnancy all maternal organ system undergoes physiological changes in order to adapt to increased metabolic demand of the foetus and prepare the maternal body for delivery. Cardiovascular changes occur throughout pregnancy: Systemic vascular resistance decreases initially due to progesterone effect and low resistance placental vascular bed later on. Cardiac output may increase up to 50% at term due to left ventricular hypertrophy. Intravascular volume expansion induces physiological anaemia. Healthy gravidas tolerate adaptation well, women with structural heart disease may experience worsening symptoms while pregnant.

Limited available data describes pregnancy safe and well-tolerated in women with mild to moderate form of ARVD, however all women with ARVD in child-bearing age should receive counselling before pregnancy.

In an ideal world all pregnant women with ARVD should be assessed by multidisciplinary team including specialist cardiologist, obstetrician and anaesthetist as soon as pregnancy discovered. Early assessment enables the medical team to plan essential investigation, maintain effective control of malignant arrhythmias and establish a robust plan for delivery and the postpartum period.

Anaesthetists are likely to encounter the following issues whilst managing pregnant women with ARVD: (1)

discontinuation of pharmacological control of malignant arrhythmias: Omission of regular antiarrhythmic drugs have been reported with minimal effect^[35]; (2) amiodarone is associated with severe adverse effect on the foetus therefore it needs to be used only to treat life-threatening arrhythmias. β -blockers may be associated with intra-uterine growth retardation however Bisoprolol is considered to be safe^[36]; (3) alteration of heart failure medications due to their teratogenic effect: While Warfarin and ACE-inhibitors may be associated with faulty foetal organogenesis, most diuretics, digoxin and low molecule weight heparin can be used without having an adverse effect on the foetus^[36,37]; and (4) worsening cardiac function and symptomatic ventricular arrhythmia: Despite of continuous rhythm control, women may experience increased incidence of palpitation. Evaluation of cardiac function with echocardiograph and holter monitor is described to be beneficial.

Labour and delivery

ARVD is not a contraindication of vaginal delivery, however significant deterioration of pre-existing heart failure might indicate surgical delivery. Planned delivery may provide a better control of perinatal events.

In labour cardiac output increases 85% above the non-pregnant level. This is due to increased venous return from the placental vessels with each uterine contraction. Furthermore, anxiety and pain results in sympathetic stimulation and increase heartrate. Low dose spinal or effective epidural anaesthesia achieves good pain relief and blunts autonomic response but also warrants higher level of haemodynamic monitoring to avoid cardiovascular instability.

Successful surgical delivery of healthy new born has been described both under regional and general anaesthesia^[35,36,38]. Suitable technique is determined by maternal choice and the degree of heart failure. There is no evidence to supports one technique over the other. The ultimate goal is to maintain cardiovascular stability. Haemodynamic instability is more common with spinal anaesthesia, epidural anaesthesia allows better control over instability and more time for adaptation.

Most commonly used oxytocin has deleterious side effects such as hypotension and tachycardia, dilution and slow administration may overcome. It is important to judge whether use of oxytocin is needed for the individual ARVD patient at all, rather than follow the routine protocol for all patients. Involvement of experienced obstetrician in these cases is important.

Postnatal period

Increased incidence of malignant arrhythmias has been reported in the third trimester and the postpartum period. High level of monitoring is recommended in the early postpartum phase. Lactation raises concern about electrolyte derangement however there is no report of ventricular tachyarrhythmia in women who opted for breast feeding. Evaluation of cardiac function 3 mo after

delivery provides good guide regarding the need for modifying pharmacological arrhythmia control.

Regional anaesthesia

Local anaesthetic drugs exert effect by blocking voltage sensitive sodium channels and inhibit propagation of action potential *via* the nerve fibres.

Regional blocks may provide anaesthesia as a sole technique or used as an adjunct to general anaesthesia to facilitate adequate analgesia and blunt stress response to pain.

Cardiovascular changes are the most important effects of central neural block. These responses are due to arterial vasodilation and decreased contractility due to sympathetic denervation. Reflex tachycardia aims to maintain cardiac output however significant decrease in systemic vascular resistance due to sympathectomy reduces venous return and paradoxically induces bradycardia or asystole.

Anaesthetists should anticipate these changes when planning central neuraxial blockade for a patient with ARVD. Remembering of non-specific symptoms such as nausea, vomiting and syncope may be helpful to avoid cardiovascular collapse.

Epidural anaesthesia provides better controlled onset of the blockade with less marked effect on cardiovascular system. However, it also uses large doses of local anaesthetics, which can cause arrhythmias after their systemic absorption.

Local anaesthetics exhibit dose dependent sodium channel blockage on the cardiac muscle, inducing prolongation of the PR interval and widening the QRS complexes. Direct cardiac toxicity depends on the potency. Bupivacaine is the most commonly used local anaesthetic agent however its higher plasma level is associated with severe adverse effect on the cardiovascular system.

There is no sufficient data to support any local anaesthetic agent being superior to other, Bupivacaine was associated with perioperative death in patients with ARVD and used successfully during surgical delivery^[29,38]. In fact, it may support the concept that perioperative death is associated with deleterious haemodynamic instability rather than the choice of the local anaesthetic agent.

Ephedrine is frequently administered concomitantly with local anaesthetic drugs with the aim to prevent rapid absorption to the circulation and avoid toxic plasma level. It also increases the duration of the blockade. Subcutaneous and extravascular administration is associated with minimal cardiovascular sequels. Intravascular use could induce hypertension, tachycardia and increased myocardial oxygen consumption predisposing patients with ARVD to malignant ventricular arrhythmias and SDC.

Laparoscopic surgery

Laparoscopic surgery an important diagnostic and

therapeutic tool and gaining increased popularity over the past two decades. Growing surgical experience and better understanding of the physiological effect of pneumoperitoneum lead to that more and more major surgical interventions are being performed laparoscopically.

Laparoscopy offers lower perioperative morbidity, better wound healing, fewer wound infection and better pain control allowing early mobilisation and shorter hospital stay.

Anaesthetists should be aware of the physiological changes induced by laparoscopic surgery whilst preparing a patient with diagnosed ARVD for surgery: Mechanical effect of pneumoperitoneum has significant cardiovascular consequences: Reduced venous return due to compression of the inferior vena cava, increased myocardial afterload and bradycardia secondary to increased systemic vascular resistance. Compensatory tachycardia precipitates malignant arrhythmias. Carbon-dioxide insufflation may induce respiratory acidosis. Perforation of the solid organs or great vessels precipitates decompensated blood loss.

Laparoscopy does not have absolute contraindications, however patients with diagnosed ARVD or advanced heart disease need to be assessed on an individual basis. Operative planning should involve surgeon, anaesthetist and specialist cardiologist. Experienced surgeon can reduce intraoperative complication and the duration of the surgical intervention. Anaesthetist should anticipate and respond to cardiovascular changes. Invasive haemodynamic monitoring may be necessary for minor procedures. Postoperative nausea and vomiting are common, prevention with combined antiemetic drugs is recommended. Persisting haemodynamic concerns should prompt early discussion with the operating surgeon and conversion to open procedure should be thought.

MANAGEMENT OF PERIOPERATIVE CARDIOVASCULAR COLLAPSE IN PATIENTS WITH SUSPECTED ARVD

Undiagnosed ARVD often presents as unexpected perioperative death in young and fit patient undergoing minor surgical intervention. Cardiovascular collapse is commonly unresponsive to cardiopulmonary resuscitation.

It such cases all anaesthetists ask for help, and it is the culture of perioperative case. Once cardiovascular collapse occurs, management should follow the ALS guidelines. Defibrillation is almost always needed. Administration of Amiodarone bolus and infusion should follow ALS guidelines. Other reversible causes should be considered, intravascular volume, electrolytes should be replaced.

Patent airway and controlled ventilation aim to maintain adequate arterial oxygen and carbon-dioxide

pressure and avoid arrhythmia induced by hypoxia and hypercarbia.

PRACTICAL CONSIDERATIONS

ARVD is a rare form of cardiomyopathy, subclinical stage may be asymptomatic or characterised by non-specific symptoms such as palpitation or chest pain. Awareness amongst anaesthetists may help to raise the suspicion. When malignant tachycardia occurs in healthy individual in the perioperative period, differential diagnosis should include ARVD. Early recognition and prompt treatment of these arrhythmias may help to avoid cardiovascular collapse.

Patients with established diagnosis of ARVD should be managed by a multidisciplinary team. Robust perioperative plan should include preoperative workup and optimisation involving a cardiologist. Surgical intervention must be performed by an experienced consultant surgeon with the least haemostatic disturbance. Experienced consultant anaesthetist in charge for the anaesthetic management should understand the pathophysiology of ARVD and physiological anomalies predisposing to adverse events. Cardiovascular stability should be maintained throughout. Malignant arrhythmias and cardiovascular collapse can occur at any time during the perioperative care therefore emergency vasoactive and anti-arrhythmia drugs and defibrillator should be available. Postoperative recovery is the best to take place in a clinical area with high level of monitoring. Stable haemodynamic parameters, adequate analgesia and temperature control, fluid and electrolyte balance aim to avoid arrhythmias and facilitate early recovery, mobilisation and hospital discharge. Once adverse event occurs at any point during perioperative care, experience cardiologist can offer valuable input.

CONCLUSION

Most anaesthetists would encounter patients with subclinical or diagnosed ARVD. Available literature on management of ARVD in the anaesthetic practice is not sufficient to establish evidence-based recommendations. Clinical data remains conflicting about the safety of the individual pharmacological agents. Careful perioperative assessment and solid management plan focusing on the maintenance of physiological stability may help to avoid perioperative loss and provide the highest level of safety in this patient population.

REFERENCES

- 1 **Dalal D**, Nasir K, Bomma C, Prakasa K, Tandri H, Piccini J, Roguin A, Tichnell C, James C, Russell SD, Judge DP, Abraham T, Spevak PJ, Bluemke DA, Calkins H. Arrhythmogenic right ventricular dysplasia: a United States experience. *Circulation* 2005; **112**: 3823-3832 [PMID: 16344387 DOI: 10.1161/CIRCULATIONAHA.105.542266]
- 2 **Thiene G**, Basso C. Arrhythmogenic right ventricular cardiomyopathy: An update. *Cardiovasc Pathol* 2001; **10**: 109-117 [PMID: 11555555 DOI: 10.1054/cup.2001.36888]

- 11485854 DOI: 10.1016/S1054-8807(01)00067-9]
- 3 **Tabib A**, Loire R, Miras A, Thivolet-Bejui F, Timour Q, Bui-Xuan B, Malicier D. Unsuspected cardiac lesions associated with sudden unexpected perioperative death. *Eur J Anaesthesiol* 2000; **17**: 230-235 [PMID: 10866005]
- 4 **Corrado D**, Fontaine G, Marcus FI, McKenna WJ, Nava A, Thiene G, Wichter T. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: need for an international registry. Study Group on Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy of the Working Groups on Myocardial and Pericardial Disease and Arrhythmias of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the World Heart Federation. *Circulation* 2000; **101**: E101-E106 [PMID: 10725299 DOI: 10.1161/01.CIR.101.11.e101]
- 5 **Borjesson M**, Pelliccia A. Incidence and aetiology of sudden cardiac death in young athletes: an international perspective. *Br J Sports Med* 2009; **43**: 644-648 [PMID: 19734497 DOI: 10.1136/bjsm.2008.054718]
- 6 **Maron BJ**. Sudden death in young athletes. *N Engl J Med* 2003; **349**: 1064-1075 [PMID: 12968091 DOI: 10.1056/NEJMra022783]
- 7 **Corrado D**, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. *N Engl J Med* 1998; **339**: 364-369 [PMID: 9691102 DOI: 10.1056/NEJM199808063390602]
- 8 **Matsumori A**, Furukawa Y, Hasegawa K, Sato Y, Nakagawa H, Morikawa Y, Miura K, Ohno Y, Tamakoshi A, Inaba Y, Sasayama S. Epidemiologic and clinical characteristics of cardiomyopathies in Japan: results from nationwide surveys. *Circ J* 2002; **66**: 323-336 [PMID: 11954944 DOI: 10.1253/circj.66.323]
- 9 **Peters S**, Trümmel M, Meyners W. Prevalence of right ventricular dysplasia-cardiomyopathy in a non-referral hospital. *Int J Cardiol* 2004; **97**: 499-501 [PMID: 15561339 DOI: 10.1016/j.ijcard.2003.10.037]
- 10 **Protonotarios N**, Tsatsopoulou A, Patsourakos P, Alexopoulos D, Gezerlis P, Simitis S, Scampardonis G. Cardiac abnormalities in familial palmoplantar keratosis. *Br Heart J* 1986; **56**: 321-326 [PMID: 2945574]
- 11 **Murray B**. Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C): a review of molecular and clinical literature. *J Genet Couns* 2012; **21**: 494-504 [PMID: 22426942 DOI: 10.1007/s10897-012-9497-7]
- 12 **Kaplinger JD**, Landstrom AP, Salisbury BA, Callis TE, Pollevick GD, Tester DJ, Cox MG, Bhuiyan Z, Bicker H, Wiesfeld AC, Hauer RN, van Tintelen JP, Jongbloed JD, Calkins H, Judge DP, Wilde AA, Ackerman MJ. Distinguishing arrhythmogenic right ventricular cardiomyopathy/dysplasia-associated mutations from background genetic noise. *J Am Coll Cardiol* 2011; **57**: 2317-2327 [PMID: 21636032 DOI: 10.1016/j.jacc.2010.12.036]
- 13 **Marcus FI**, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Sanborn DM, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation* 2010; **121**: 1533-1541 [PMID: 20172911 DOI: 10.1161/CIRCULATIONAHA.108.840827]
- 14 **Tavano A**, Maurel B, Gaubert JY, Varoquaux A, Cassagneau P, Vidal V, Bartoli JM, Moulin G, Jacquier A. MR imaging of arrhythmogenic right ventricular dysplasia: What the radiologist needs to know. *Diagn Interv Imaging* 2015; **96**: 449-460 [PMID: 25736879 DOI: 10.1016/j.diii.2014.07.009]
- 15 **Kiès P**, Bootsma M, Bax J, Schaliij MJ, van der Wall EE. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: screening, diagnosis, and treatment. *Heart Rhythm* 2006; **3**: 225-234 [PMID: 16443541 DOI: 10.1016/j.hrthm.2005.10.018]
- 16 **Munkholm J**, Christensen AH, Svendsen JH, Andersen CB. Usefulness of immunostaining for plakoglobin as a diagnostic marker of arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol* 2012; **109**: 272-275 [PMID: 22036107 DOI: 10.1016/j.amjcard.2011.08.044]
- 17 **Asimaki A**, Tandri H, Huang H, Halushka MK, Gautam S, Basso C, Thiene G, Tsatsopoulou A, Protonotarios N, McKenna WJ, Calkins H, Saffitz JE. A new diagnostic test for arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med* 2009; **360**: 1075-1084 [PMID: 19279339 DOI: 10.1056/NEJMoa0808138]
- 18 **Sen-Chowdhry S**, Morgan RD, Chambers JC, McKenna WJ. Arrhythmogenic cardiomyopathy: etiology, diagnosis, and treatment. *Annu Rev Med* 2010; **61**: 233-253 [PMID: 20059337 DOI: 10.1146/annurev.med.052208.130419]
- 19 **Saguner AM**, Bruckhorst C, Duru F. Arrhythmogenic ventricular cardiomyopathy: A paradigm shift from right to biventricular disease. *World J Cardiol* 2014; **6**: 154-174 [PMID: 24772256 DOI: 10.4330/wjc.v6.i4.154]
- 20 **Wichter T**, Paul TM, Eckardt L, Gerdes P, Kirchhof P, Böcker D, Breithardt G. Arrhythmogenic right ventricular cardiomyopathy. Antiarrhythmic drugs, catheter ablation, or ICD? *Herz* 2005; **30**: 91-101 [PMID: 15875097 DOI: 10.1007/s00059-005-2677-6]
- 21 **Ermakov S**, Scheinman M. Arrhythmogenic Right Ventricular Cardiomyopathy - Antiarrhythmic Therapy. *Arrhythm Electrophysiol Rev* 2015; **4**: 86-89 [PMID: 26835106 DOI: 10.15420/aer.201-5.04.02.86]
- 22 **Mugnai G**, Tomei R, Dugo C, Tomasi L, Morani G, Vassanelli C. Implantable cardioverter-defibrillators in patients with arrhythmogenic right ventricular cardiomyopathy: the course of electronic parameters, clinical features, and complications during long-term follow-up. *J Interv Card Electrophysiol* 2014; **41**: 23-29 [PMID: 24928487 DOI: 10.1007/s10840-014-9920-0]
- 23 **Dalal D**, Jain R, Tandri H, Dong J, Eid SM, Prakasa K, Tichnell C, James C, Abraham T, Russell SD, Sinha S, Judge DP, Bluemke DA, Marine JE, Calkins H. Long-term efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol* 2007; **50**: 432-440 [PMID: 17662396 DOI: 10.1016/j.jacc.2007.03.049]
- 24 **Staïkou C**, Chondrogiannis K, Mani A. Perioperative management of hereditary arrhythmogenic syndromes. *Br J Anaesth* 2012; **108**: 730-744 [PMID: 22499746 DOI: 10.1093/bja/aes105]
- 25 **Alexoudis AK**, Spyridonidou AG, Vogiatzaki TD, Iatrou CA. Anaesthetic implications of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Anaesthesia* 2009; **64**: 73-78 [PMID: 19087010 DOI: 10.1111/j.1365-2044.2008.05660.x]
- 26 **Valchanov K**, Goddard M, Ghosh S. Anesthesia for heart transplantation in patients with arrhythmogenic right ventricular dysplasia. *J Cardiothorac Vasc Anesth* 2014; **28**: 355-357 [PMID: 23994174 DOI: 10.1053/j.jvca.2013.02.025]
- 27 **Bastien O**, Guérin JM, Artru F, Lehot JJ. Arrhythmogenic right ventricular dysplasia: an underestimated cause of perioperative death? *J Cardiothorac Vasc Anesth* 2002; **16**: 357-358 [PMID: 12073212 DOI: 10.1053/jcan.2002.124149]
- 28 **Bonnet F**, Samain E, Bocquet R, Le Corre F, Marty J. Perioperative management of severe head injury in a patient with arrhythmogenic right ventricular dysplasia. *Anesthesiology* 2001; **95**: 255-256 [PMID: 11465565]
- 29 **Houfani B**, Meyer P, Merckx J, Roure P, Padovani JP, Fontaine G, Carli P. Postoperative sudden death in two adolescents with myelomeningocele and unrecognized arrhythmogenic right ventricular dysplasia. *Anesthesiology* 2001; **95**: 257-259 [PMID: 11465566 DOI: 10.1097/0000542-200107000-00037]
- 30 **Martínez Torrente F**, Orts Castro A, García-Montoto F, Pérez-Cerdá F. Patient with right ventricular arrhythmogenic dysplasia, ascites and ulcerative colitis: anesthetic management during major abdominal surgery. *Rev Esp Anestesiol Reanim* 2005; **52**: 631-633 [PMID: 16435619]
- 31 **Morita K**, Takeuchi M, Oe K, Iwasaki T, Taga N, Hirakawa M, Sano S. Perioperative management of Fontan operation for two patients with arrhythmogenic right ventricular dysplasia. *J Anesth* 2002; **16**: 169-172 [PMID: 14517671 DOI: 10.1007/s005400200015]
- 32 **Toh KW**, Nadesan K, Sie MY, Vijeyasingam R, Tan PS. Postoperative death in a patient with unrecognized arrhythmogenic right ventricular dysplasia syndrome. *Anesth Analg* 2004; **99**: 350-352, table of contents [PMID: 15271703 DOI: 10.1213/01.ANE.0000132996.12248.B0]

- 33 **Massen H**, Cosnay JP, Bouzaher M, Mercat C. Arrhythmogenic right ventricular dysplasia revealed during anesthesia. *Ann Fr Anesth Reanim* 1986; **5**: 436-440 [PMID: 2430492 DOI: 10.1016/S0750-7658(86)80014-4]
- 34 **De Backer D**, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; **362**: 779-789 [PMID: 20200382 DOI: 10.1056/NEJMoa0907118]
- 35 **Hodes AR**, Tichnell C, Te Riele AS, Murray B, Groeneweg JA, Sawant AC, Russell SD, van Spaendonck-Zwarts KY, van den Berg MP, Wilde AA, Tandri H, Judge DP, Hauer RN, Calkins H, van Tintelen JP, James CA. Pregnancy course and outcomes in women with arrhythmogenic right ventricular cardiomyopathy. *Heart* 2016; **102**: 303-312 [PMID: 26719359 DOI: 10.1136/heartjnl-2015-308624]
- 36 **Krul SP**, van der Smagt JJ, van den Berg MP, Sollic KM, Pieper PG, van Spaendonck-Zwarts KY. Systematic review of pregnancy in women with inherited cardiomyopathies. *Eur J Heart Fail* 2011; **13**: 584-594 [PMID: 21482599 DOI: 10.1093/eurjhf/hfr040]
- 37 Burt C, Durbridge J. Management of cardiac disease in pregnancy. *BJA Education* 2009; **9**: 44-47 [DOI: 10.1093/bjaceaccp/mkp005]
- 38 **Bauce B**, D'Aliento L, Frigo G, Russo G, Nava A. Pregnancy in women with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Eur J Obstet Gynecol Reprod Biol* 2006; **127**: 186-189 [PMID: 16337730 DOI: 10.1016/j.ejogrb.2005.10.011]

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Anesthetic considerations for liver diseases unique to pregnancy

Berrin Gunaydin, Ayca Tas Tuna

Berrin Gunaydin, Department of Anesthesiology, Gazi University School of Medicine, 06500 Ankara, Turkey

Ayca Tas Tuna, Department of Anesthesiology, Sakarya University School of Medicine, 54100 Sakarya, Turkey

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Correspondence to: Berrin Gunaydin, MD, PhD, Professor of Anesthesia, Department of Anesthesiology, Gazi University School of Medicine, Besevler, 06500 Ankara, Turkey. gunaydin@gazi.edu.tr
Telephone: +90-312-2025318

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Abstract

Liver diseases that are most unique to pregnancy consist of hyperemesis gravidarum, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy,

and hemolysis, elevated liver enzymes and low platelets syndrome. In this review, risk factors, etiology, symptoms, diagnosis, prognosis and treatment of each entity followed by principles of anesthetic management based on the case reports or retrospective records will be addressed.

Key words: Liver disease; Pregnancy; Anesthesia

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Core tip: Liver diseases like hyperemesis gravidarum, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy and hemolysis, elevated liver enzymes and low platelets are challenging for anesthesiologists because of the increased risk of morbidity and mortality. Therefore, general and specific anesthetic management strategies are of utmost important. In this review, the risk factors, etiology, symptoms, diagnosis, prognosis and treatment of these liver diseases during pregnancy and general principles of anesthetic management based on our case report and retrospective records will be addressed.

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INTRODUCTION

Most unique liver diseases that occur during pregnancy are hyperemesis gravidarum (HG), acute fatty liver of pregnancy (AFLP), intrahepatic cholestasis of pregnancy (IHCP), and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome^[1,2]. We aim to present risk factors, etiology, symptoms, diagnosis, and prognosis briefly and as well as discuss the treatment of each

entity, principles of anesthetic management based on the current literature.

HG

HG, generally occurs generally at 4-10 wk of gestation up to 20 weeks' gestation^[3-5]. There are risk factors such as history of HG, hyperthyroidism, psychiatric illness, molar pregnancy, preexisting diabetes, multiple gestations, multiparity, increased body mass index, and excessive daily intake of saturated fat before pregnancy are some of the common risk factors^[1]. Female fetus and maternal *Helicobacter pylori* infection might be considered as additional risk factors^[6]. The incidence, etiology, symptoms, diagnosis and treatment of the disease were summarized in Table 1^[5,7-17].

We would like to underline our established therapeutic plan based on a 21-year-old woman (G1, P0) with a diagnosed HG without remarkable medical history. She was admitted to our unit at 19^[1] weeks' gestation. She was suffering from nausea, vomiting and weight loss refractory to medical treatment though she was treated in another hospital before admission. Her current weight was 56 kg (Pre-pregnancy weight 73 kg), and BMI was 18.3 kg/m². Her vital signs including blood pressure and heart rate were 90/60 mmHg and 90 beat/min, respectively. Blood and urine laboratory results and thyroid function tests were within normal clinical limits. Obstetric and abdominal USG were unremarkable. Medical treatment was started with metochlopramide and vitamin B during IV total parenteral nutrition. Fluid intake and urine output were adjusted accordingly. Because of persistent refractory nausea and vomiting, metoclopramide was switched to domperidon. For differential diagnosis, endoscopy was planned but 1st endoscopy attempt without sedation was unsuccessful. Therefore, 2nd endoscopy was planned using propofol under monitored anesthesia care (MAC). The endoscopy revealed minimal superficial gastritis and motility dysfunction (with no pyloric stenosis and helicobacteria presence). Although there was rarely need for anesthesia in HG since that disease usually seen during early pregnancy period, we performed sedation with propofol which was a safe intravenous anesthetic agent in liver diseases under MAC.

AFLP

The AFLP is observed 1 in 10000-15000 pregnancies^[18]. It often develops between 27-40 weeks' gestation, but may be undiagnosed until the postpartum period^[1].

Advanced maternal age, primiparity, multiple pregnancies, preeclampsia, male fetus, being underweight, the use of non-steroidal anti-inflammatory drugs and previous AFLP are considered to be some of the risk factors^[1,19]. The incidence of AFLP is high in women with a genetic mutation. Basically, mitochondrial fatty acid oxidation pathway is affected. Fetus has a long-chain 3-hydroxyacyl-coenzyme A dehydrogenase defi-

ency^[7,20]. The incidence, etiology, symptoms, diagnosis and treatment of AFLP were shown in Table 1^[7,18,20-29].

Primary obstetric management is to make immediate delivery decision since recovery before delivery is not possible. The anesthesia technique either regional or general must be discussed. General anesthesia is required in patients with coagulopathy because of the concern for regional anesthesia related hematoma risk^[1]. Most of the patients recover within 48-72 h after delivery with improved aminotransferase levels^[22]. However, patients with coagulopathy, encephalopathy, or hypoglycemia require intensive care admission^[26].

Perioperative care includes establishing adequate intravenous accesses readily available for cross-matched blood and blood products against increased risk of postpartum hemorrhage (PPH)^[28].

Clinical and laboratory findings, anesthetic managements with maternal and neonatal outcomes of 28 cases from Shanghai Public Health Center were retrospectively reviewed over 5 years. Cesarean delivery was performed under either neuraxial ($n = 16$) or general anesthesia ($n = 12$) with rapid sequence induction (RSI). Two maternal deaths (7.1%) without fetal deaths were recorded. As a result of this retrospective study, recommendation of general anesthesia with RSI in case of severe coagulopathy was reconfirmed^[29].

IHCP

The incidence of IHCP is approximately 1-2 in 1000 pregnancies. Generally it manifests either in the second or third trimester, around 30 weeks' gestation. After delivery, symptoms generally resolve^[30]. According to the recent reports, the incidence varies between 1.5%-4%^[1].

Accused common risk factors are advanced maternal age, multiparity, family history, preexisting liver disease, or history of cholestasis while taking oral contraceptives^[31,32].

The incidence, etiology, symptoms, diagnosis and treatment of IHCP were also shown in Table 1^[1,30-51].

Diagnosis is based on clinical signs and laboratory tests. Elevated bilirubin levels (< 6 mg/dL), and elevated transaminases (approximately 20 times than normal values). The most sensitive diagnostic biomarker is the elevation in the fasting serum bile acid level. Parturients generally have bile acid levels higher than 10 μ mol/L. The degree of disease as mild, moderate or severe is made according to bile acid levels (Mild: 10-39 μ mol/mL, moderate: 40-99 μ mol/mL and severe: ≥ 100 μ mol/mL)^[38].

We have retrospectively documented maternal, fetal and neonatal outcomes of parturients with IHCP delivered in Gazi University. Maternal outcomes were generally good as indicated in many previous reports^[28,37,47,48]. Twenty-seven percent of our cases had normal spontaneous vaginal delivery, while the rest (73%) underwent cesarean delivery. Approximately

Table 1 The incidence, etiology, symptoms, diagnosis and treatment of the liver disease unique to pregnancy

Disease	Incidence	Etiology	Symptoms	Diagnosis	Prognosis	Treatment
Hyperemesis gravidarum ^[3-17]	1-20/1000 pregnancies (< 2%) ^[5]	Psychological predisposition Hormones (human chorionic gonadotropin, estradiol) ^[7]	Severe nausea and vomiting Dehydration Malnutrition Poor weight gain ^[1,7]	Diagnosis by clinical presentation (persistent vomiting, acute starvation and weight loss) Increased levels of liver enzymes (aminotransferase, alkaline phosphatase and amylase) ^[1,3,8-12] Rarely, liver biopsy is needed ^[1,11,12]	Unchanged maternal and fetal outcomes after use of safe antiemetics Increased risk of low-birth-weight infants, preterm birth, preeclampsia, and placental abruption in the 2 nd trimester ^[8,16,17]	Avoid nausea triggering substances Medical and supportive therapy (ginger, multivitamin or Vit B6 with H1 receptor antagonist doxylamine) Treatment of dehydration (intravenous infusion of fluids, metoclopramide or promethazine with another H1 receptor antagonist dimenhydramine) ^[1,8,13-15]
Acute fatty liver of pregnancy ^[18-29]	1/10000-15000 pregnancies ^[18]	Mutations in LCHAD ^[1,21]	Nausea, vomiting, anorexia lethargy, abdominal pain, ascites, progressive jaundice Polyuria and polydipsia due to transient diabetes insipidus Acute renal failure Hepatic encephalopathy Hypertension, proteinuria and edema ^[1,4,22,23]	Diagnosis by clinical and laboratory findings (increased levels of aminotransferases, ammonia, bilirubin, leukocytosis, hypoglycemia, thrombocytopenia, neutrophilia, coagulopathy, renal dysfunction) ^[20,22,24] Tomography and ultrasonography are unremarkable ^[7] Liver biopsy reveals microvesicular steatosis ^[25]	Liver function improves within a week to months ^[27] Preterm delivery (75%) approximately at 34 wk gestation Check all mothers with AFLP for defects in fatty acid oxidation ^[1]	Immediate hospitalization Supportive measures (glucose infusion, readily available blood products) Prompt delivery
Intrahepatic cholestasis of pregnancy ^[1,30-51]	1-2/1000 pregnancies ^[1]	Multifactorial genetic (mutations in the MDR3 gene) Hormonal Exogenous factors (<i>e.g.</i> , progesterone) Abnormal biliary transport ^[25,33-35]	Generalized peripheral pruritus (1 st sign) Chills and abdominal pain Diarrhea or steatorrhea ^[36,37]	Diagnosis by clinical symptoms and/or laboratory tests (increased levels of fasting serum bile acid and elevated bilirubin and transaminase levels) ^[38] Liver biopsy is needed only in severe cases and biopsy reveals cholestasis with minimal or no inflammatory changes ^[39]	Good maternal outcome (laboratory results resolve within 2-8 wk postpartum) ^[7] Compromised fetal outcome (spontaneous preterm labor, meconium-stained fluid with some perinatal mortality) in moderate and severe forms ^[1,42-46]	Symptomatic medical treatment (ursodeoxycholic acid: UDCA which is B Class safe drug for pregnancy and breastfeeding by FDA) ^[40,41] Optimal timing of delivery at the best possible fetal maturity ^[45]
HELLP syndrome ^[1, 51-62]	0.1%-0.6% ^[1,52]	Usually presents with preeclampsia (4%-12% are with severe preeclampsia) Endothelial injury with fibrin deposit is the underlying mechanism of the disease ^[54]	Right upper quadrant or epigastric pain Nausea and vomiting Malaise Nonspecific viral-like symptoms headache visual symptoms ^[55]	Liver biopsy is not necessary but if performed sinusoidal fibrin thrombin, hemorrhage, and hepatocellular necrosis might be observed ^[25] Laboratory findings Platelet count < 100000/ μ L Serum aspartate aminotransferase > 70 U/L Serum lactic dehydrogenase > 600 U/L ^[56]	Maternal death (1%) Perinatal death (7.4%-20.4%) Pulmonary edema Acute renal failure DIC Abruptio placenta Liver hemorrhage or failure ARDS Retinal detachment Stroke Blood transfusion related complications	Provide transfer to tertiary care center after confirmed diagnosis Delivery > 34 weeks' gestation is recommended if possible Prophylaxis of seizures with magnesium during labor and 24 h postpartum ^[58]

HELLP: Hemolysis, elevated liver enzymes and low platelets; LCHAD: Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase; ARDS: Acute respiratory distress syndrome; AFLP: Acute fatty liver of pregnancy; FDA: Food and Drug Administration.

18.5% of cesarean deliveries were not elective or planned. When anesthesia and/or analgesia choices were evaluated in whole, we performed combined spinal epidural (CSE) for labor analgesia only in 1 patient. According to the records of cesarean deliveries,

rates of neuraxial and general anesthesia were 85% and 15%, respectively. Among neuraxial anesthesia choices, spinal anesthesia (96%) was the mostly preferred one. Regarding neonatal outcomes, birth weight and Apgar scores were good as well. However,

there were 2 preterm births and 2 preterm labors from mild and severe IHCP cases (one from each). Hepatitis in 2 newborns was observed in parturients with mild IHCP. But the worst fetal outcome observed in a parturient having severe IHCP was perinatal fetal death at the 34 weeks' of gestation. Anesthesia choices for delivery might be challenging in IHCP. Due to the physiologic decrease in gall bladder contractility, pregnant women tend to have a sort of physiologic cholestasis. The cholestasis might lead to malabsorption of vitamin K. Vitamin K is a cofactor responsible from synthesis of coagulation factors II, VII, IX and X. Therefore, coagulation abnormalities might be expected in parturients with IHCP. Additionally, increased liver enzymes; aspartate aminotransferase (AST) and predominantly ALT are considered to be determinants of liver diseases^[1,28,37,47-49]. However, in a recent retrospective study investigating the incidence of coagulopathy in parturients with IHCP, no abnormal coagulation studies were found even in the presence of significantly increased liver enzymes^[50]. The authors reported that the presence of coagulopathy in parturients with isolated IHCP was low and the routine coagulation studies were not necessary except patients having IHCP with coexisting preeclampsia^[50]. Similarly, we had neither abnormal coagulation parameters nor we came across any patient with coexisting preeclampsia in our study.

Severity of IHCP, especially bile acid levels higher than 40 $\mu\text{mol/L}$, may affect pregnancy outcomes^[46,51]. Based on these studies, we similarly classified our cases having bile acid level ≥ 10 -39 $\mu\text{mol/L}$, 40-99 $\mu\text{mol/L}$ and ≥ 100 $\mu\text{mol/L}$ as mild, moderate and severe IHCP, respectively. In the present study the rates of mild, moderate and severe IHCP were 65%, 21% and 14%, respectively. When we compared our studies in this regard, the incidence of mild IHCP was higher but severe IHCP was less than that of study by Brouwers *et al.*^[51]. In mild cases obstetric management includes delivery at 38 weeks' gestation but early delivery at 36 weeks' can be considered in severe cases due to the high risk of fetal distress/death, jaundice or unbearable maternal pruritis despite ursodeoxy cholic acid (UDC) treatment^[28,37,47-51]. In contrast to the 14% of CS rate in Brouwers *et al.*^[51]'s study, we documented much higher CS rate, which was 73%. However, our high CS rate was consistent with 65% rate of DeLeon *et al.*^[50]. Currently, we have observed adverse outcomes including preterm labor and birth and perinatal fetal death in severe IHCP class parturients.

Pregnancy associated liver diseases and/or abnormalities in conjunction with their interpretation have been extensively studied^[2,25,26,32]. Our maternal and fetal-neonatal outcomes according to the elevated bile acid levels were comparable to recent retrospective studies^[50,51]. However, the present retrospective records including 37 cases with IHCP delivered in Gazi University in one-year period might be helpful to provide better understanding of anesthetic management.

Consequently, parturients with IHCP having normal coagulation parameters despite increased liver enzymes preoperatively underwent cesarean delivery mostly under spinal anesthesia uneventfully. Although maternal outcomes were generally good, adverse fetal and neonatal outcomes may occur more likely in severe IHCP.

HELLP SYNDROME

HELLP syndrome is commonly associated with hypertension, proteinuria, and edema develop either in the second or third trimester. HELLP syndrome has an incidence of 0.1%-0.6% that develops usually in the 3rd trimester. The rate of HELLP patients with severe preeclampsia is 4%-12%^[52]. While 70% of patients with HELLP syndrome present before delivery, 30% of them develop in the postpartum period^[1].

Some of the risk factors for HELLP syndrome are nulliparity and advanced maternal age^[53]. The incidence, etiology, symptoms, diagnosis and treatment of HELLP syndrome were indicated in Table 1 as well^[1,51-62].

Fifty percent of patients with HELLP syndrome might be free of all diagnostic criteria. Maternal morbidity varies due to the degree of thrombocytopenia. According to the Mississippi classification for HELLP, class 1 corresponds to platelet count $\leq 50000/\mu\text{L}$, class 2 corresponds to platelet count greater than > 50000 but $\leq 100000/\mu\text{L}$, while class 3 corresponds to platelet count $100000 - \leq 150000/\mu\text{L}$ ^[57].

HELLP syndrome often progresses and may eventually compromise maternal and fetal outcome. If diagnosis is controversial, hypertension should be controlled by available intravenous antihypertensive drugs (hydralazine or labetalol)^[58].

Delivery is recommended ≥ 34 weeks' gestation. Intravenous magnesium sulfate (4-g loading dose followed by 2 g/h) should be administered for seizure prophylaxis during labor and for 24 h postpartum^[58]. In case of active labor, a vaginal delivery may be proceeded if there is no fetal distress or risk of disseminated intravascular coagulopathy. Additionally, in case of coexistence with multi-organ dysfunction, renal failure, or abruptio, immediate cesarean delivery should be performed because induction of labor is not indicated.

Patients with HELLP syndrome generally receive platelet transfusion if the platelet count is $< 20000/\mu\text{L}$, if $< 50000/\mu\text{L}$ and cesarean delivery is mandatory. There is no need to transfuse platelet more than once, since thrombocytopenia improves after delivery^[59].

For choosing method of analgesia, epidural block is generally contraindicated if platelet count is less than $75000/\mu\text{L}$ but is also up to the experience of the anesthesiologist. Patients should be monitored for at least 48 h in the postpartum period to avoid pulmonary edema. Laboratory abnormalities usually regress 24 h postpartum and almost completely recover 48 h postpartum^[1].

HELLP syndrome is associated with increased risk of maternal and fetal morbidity and mortality. Rate

of maternal death is approximately 1%. Noteworthy maternal complications include pulmonary edema, acute renal failure, DIC, abruptio placenta, liver hemorrhage or failure, ARDS, retinal detachment, stroke and adverse events due to blood transfusion^[1].

The rate of perinatal death varies between 7.4%-20.4%, depending on the gestational age and concurrent factors related to the pregnancy. The highest morbidity and mortality rates are observed < 28 weeks' gestation^[60]. Most perinatal morbidity is due to prematurity that may cause to RDS, bronchopulmonary dysplasia, intracerebral hemorrhage, and necrotizing enterocolitis.

General anesthesia for CS has been the most commonly preferred technique in HELLP syndrome. However, high rate of use of regional anesthesia for CS has been documented in a review of 102 cases with preterm HELLP syndrome^[61]. According to review of 102 charts, number of antepartum and postpartum HELLP were 95 and 7, respectively. Mean gestational age was 30.6 ± 2.7 (23-36) wk. Most of the parturients underwent regional anesthesia ($n = 65$). Cases having preoperative mean platelet count of $113000/\mu\text{L}$ ($n = 53$) underwent CS under CSE, while spinal anesthesia was performed in pregnant women ($n = 12$) having preoperative platelet count of $95000/\mu\text{L}$. Interestingly, 2 patients with mean platelet count < $50000/\mu\text{L}$ underwent CS with CSE. One of these patients received platelet transfusion immediately before CSE. Luckily, epidural hematoma has not been reported in none of the patients received regional anesthesia^[61].

However, subarachnoid hematoma following spinal anesthesia in a 39-year-old having G3, P2 (151 cm and 52 kg) with severe preeclampsia associated HELLP delivered at 27 weeks' gestation was reported. A 23 G Quincke spinal needle was used to inject 2.5 mL of hyperbaric bupivacaine for spinal block. Apgar scores of a 696 g of baby were 6 and 9 at 1 and 5 min, respectively. Duration of surgery was approximately 37 min with approximately 400 mL blood loss. Complete recovery of motor block was achieved 5 h after spinal anesthesia. Although preoperative platelet count was $91000/\mu\text{L}$, it declined progressively to $30000/\mu\text{L}$ postoperatively (2nd day). Patient was suffering from numbness on the posterior aspect of her thigh and the toes of her right leg and her bladder was insensitive to fullness (urinary retention). Neurologic examination revealed flaccid paraparesis. Power in her right hip was 4/5, while it was 3/5 in her right knee, ankle and toes. There was sensory deficit in her right leg between L3-S5 dermatomes, while it was between L4-S5 dermatomes in her left leg. Spinal subarachnoid hematoma compressing cauda equina was observed in the magnetic resonance imaging. Medical treatment including Vit B12 and PG E1 against neurologic deficit, oral neostigmine + bladder exercise for urinary retention, flurbiprofen for relieving headache and neck pain and rehabilitation for paraparesis were performed. Complete recovery was observed 3 mo after conservative treatment (hematoma

regression)^[62].

PRINCIPLES OF ANESTHETIC MANAGEMENT

Regional anesthesia is recommended in patients with advanced liver disease whenever possible because of the less systemic effects of the locally administered drugs. Regional anesthesia is superior than general anesthesia due to possible liver dysfunction leading to delayed metabolism of general anesthetic drugs. Either central or peripheral blocks could be considered in liver dysfunction and/or failure. Total drug dose used in peripheral block should be cautiously calculated and close monitoring is advocated for side effects^[49]. Regarding local anesthetic drugs, $t_{1/2\text{elim}}$ of lidocaine increases 3 fold from 108 to 296 min. Meanwhile, increased volume of distribution (Vd) of lidocaine offers some protection against toxicity. $\alpha 1$ acid GP is synthesized even in end stage liver disease which provides some protection against toxicity as well. However, clearance of ropivacaine is less in the end stage liver disease than normal. For ester type local anesthetic drugs, though pseudocholin esterase enzyme production in the liver may decrease in disease state, overall clearance of chlorprocaine is unclear.

Although coagulopathy is an absolute contraindication for regional anesthesia, it can be recommended in selected patients having acceptable coagulation profile. Regional anesthesia blunts hemodynamic effects of stress hormones in the circulation. These hormones depress immune function as well^[63]. In all cases, arterial blood pressure should be maintained and sympathetic stimulation should be avoided.

Considering general anesthesia, isoflurane seems to be a better choice^[64]. When sevoflurane or desflurane were compared with isoflurane, sevoflurane could have some advantages over others without significant differences among them^[65,66]. Nitrous oxide was used to be an inhalation anesthetic despite risk of accumulation of gas in the closed spaces leading to distension^[49]. However, liver cell injury with xenon anesthesia has been shown to be impossible which might be a promising alternative agent^[67].

Successful use of opioids has been reported in liver disease despite there were concerns with delayed drug clearance and prolonged half-life. Fentanyl, if used in relatively moderate doses, is a good choice without affecting oxygen supply, or requirements of the liver^[68,69].

The rate of oddi sphincter spasm was nearly 3% due to opioids. Medical treatment can be provided with atropine, naloxane, glucagon, nitroglycerin, volatile anesthetics, or antispasmodic drugs. Anesthesia induction and maintenance are provided with possibly safe drugs and pulmonary and cardiovascular measures should be maintained. Anesthetic management using inhalation agents (isoflurane, desflurane or sevoflurane), alone or in combination with small doses of fentanyl

seems to be reasonable. Anesthetist must consider the altered pharmacokinetics in liver disease. Half-life of lidocaine and benzodiazepines may increase by more than 300% and 100%, respectively. Drugs, like sodium thiopentone, highly bound to albumin have a decreased Vd. Therefore, doses should be adjusted accordingly. Among intravenous anesthetic agents, propofol is the most favorable one for liver diseases. It has a short half-life even in cirrhosis. However, either edema or increased gamma globulin resulting in the increased Vd may require to increase the first effective dose of many drugs^[49].

Long acting narcotics and sedatives should be avoided in cirrhotic patients. Fentanyl or sufentanil and oxazepam or lorazepam, in conjunction with sevoflurane or propofol are recommended^[40,70].

For non-depolarizing muscle relaxants, vecuronium and atracurium are recommended because these muscle relaxants are not metabolized mainly in the liver. Clearance and elimination half-life of atracurium are preserved even in impaired liver or renal function. Because of larger Vd, elimination half-life is shorter in severe hepatorenal dysfunction than that of healthy individuals. Therefore, muscle relaxants are used guided by neuromuscular block monitoring^[49].

Suxamethonium which is a depolarizing muscle relaxant is used for providing RSI. It has a prolonged half-life due to decreased serum cholinesterase concentrations in liver dysfunction and during pregnancy.

Both vecuronium and rocuronium have prolonged elimination in severe cases. Either atracurium or cisatracurium may be a better option because of independent metabolism of liver and kidney^[71].

Consequently, rational selection of anesthetic drugs and close monitoring are the key factors for providing safe anesthesia.

POSTOPERATIVE CARE

Even though delayed clearance is a concern in severe liver disease, intravenous opioids can be administered for postoperative analgesia. Neuraxial opioids, especially a single dose of morphine, may obviate any accumulation issues. Advanced liver disease can lead to hepatic encephalopathy. Neurologic deterioration in the postoperative period may result from the residual effects of anesthetic agents, acute liver decompensation, or an intracranial process. Neurologic observation and liver function monitoring is essential to the proper postoperative management of pregnant women with advanced liver disease^[49].

SPECIFIC ANESTHETIC CONSIDERATIONS

Pregnant woman with either mild IHCP or uncomplicated liver transplantation may be managed in the same manner as a healthy parturient assuming that

hepatic synthetic and metabolic functions were intact. Only coagulopathy should be excluded or corrected before regional anesthesia if possible^[1].

According to a retrospective cohort study including 319 parturients with or without coagulation tests, no neuraxial hematoma was observed even in case of liver enzyme elevations > 5 times than normal. Postpartum hemorrhage after vaginal or cesarean delivery was 2.4% and 6.3%, respectively. Based on these results, routine coagulation test monitoring in IHCP to minimize neuraxial anesthesia complications or predict postpartum hemorrhage was not necessary. Therefore, neuraxial anesthesia is not necessarily be delayed or avoided in pregnant patient with IHCP^[50].

Anesthesia selection for AFLP should be individualized. General anesthesia with RSI is recommended in case of severe coagulopathy. Perioperative anesthetic care includes establishing adequate iv access with readily available cross matched blood and blood products since PPH is anticipated^[49].

In summary, particularly spinal anesthesia is the 1st choice for patients with HELLP syndrome scheduled to undergo CS if there is no progressive thrombocytopenia. Close patient monitoring is a must against hemorrhagic complications, DIC or eclampsia at all times. If neuraxial anesthesia is contraindicated, general anesthesia with RSI should be performed especially in hypertensive patients. Additionally, risk of aspiration due to full stomach and/or difficult airway should be taken into account. General anesthesia is indicated as a 1st option when platelets < 80000/ μ L (class 1 or partially class 2 HELLP syndrome)^[71].

In conclusion, selection of either general or regional, or MAC alone may not be sufficient enough for good survival and better outcomes because induction of a safe anesthesia in this specific group needs special attention and care with rational choice of drugs under constant careful monitoring. Prevention of further liver injury can be provided by optimizing hepatic blood flow and oxygenation. Effects of anesthesia type and local and general anesthetic drugs on the liver should be carefully considered as well.

REFERENCES

- 1 **Sasaki KJ.** Liver Disease and Pregnancy. [updated 2015 Aug 27]. Available from: URL: <http://emedicine.medscape.com/article/188143-overview#a1>
- 2 **Hepburn IS, Schade RR.** Pregnancy-associated liver disorders. *Dig Dis Sci* 2008; **53**: 2334-2358 [PMID: 18256934 DOI: 10.1007/s10620-007-0167-9]
- 3 **Riely CA.** Liver disease in the pregnant patient. *American College of Gastroenterology. Am J Gastroenterol* 1999; **94**: 1728-1732 [PMID: 10406228 DOI: 10.1111/j.1572-0241.1999.01199.x]
- 4 **Lee NM, Brady CW.** Liver disease in pregnancy. *World J Gastroenterol* 2009; **15**: 897-906 [PMID: 19248187 DOI: 10.3748/wjg.15.897]
- 5 **Fairweather DV.** Nausea and vomiting in pregnancy. *Am J Obstet Gynecol* 1968; **102**: 135-175 [PMID: 4877794 DOI: 10.1016/0002-9378(68)90445-6]
- 6 **Golberg D, Szilagyi A, Graves L.** Hyperemesis gravidarum

- and *Helicobacter pylori* infection: a systematic review. *Obstet Gynecol* 2007; **110**: 695-703 [PMID: 17766620 DOI: 10.1097/01.AOG.0000278571.93861.26]
- 7 **Schutt VA**, Minuk GY. Liver diseases unique to pregnancy. *Best Pract Res Clin Gastroenterol* 2007; **21**: 771-792 [PMID: 17889807 DOI: 10.1016/j.bpg.2007.05.004]
 - 8 **American College of Obstetrics and Gynecology**. ACOG (American College of Obstetrics and Gynecology) Practice Bulletin: nausea and vomiting of pregnancy. *Obstet Gynecol* 2004; **103**: 803-814 [PMID: 15051578 DOI: 10.1097/00006250-200404000-00045]
 - 9 **Adams RH**, Gordon J, Combes B. Hyperemesis gravidarum. I. Evidence of hepatic dysfunction. *Obstet Gynecol* 1968; **31**: 659-664 [PMID: 5646397 DOI: 10.1097/00006250-196805000-00011]
 - 10 **Larrey D**, Rueff B, Feldmann G, Degott C, Danan G, Benhamou JP. Recurrent jaundice caused by recurrent hyperemesis gravidarum. *Gut* 1984; **25**: 1414-1415 [PMID: 6510771 DOI: 10.1136/gut.25.12.1414]
 - 11 **Abell TL**, Riely CA. Hyperemesis gravidarum. *Gastroenterol Clin North Am* 1992; **21**: 835-849 [PMID: 1478739]
 - 12 **Hay JE**. Liver disease in pregnancy. *Hepatology* 2008; **47**: 1067-1076 [PMID: 18265410 DOI: 10.1002/hep.22130]
 - 13 **Matthews A**, Haas DM, O'Mathúna DP, Dowswell T. Interventions for nausea and vomiting in early pregnancy. *Cochrane Database Syst Rev* 2015; **(9)**: CD007575 [PMID: 26348534 DOI: 10.1002/14651858.CD007575]
 - 14 **Sahakian V**, Rouse D, Sipes S, Rose N, Niebyl J. Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebo-controlled study. *Obstet Gynecol* 1991; **78**: 33-36 [PMID: 2047064]
 - 15 **Quinla JD**, Hill DA. Nausea and vomiting of pregnancy. *Am Fam Physician* 2003; **68**: 121-128 [PMID: 12887118]
 - 16 **Bolin M**, Åkerud H, Cnattingius S, Stephansson O, Wikström AK. Hyperemesis gravidarum and risks of placental dysfunction disorders: a population-based cohort study. *BJOG* 2013; **120**: 541-547 [PMID: 23360164 DOI: 10.1111/1471-0528.12132]
 - 17 **Veenendaal MV**, van Abeelen AF, Painter RC, van der Post JA, Roseboom TJ. Consequences of hyperemesis gravidarum for offspring: a systematic review and meta-analysis. *BJOG* 2011; **118**: 1302-1313 [PMID: 21749625 DOI: 10.1111/j.1471-0528.2011.03023.x]
 - 18 **Watson WJ**, Seeds JW. Acute fatty liver of pregnancy. *Obstet Gynecol Surv* 1990; **45**: 585-591 [PMID: 2204851 DOI: 10.1097/0006254-199009000-00004]
 - 19 **Ibdah JA**. Acute fatty liver of pregnancy: an update on pathogenesis and clinical implications. *World J Gastroenterol* 2006; **12**: 7397-7404 [PMID: 17167825 DOI: 10.3748/wjg.v12.i46.7397]
 - 20 **Browning MF**, Levy HL, Wilkins-Haug LE, Larson C, Shih VE. Fetal fatty acid oxidation defects and maternal liver disease in pregnancy. *Obstet Gynecol* 2006; **107**: 115-120 [PMID: 16394048 DOI: 10.1097/01.AOG.0000191297.47183.bd]
 - 21 **Benjaminov FS**, Heathcote J. Liver disease in pregnancy. *Am J Gastroenterol* 2004; **99**: 2479-2488 [PMID: 15571598 DOI: 10.1111/j.1572-0241.2004.30231.x]
 - 22 **Nelson DB**, Yost NP, Cunningham FG. Acute fatty liver of pregnancy: clinical outcomes and expected duration of recovery. *Am J Obstet Gynecol* 2013; **209**: 456.e1-456.e7 [PMID: 23860212 DOI: 10.1016/j.ajog.2013.07.006]
 - 23 **Minakami H**, Morikawa M, Yamada T, Yamada T, Akaishi R, Nishida R. Differentiation of acute fatty liver of pregnancy from syndrome of hemolysis, elevated liver enzymes and low platelet counts. *J Obstet Gynaecol Res* 2014; **40**: 641-649 [PMID: 24428400 DOI: 10.1111/jog.12282]
 - 24 **Ko H**, Yoshida EM. Acute fatty liver of pregnancy. *Can J Gastroenterol* 2006; **20**: 25-30 [PMID: 16432556 DOI: 10.1155/2006/638131]
 - 25 **Joshi D**, James A, Quaglia A, Westbrook RH, Heneghan MA. Liver disease in pregnancy. *Lancet* 2010; **375**: 594-605 [PMID: 20159293 DOI: 10.1016/S0140-6736(09)61495-1]
 - 26 **Kia L**, Rinella ME. Interpretation and management of hepatic abnormalities in pregnancy. *Clin Gastroenterol Hepatol* 2013; **11**: 1392-1398 [PMID: 23707777 DOI: 10.1016/j.cgh.2013.05.016]
 - 27 **Knight M**, Nelson-Piercy C, Kurinczuk JJ, Spark P, Brocklehurst P. A prospective national study of acute fatty liver of pregnancy in the UK. *Gut* 2008; **57**: 951-956 [PMID: 18332072 DOI: 10.1136/gut.2008.148676]
 - 28 **Kamimura K**, Abe H, Kawai H, Kamimura H, Kobayashi Y, Nomoto M, Aoyagi Y, Terai S. Advances in understanding and treating liver diseases during pregnancy: A review. *World J Gastroenterol* 2015; **21**: 5183-5190 [PMID: 25954092 DOI: 10.3748/wjg.v21.i17.5183]
 - 29 **Zhou G**, Zhang X, Ge S. Retrospective analysis of acute fatty liver of pregnancy: twenty-eight cases and discussion of anesthesia. *Gynecol Obstet Invest* 2013; **76**: 83-89 [PMID: 23796980 DOI: 10.1159/000351565]
 - 30 **Knox TA**, Olans LB. Liver disease in pregnancy. *N Engl J Med* 1996; **335**: 569-576 [PMID: 8678935 DOI: 10.1056/NEJM199608223350807]
 - 31 **Reyes H**. Sex hormones and bile acids in intrahepatic cholestasis of pregnancy. *Hepatology* 2008; **47**: 376-379 [PMID: 18220280 DOI: 10.1002/hep.22139]
 - 32 **Than NN**, Neuberger J. Liver abnormalities in pregnancy. *Best Pract Res Clin Gastroenterol* 2013; **27**: 565-575 [PMID: 24090943 DOI: 10.1016/j.bpg.2013.06.015]
 - 33 **Jacquemin E**, Cresteil D, Manouvrier S, Boute O, Hadchouel M. Heterozygous non-sense mutation of the MDR3 gene in familial intrahepatic cholestasis of pregnancy. *Lancet* 1999; **353**: 210-211 [PMID: 9923886 DOI: 10.1016/S0140-6736(05)77221-4]
 - 34 **Reyes H**, Simon FR. Intrahepatic cholestasis of pregnancy: an estrogen-related disease. *Semin Liver Dis* 1993; **13**: 289-301 [PMID: 8235718 DOI: 10.1055/s-2007-1007357]
 - 35 **Meng LJ**, Reyes H, Axelson M, Palma J, Hernandez I, Ribalta J, Sjövall J. Progesterone metabolites and bile acids in serum of patients with intrahepatic cholestasis of pregnancy: effect of ursodeoxycholic acid therapy. *Hepatology* 1997; **26**: 1573-1579 [PMID: 9398000 DOI: 10.1002/hep.510260627]
 - 36 **Kondrackiene J**, Kupcinskas L. Intrahepatic cholestasis of pregnancy-current achievements and unsolved problems. *World J Gastroenterol* 2008; **14**: 5781-5788 [PMID: 18855975 DOI: 10.3748/wjg.14.5781]
 - 37 **Bacq Y**. Liver diseases unique to pregnancy: a 2010 update. *Clin Res Hepatol Gastroenterol* 2011; **35**: 182-193 [PMID: 21310683 DOI: 10.1016/j.clinre.2010.11.011]
 - 38 **Lata I**. Hepatobiliary diseases during pregnancy and their management: An update. *Int J Crit Illn Inj Sci* 2013; **3**: 175-182 [PMID: 24404454 DOI: 10.4103/2229-5151.119196]
 - 39 **Steven MM**. Pregnancy and liver disease. *Gut* 1981; **22**: 592-614 [PMID: 7021334 DOI: 10.1136/gut.22.7.592]
 - 40 **Liu Y**, Qiao F, Liu H, Liu D. Ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy. *J Huazhong Univ Sci Technolog Med Sci* 2006; **26**: 350-352 [PMID: 16961291 DOI: 10.1007/BF02829573]
 - 41 **Kondrackiene J**, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. *Gastroenterology* 2005; **129**: 894-901 [PMID: 16143129 DOI: 10.1053/j.gastro.2005.06.019]
 - 42 **Rioseco AJ**, Ivankovic MB, Manzur A, Hamed F, Kato SR, Parer JT, Germain AM. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. *Am J Obstet Gynecol* 1994; **170**: 890-895 [PMID: 8141222 DOI: 10.1016/S0002-9378(94)70304-3]
 - 43 **Falconer JD**, Smith AN, Eastwood MA. The effects of bile acids on colonic motility in the rabbit. *Q J Exp Physiol Cogn Med Sci* 1980; **65**: 135-144 [PMID: 6902962 DOI: 10.1113/expphysiol.1980.sp002497]
 - 44 **Kirwan WO**, Smith AN, Mitchell WD, Falconer JD, Eastwood MA. Bile acids and colonic motility in the rabbit and the human. *Gut* 1975; **16**: 894-902 [PMID: 1193418 DOI: 10.1136/gut.16.11.894]
 - 45 **Roncaglia N**, Arreghini A, Locatelli A, Bellini P, Andreotti C, Ghidini A. Obstetric cholestasis: outcome with active management. *Eur J Obstet Gynecol Reprod Biol* 2002; **100**: 167-170 [PMID: 11750958 DOI: 10.1016/S0301-2115(01)00463-8]
 - 46 **Giantz A**, Marschall HU, Mattsson LA. Intrahepatic cholestasis

- of pregnancy: Relationships between bile acid levels and fetal complication rates. *Hepatology* 2004; **40**: 467-474 [PMID: 15368452 DOI: 10.1002/hep.20336]
- 47 **Ahmed KT**, Almashtawi AA, Rahman RN, Hammoud GM, Ibdah JA. Liver diseases in pregnancy: diseases unique to pregnancy. *World J Gastroenterol* 2013; **19**: 7639-7646 [PMID: 24282353 DOI: 10.3748/wjg.v19.i43.7639]
 - 48 **Goel A**, Jamwal KD, Ramachandran A, Balasubramanian KA, Eapen CE. Pregnancy-related liver disorders. *J Clin Exp Hepatol* 2014; **4**: 151-162 [PMID: 25755551 DOI: 10.1016/j.jceh.2013.03.220]
 - 49 **Rahimzadeh P**, Safari S, Faiz SH, Alavian SM. Anesthesia for patients with liver disease. *Hepat Mon* 2014; **14**: e19881 [PMID: 25031586 DOI: 10.5812/hepatmon.19881]
 - 50 **DeLeon A**, De Oliveira GS, Kalayil M, Narang S, McCarthy RJ, Wong CA. The incidence of coagulopathy in pregnant patients with intrahepatic cholestasis: should we delay or avoid neuraxial analgesia? *J Clin Anesth* 2014; **26**: 623-627 [PMID: 25439411 DOI: 10.1016/j.jclinane.2014.04.013]
 - 51 **Brouwers L**, Koster MP, Page-Christiaens GC, Kemperman H, Boon J, Evers IM, Bogte A, Oudijk MA. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. *Am J Obstet Gynecol* 2015; **212**: 100.e1-100.e7 [PMID: 25046809 DOI: 10.1016/j.ajog.2014.07.026]
 - 52 **Mihu D**, Costin N, Mihu CM, Seicean A, Ciortea R. HELLP syndrome - a multisystemic disorder. *J Gastrointest Liver Dis* 2007; **16**: 419-424 [PMID: 18193124]
 - 53 **Fitzpatrick KE**, Hinshaw K, Kurinczuk JJ, Knight M. Risk factors, management, and outcomes of hemolysis, elevated liver enzymes, and low platelets syndrome and elevated liver enzymes, low platelets syndrome. *Obstet Gynecol* 2014; **123**: 618-627 [PMID: 24499757 DOI: 10.1097/AOG.0000000000000140]
 - 54 **Groot E**, de Groot PG, Fijnheer R, Lenting PJ. The presence of active von Willebrand factor under various pathological conditions. *Curr Opin Hematol* 2007; **14**: 284-289 [PMID: 17414220 DOI: 10.1097/MOH.0b013e3280dce531]
 - 55 **Audibert F**, Friedman SA, Frangieh AY, Sibai BM. Clinical utility of strict diagnostic criteria for the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. *Am J Obstet Gynecol* 1996; **175**: 460-464 [PMID: 8765269 DOI: 10.1016/S0002-9378(96)70162-X]
 - 56 **Rose CH**, Thigpen BD, Bofill JA, Cushman J, May WL, Martin JN. Obstetric implications of antepartum corticosteroid therapy for HELLP syndrome. *Obstet Gynecol* 2004; **104**: 1011-1014 [PMID: 15516393 DOI: 10.1097/01.AOG.0000143262.85124.e8]
 - 57 **Martin JN**, Blake PG, Lowry SL, Perry KG, Files JC, Morrison JC. Pregnancy complicated by preeclampsia-eclampsia with the syndrome of hemolysis, elevated liver enzymes, and low platelet count: how rapid is postpartum recovery? *Obstet Gynecol* 1990; **76**: 737-741 [PMID: 2216215 DOI: 10.1097/00006250-199011000-00001]
 - 58 **Padden MO**. HELLP syndrome: recognition and perinatal management. *Am Fam Physician* 1999; **60**: 829-36, 839 [PMID: 10498110]
 - 59 **Geary M**. The HELLP syndrome. *Br J Obstet Gynaecol* 1997; **104**: 887-891 [PMID: 9255078 DOI: 10.1111/j.1471-0528.1997.tb14346.x]
 - 60 **Habli M**, Eftekhari N, Wiebracht E, Bombrys A, Khabbaz M, How H, Sibai B. Long-term maternal and subsequent pregnancy outcomes 5 years after hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. *Am J Obstet Gynecol* 2009; **201**: 385.e1-385.e5 [PMID: 19716544 DOI: 10.1016/j.ajog.2009.06.033]
 - 61 **Palit S**, Palit G, Vercauteren M, Jacquemyn Y. Regional anaesthesia for primary caesarean section in patients with preterm HELLP syndrome: a review of 102 cases. *Clin Exp Obstet Gynecol* 2009; **36**: 230-234 [PMID: 20101854]
 - 62 **Koyama S**, Tomimatsu T, Kanagawa T, Sawada K, Tsutsui T, Kimura T, Chang YS, Wasada K, Imai S, Murata Y. Spinal subarachnoid hematoma following spinal anesthesia in a patient with HELLP syndrome. *Int J Obstet Anesth* 2010; **19**: 87-91 [PMID: 19945267 DOI: 10.1016/j.ijoa.2009.05.007]
 - 63 **Lautt WW**. The 1995 Ciba-Geigy Award Lecture. Intrinsic regulation of hepatic blood flow. *Can J Physiol Pharmacol* 1996; **74**: 223-233 [PMID: 8773400 DOI: 10.1139/y96-029]
 - 64 **Gelman S**. General anesthesia and hepatic circulation. *Can J Physiol Pharmacol* 1987; **65**: 1762-1779 [PMID: 3319112 DOI: 10.1139/y87-276]
 - 65 **Armbruster K**, Nöldge-Schomburg GF, Dressler IM, Fittkau AJ, Haberstroh J, Geiger K. The effects of desflurane on splanchnic hemodynamics and oxygenation in the anesthetized pig. *Anesth Analg* 1997; **84**: 271-277 [PMID: 9024014 DOI: 10.1097/0000539-199702000-00007]
 - 66 **O'Connor CJ**, Rothenberg DM, Tuman KJ. Anesthesia and the hepatobiliary system. In: Miller RD, editor. *Miller's Anesthesia*. 6th ed. Philadelphia: Churchill Livingstone/Elsevier, 2005: 2209-2229
 - 67 **Dabbagh A**, Rajaei S. Xenon: a solution for anesthesia in liver disease? *Hepat Mon* 2012; **12**: e8437 [PMID: 23300498 DOI: 10.5812/hepatmon.8437]
 - 68 **Hoetzel A**, Ryan H, Schmidt R. Anesthetic considerations for the patient with liver disease. *Curr Opin Anaesthesiol* 2012; **25**: 340-347 [PMID: 22450699 DOI: 10.1097/ACO.0b013e3283532b02]
 - 69 **Kiamanesh D**, Rumley J, Moitra VK. Monitoring and managing hepatic disease in anaesthesia. *Br J Anaesth* 2013; **111** Suppl 1: i50-i61 [PMID: 24335399 DOI: 10.1093/bja/aet378]
 - 70 **Kurosawa M**, Unno T, Aikawa Y, Yoneda M. Neural regulation of hepatic blood flow in rats: an in vivo study. *Neurosci Lett* 2002; **321**: 145-148 [PMID: 11880193 DOI: 10.1016/S0304-3940(01)02509-5]
 - 71 **del-Rio-Vellosillo M**, Garcia-Medina JJ. Anesthetic considerations in HELLP syndrome. *Acta Anaesthesiol Scand* 2016; **60**: 144-157 [PMID: 26446688 DOI: 10.1111/aas.12639]

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Awareness during anesthesia: Current status in Japan

Yasuhiro Morimoto

Yasuhiro Morimoto, Department of Anesthesia, Ube Industries Central Hospital, Yamaguchi 755-0151, Japan

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Correspondence to: Yasuhiro Morimoto, MD, Department of Anesthesia, Ube Industries Central Hospital, 750 Nishikiwa Ube, Yamaguchi 755-0151, Japan. yasumorimo@gmail.com
 Telephone: +81-836-222291

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Abstract

Intraoperative awareness is the explicit recall of sensory perceptions during general anesthesia. I presume the epidemiology and characteristics of intraoperative awareness from these surveys in Japan. A questionnaire survey was conducted *via* the Internet. The first survey was conducted in 2008. Our survey showed 17% of anesthesiologists experienced definite or possible awareness. The second survey was conducted to

evaluate the first survey in detail in 2008. A total of 172 anesthesiologists answered. The total number of reported anesthetic cases was 85156. Twenty-four cases of definite or possible awareness were reported by 21 anesthesiologists. The most surprising finding was total intravenous anesthesia (TIVA) was used in 21 of the 24 cases. The third survey was conducted in 2011 as a continuous survey. Six cases of definite or possible awareness were reported by six anesthesiologists (7%). Two cases were maintained by TIVA, and 2 cases were sevoflurane. The survey showed 76% anesthesiologists routinely use bispectral index (BIS) for TIVA, but for sevoflurane only 27% anesthesiologists routinely use BIS. The incidence of intraoperative awareness decreased in the third survey. The continuous survey revealed the current status of daily anesthesia and the results might be used to prevent the awareness during general anesthesia.

Key words: Awareness; Bispectral index; Sevoflurane; Total intravenous anesthesia

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Core tip: The epidemiology and characteristics of intraoperative awareness from these surveys in Japan are reviewed in this manuscript. The incidence of intraoperative awareness decreased in the third survey. The continuous survey revealed the current status of daily anesthesia and the results might be used to prevent the awareness during general anesthesia.

Morimoto Y. Awareness during anesthesia: Current status in Japan. *World J Anesthesiol* 2016; 5(3): 62-66 Available from: URL: <http://www.wjgnet.com/2218-6182/full/v5/i3/62.htm> DOI: <http://dx.doi.org/10.5313/wja.v5.i3.62>

INTRODUCTION

Intraoperative awareness is a rare but still serious

problem in clinical anesthesia. It is defined as an explicit recall of sensory and auditory awareness during general anesthesia. The incidence of intraoperative awareness has been reported as 0.1%-0.2%^[1,2]. Although this problem is rare, some patients might suffer prolonged psychological side effects, including post-traumatic stress disorders.

Widespread changes have occurred after the introduction of remifentanyl in Japan in 2007. This caused a reduction of the maintenance dose or concentrations in volatile anesthesia. These changes might induce the increase in the incidence of intraoperative awareness. Therefore, we conducted three separate questionnaire surveys of anesthesiologists from 2008 through 2011. From the results of these surveys, we were able to make presumptions about the epidemiology and characteristics of intraoperative awareness, and discuss recommendations to decrease its incidence.

THE FIRST SURVEY

Remifentanyl was released in Japan in 2007, followed by widespread changes in anesthesiology procedures. The doses of anesthetics used in combination with remifentanyl might decrease. Moreover, the choice of total intravenous anesthesia (TIVA) increased. These changes might have increased the incidence of awareness.

The incidence of awareness during general anesthesia has not been evaluated prospectively in Japan. Therefore, we conducted a questionnaire survey in 2008^[3]. The purpose of the survey was to assess the status of anesthesia after the release of remifentanyl and the incidence of intraoperative awareness during remifentanyl anesthesia.

Letters were sent to the chief staff anesthesiologists in Japanese hospitals to response the survey. The responders answered the survey questions anonymously on an open access website. It was designed to acquire the information concerning daily clinical anesthesia, choice of anesthetics, and experiences of intraoperative awareness during 2007.

Awareness cases in the first survey

A total of 145 anesthesiologists responded to the survey. Five (3%) anesthesiologists reported cases of definite awareness, and 21 (14%) anesthesiologists reported cases of possible awareness.

The relationship between daily anesthesia practice and experience with intraoperative awareness was evaluated. Concerning the standard maintenance concentration of sevoflurane in combination with remifentanyl, 7% of the anesthesiologists used 0.7%, 44% used 1%, 30% used 1.2%, and 16% used 1.5%. These low concentrations might be explained by the manufacturer's usage guide for remifentanyl stating that sevoflurane should be used at a 1.0% concentration in combination with remifentanyl. The choice of sevoflur-

ane concentrations might also have been influenced by a report by Manyam *et al*^[4] that recommended 0.75% sevoflurane in combination with remifentanyl. Figure 1 shows the relationship between cases of awareness reported by the anesthesiologists and their standard maintenance sevoflurane concentration. The anesthesiologists who experienced definite awareness cases maintained sevoflurane concentrations below 1.0%. Cases of intraoperative awareness were significantly lower for anesthesiologists who maintained sevoflurane concentrations above 1.2% than for those who maintained concentrations below 1.0%. This result is compatible with a study by Avidan *et al*^[5] that found the incidence of awareness in patients maintained with end-tidal volatile anaesthetic concentrations above 0.7 minimum alveolar concentration (1.2%-1.4% sevoflurane) was 0.1%, which is compatible with the incidence in patients maintained at target bispectral index (BIS) values between 40 and 60. Our results show that, after the release of remifentanyl, the incidence of intraoperative awareness might have been higher because 17% of anesthesiologists experienced definite or possible awareness cases in one year. Maintaining sevoflurane concentrations below 1.0% might be associated with a high risk for intraoperative awareness. Our results indicate that maintaining volatile anesthetic concentrations is the most important factor in preventing intraoperative awareness.

THE SECOND SURVEY

To get more detailed information, the second survey was planned^[6]. The second survey was planned to obtain information concerning the cases involving intraoperative awareness in 2008. The survey method was similar to that of the first survey. A total of 172 anesthesiologists responded to the second survey. The total number of general anesthesia cases in 2008 was 85156 in this survey. Twenty-one anesthesiologists reported 24 cases of definite or possible awareness, of which 14 were cases of definite awareness and 10 were possible awareness. One patient experienced definite awareness twice, and another patient suffered possible awareness three times. The incidence of intraoperative awareness, including cases of possible awareness, was 0.028%. Many previous studies demonstrate a higher incidence of about 0.2%^[1,2]. However, the results of a retrospective study revealed that the actual incidence of awareness is underestimated. For example, a recent report^[7] from the Fifth National Audit Project (NAP5), the national United Kingdom survey of intraoperative awareness during general anesthesia based on voluntary reporting by doctors, estimated that the incidence of awareness in general anesthesia was as low as 1:15414. Our survey results are consistent with the results of a retrospective study reported by Mashour *et al*^[8]. The results of our study indicate that the incidence of awareness during anesthesia in Japan is compatible

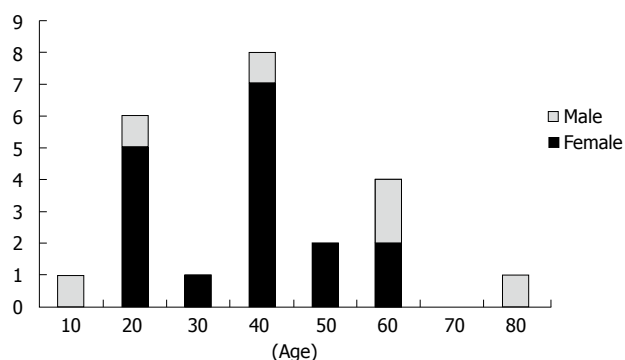


Figure 1 Patient demographics of definite and possible awareness cases. Sixteen (67%) were < 50 years old, 6 (26%) were men, and 17 (74%) were women.

with the incidence reported in other countries.

Awareness cases in the second survey

The most surprising finding from the second survey was that propofol was used as the anesthetic in TIVA in 21 of the 24 cases. Therefore, our results provide information about the characteristics of awareness in TIVA. Based on the data about daily anesthesia acquired from the survey, 16% of anesthesiologists reported using mostly propofol, 17% used more propofol than volatile anesthetics, 9% used propofol and volatile anesthetics equally, 26% used more volatile anesthetics than propofol, and 32% used mainly volatile anesthetics. This result indicates that volatile anesthetics were chosen more commonly than propofol. Our survey indicates that TIVA might be a risk for intraoperative awareness.

TIVA's role as a risk for intraoperative awareness is still controversial. No prospective studies evaluated the incidence of awareness between the anesthetics. However, some studies have stated to TIVA as a risk factor for awareness^[9]. One reported risk is associated with the failures of infusion pumps. The absence of real-time feedback of blood anesthetic concentrations might also be a risk factor. Moreover, the inter-individual variability in need of anesthetics essential to prevent movement during the noxious stimulation may be not as much of volatile anesthetics than TIVA^[10]. The target-controlled infusion system predicts the plasma anesthetics concentrations, which might be different from the actual concentration. Therefore, the use of brain monitoring, including BIS, is essential. In our survey, BIS monitoring was used in seven (33%) out of 21 awareness cases that were maintained by TIVA. This shows that the use of a BIS monitor could not prevent all cases of awareness. The usefulness of BIS to prevent awareness in TIVA should be evaluated in a future study.

In our survey, 16 (67%) of the patients experiencing awareness during general anesthesia were below 50 years of age, and the majority of patients were female (Figure 1). Similarly, previous studies showed that the incidence of awareness is higher in female patients^[11]. Moreover, women recovered from propofol anesthesia

Table 1 Descriptions of awareness cases

Case	Age	Sex	Anesthetics	BIS monitoring	Detail
1	30	M	Sevoflurane	-	Low sevoflurane concentration before surgery
2	50	M	Sevoflurane	+	Low sevoflurane concentration during bleeding
3	70	F	TIVA	-	
4	80	F	TIVA	-	Trouble in infusion pump

BIS: Bispectral index; TIVA: Total intravenous anesthesia; M: Male; F: Female.

more rapidly than men^[12]. This might indicate that women are less sensitive to propofol.

The reported surgical procedures included one craniotomy, four facial operations, seven neck and chest wall operations, one cardiac operation, three gynecologic operations, three operations for fractures of the leg, and one spinal operation. The results indicate that the surgical procedures with the highest risk for awareness are cervicofacial and chest wall surgery. In brief, surgery in the upper part of body produced the highest risk of awareness. Gynecologic and orthopedic procedures were the next most likely to be associated with intraoperative awareness.

The high incidence of awareness in cervicofacial surgery^[2] has not reported previously. Although the reasons are unclear, it is thought that visual and auditory stimulation during surgery play a part^[12]. The higher risk during orthopedic surgery supports this hypothesis because elevated levels of acoustic stimulation are common during orthopedic operations. There might also be an increased risk of awareness when general anesthesia is maintained by TIVA.

THE THIRD SURVEY

The third survey was conducted in 2011 as a continuous survey^[13]. We particularly sought to evaluate whether TIVA is a risk factor for intraoperative awareness. The survey was designed to obtain information regarding cases involving intraoperative awareness in 2010. Responses were received from 119 anesthesiologists. Because of incomplete data, only 91 responses were analyzed. Respondents reported 29340 general anesthesia cases in 2010; volatile anesthetics were used in 18109 cases, and propofol was used in 10184 cases.

Anesthesiologists reported six cases of definite or possible awareness. By the third survey, the incidence of awareness, including possible awareness, was 0.02%. This result is similar to the result of the second survey. Sevoflurane and propofol were used for maintenance of general anesthesia in four cases, two cases for each anesthetic (Table 1). The remaining two cases involved caesarean deliveries. Therefore, the incidence of intraoperative awareness in procedures

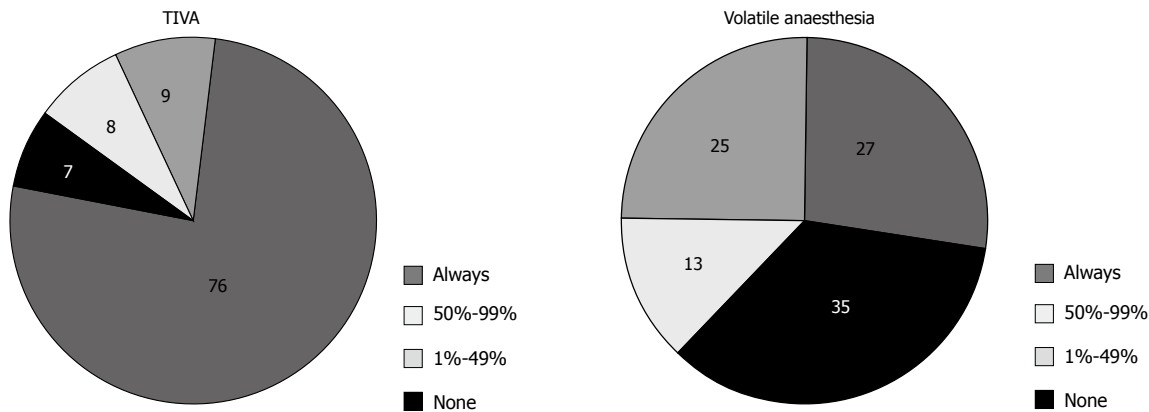


Figure 2 Use of bispectral index monitoring in total intravenous anesthesia or volatile anesthesia. Use of BIS monitoring was more frequent during TIVA than volatile anesthesia. BIS: Bispectral index; TIVA: Total intravenous anesthesia.

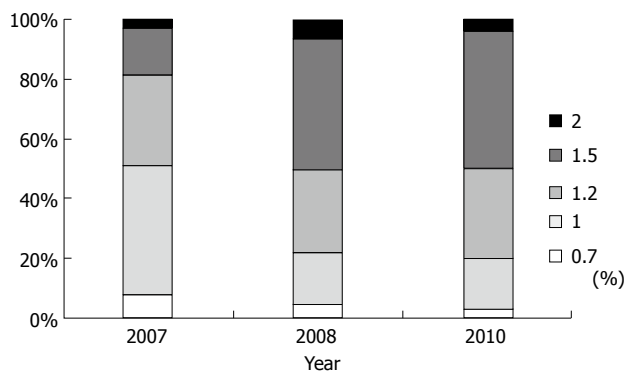


Figure 3 Standard maintenance sevoflurane concentration for daily clinical anesthesia in the three surveys.

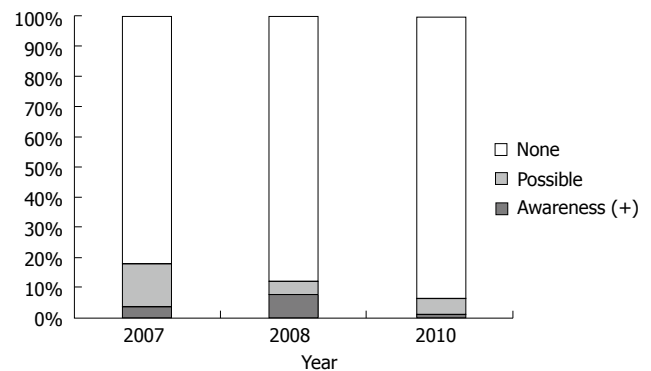


Figure 4 The experience of awareness cases by respondents in the three surveys. Experience of awareness decreased in the third survey.

with volatile agents and TIVA was 0.011%, and 0.019%, respectively. The difference in the incidence of awareness between volatile anesthesia and TIVA was not statistically significant ($P = 0.622$).

The survey results show that 74% of anesthesiologists routinely used BIS for TIVA, but only 28% of anesthesiologists routinely used BIS for volatile anesthesia (Figure 2). Use of BIS monitoring was more frequent during TIVA than volatile anesthesia ($P < 0.01$). These results suggest that anesthesiologists feel that there is a need for BIS monitoring when they use TIVA for maintenance of general anesthesia, perhaps because propofol has a wide variability in dosing.

The results of our second survey, which showed that TIVA was a risk factor for awareness, might have affected the frequency with which anesthesiologists used BIS monitoring. This concept is supported by the results of a review by Avidan *et al*^[5]. The authors recommended using an end-tidal anesthetic concentration alarm rather than BIS when a volatile agent is used as the primary anesthetics. On the other hand, they suggested using BIS when volatile anesthetics are not used, because BIS monitoring prevents awareness in TIVA.

In one of two reported awareness cases, the patient might have awakened when sevoflurane was maintained at a low concentration before surgery; in

the second case, the patient might have awakened when the sevoflurane concentration dropped because of hypotension caused by massive blood loss. These awareness cases could have been prevented if the sevoflurane concentration had been maintained above a certain level. There should be a further decrease in the incidence of awareness shortly.

COMPARISON OF RESULTS OF THE THREE SURVEYS

We conducted three surveys at separate times. The results were quickly disseminated to Japanese anesthesiologists after each survey. Figure 3 shows the standard maintenance sevoflurane concentration for daily clinical anesthesia reported in each of the three surveys. In the first survey, only 20% of the anesthesiologists used a sevoflurane concentration above 1.5%. However, in the second and third surveys, about 50% of the anesthesiologists used sevoflurane concentrations above 1.5%. This increased use of higher sevoflurane concentrations might be the reason for the lower incidence of awareness under sevoflurane reported in the second and third surveys. In the first survey, 18% of the anesthesiologists experienced cases

of intraoperative awareness, including possible cases. However, this decreased to 7% in the third survey (Figure 4). Moreover, the tendency of TIVA to be a risk factor for intraoperative awareness was not observed. The continuous survey revealed the current status of anesthesia in Japan, and the results might be used to prevent awareness during general anesthesia.

In conclusion, awareness with explicit recall during general anesthesia remains a problem that should be prevented. Understanding the incidence of awareness and the status of daily anesthesia are one possible approach to a cure for this problem.

REFERENCES

- 1 **Ghoneim MM.** Awareness during anesthesia. *Anesthesiology* 2000; **92**: 597-602 [PMID: 10691248 DOI: 10.1097/00000542-200002000-00043]
- 2 **Sebel PS, Bowdle TA, Ghoneim MM, Rampil IJ, Padilla RE, Gan TJ, Domino KB.** The incidence of awareness during anesthesia: a multicenter United States study. *Anesth Analg* 2004; **99**: 833-839, table of contents [PMID: 15333419 DOI: 10.1213/01.ANE.00-00130261.90896.6C]
- 3 **Morimoto Y, Nogami Y.** Intraoperative awareness during sevoflurane-remifentanyl anesthesia. *Rinshomasui (J Clin Anesth)* 2009; **33**: 1283-1285
- 4 **Manyam SC, Gupta DK, Johnson KB, White JL, Pace NL, Westenskow DR, Egan TD.** Opioid-volatile anesthetic synergy: a response surface model with remifentanyl and sevoflurane as prototypes. *Anesthesiology* 2006; **105**: 267-278 [PMID: 16871060 DOI: 10.1097/00000542-200608000-00009]
- 5 **Avidan MS, Mashour GA.** Prevention of intraoperative awareness with explicit recall: making sense of the evidence. *Anesthesiology* 2013; **118**: 449-456 [PMID: 23263014 DOI: 10.1097/ALN.0b013-e31827ddd2c]
- 6 **Morimoto Y, Nogami Y, Harada K, Tsubokawa T, Masui K.** Awareness during anesthesia: the results of a questionnaire survey in Japan. *J Anesth* 2011; **25**: 72-77 [PMID: 21153846 DOI: 10.1007/s00540-010-1050-y]
- 7 **Pandit JJ, Cook TM, Jonker WR, O'Sullivan E.** A national survey of anaesthetists (NAP5 Baseline) to estimate an annual incidence of accidental awareness during general anaesthesia in the UK. *Anaesthesia* 2013; **68**: 343-353 [PMID: 23488832 DOI: 10.1111/anae.12190]
- 8 **Mashour GA, Wang LY, Turner CR, Vandervest JC, Shanks A, Tremper KK.** A retrospective study of intraoperative awareness with methodological implications. *Anesth Analg* 2009; **108**: 521-526 [PMID: 19151282 DOI: 10.1213/ane.0b013e3181732b0c]
- 9 **Errando CL, Sigl JC, Robles M, Calabuig E, García J, Arocas F, Higuera R, Del Rosario E, López D, Peiró CM, Soriano JL, Chaves S, Gil F, García-Aguado R.** Awareness with recall during general anaesthesia: a prospective observational evaluation of 4001 patients. *Br J Anaesth* 2008; **101**: 178-185 [PMID: 18515816 DOI: 10.1093/bja/aen144]
- 10 **Vuyk J, Lim T, Engbers FH, Burm AG, Vletter AA, Bovill JG.** Pharmacodynamics of alfentanil as a supplement to propofol or nitrous oxide for lower abdominal surgery in female patients. *Anesthesiology* 1993; **78**: 1036-1045; discussion 23A [PMID: 8512096 DOI: 10.1097/00000542-199306000-00005]
- 11 **Domino KB, Posner KL, Caplan RA, Cheney FW.** Awareness during anesthesia: a closed claims analysis. *Anesthesiology* 1999; **90**: 1053-1061 [PMID: 10201677 DOI: 10.1097/00000542-199904000-00019]
- 12 **Gan TJ, Glass PS, Sigl J, Sebel P, Payne F, Rosow C, Embree P.** Women emerge from general anesthesia with propofol/alfentanil/nitrous oxide faster than men. *Anesthesiology* 1999; **90**: 1283-1287 [PMID: 10319774 DOI: 10.1097/00000542-199905000-00010]
- 13 **Thiele RH, Knipper E, Dunn LK, Nemergut EC.** Auditory stimuli as a contributor to consciousness while under general anesthesia. *Med Hypotheses* 2013; **80**: 568-572 [PMID: 23419669 DOI: 10.1016/j.mehy.2013.01]

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Retrospective Study

Intrathecal morphine *vs* femoral nerve block for postoperative-analgesia after total knee arthroplasty: A two-year retrospective analysis

Kalindi DeSousa, Rajkumar Chandran

Kalindi DeSousa, Rajkumar Chandran, Department of Anaesthesia, Changi General Hospital, Singapore 529889, Singapore

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Correspondence to: Kalindi DeSousa, FFARCSI, MD, DA, Senior Consultant, Department of Anaesthesia, Changi General Hospital, 2 Simei Street 3, Singapore 529889, Singapore. kalindidesousa@gmail.com
Telephone: +65-98176186

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Abstract

AIM

To compare the efficacy of intrathecal morphine and single shot femoral nerve block for patients undergoing primary total knee arthroplasty.

METHODS

Data was extracted from electronic medical records and case-paper record files of patients who underwent unilateral primary total knee arthroplasty under spinal anesthesia using bupivacaine 12.5 mg with intrathecal morphine (ITM) 0.2 mg and under general anesthesia (GA) with single shot femoral nerve block (FNB) using 20 mL 0.5% bupivacaine at our hospital in 2013 and 2014. All patients had received peri-articular infiltration as per the hospital protocol. Data for gender, age, weight, American Society of Anesthesiologists status, total surgical time, postoperative pain score using visual analogue scale (VAS) from 1 to 10 at 6 h, 12 h and 24 h postoperatively, 24 h opioid consumption, use of oral multimodal analgesia, postoperative high dependency unit (HDU) admission and the time to discharge from the hospital was collected. The data was analyzed using Mann-Whitney *U* test for continuous variables and Fischer's exact-*t*-test for categorical variables.

RESULTS

Twenty-two patients in ITM group and 32 patients in FNB group were analyzed. Median pain scores using VAS in ITM group were significantly lower at 6 h (0.0 *vs* 2.0, *P* < 0.001), 12 h (0.0 *vs* 2.0, *P* < 0.001) and 24 h (0.0 *vs* 2.0, *P* < 0.001) postoperatively. Also,

postoperative morphine consumption in ITM group was significantly lower ($P < 0.001$). However, median of non-steroid anti-inflammatory drug unit requirement in 24 h postoperatively was statistically significant higher in ITM compared to FNB group (2.0 vs 1.0, $P = 0.025$). The difference in postoperative paracetamol consumption in 24 h was not statistically significant ($P = 0.147$). There was no significant difference in the postoperative HDU admission or time to discharge from the hospital. No respiratory depression in either group was noticed.

CONCLUSION

The ITM group patients had much lower pain scores and morphine requirement in the first 24 hour post-operatively compared to FNB group.

Key words: Postoperative analgesia; Intrathecal morphine; Femoral nerve block; Total knee arthroplasty; Pain after total knee arthroplasty

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Core tip: In this retrospective analysis, intrathecal morphine (ITM) with spinal anesthesia and single shot femoral nerve block (FNB) with general anesthesia were compared in 54 patients undergoing primary total knee arthroplasty over two years at our institute. Pain scores and morphine consumption in 1st 24 h after surgery were significantly lower in ITM group compared to FNB group ($P < 0.001$); while complication rates, high dependency unit admission rates, and time to discharge from the hospital were similar in both groups. Also, patients in ITM group were highly satisfied ($P < 0.001$).

DeSousa K, Chandran R. Intrathecal morphine vs femoral nerve block for postoperative-analgesia after total knee arthroplasty: A two-year retrospective analysis. *World J Anesthesiol* 2016; 5(3): 67-72 Available from: URL: <http://www.wjgnet.com/2218-6182/full/v5/i3/67.htm> DOI: <http://dx.doi.org/10.5313/wja.v5.i3.67>

INTRODUCTION

Total knee arthroplasty (TKA) leads to considerable post-operative pain, which requires optimal control for early mobilization as per the current trend. Femoral nerve block (FNB) and intrathecal morphine (ITM) are commonly used techniques for postoperative analgesia since the recommendation by PROSPECT group^[1] as a part of multimodal technique with non-steroid anti-inflammatory drugs and centrally acting drugs like paracetamol and systemic opioids. To compare the efficacy of these methods, we performed a retrospective analysis of patients who underwent unilateral primary TKA with single shot FNB with general anesthesia (GA) and ITM with spinal anesthesia (SA) in the year 2013 and 2014 at our hospital. Earlier, low dose ITM and ultrasound guided FNB have been compared albeit both

groups had received SA^[2]. In this study, Frassanito *et al*^[2] 0.1 mg ITM was found to be safe and more efficient compared to single shot FNB using 25 mL 0.75% ropivacaine though the lower pain scores and morphine consumption in ITM group compared to FNB group were not statistically significant.

MATERIALS AND METHODS

Methods

After permission from the hospital ethics committee, and approval by SingHealth centralized institutional review board, data was extracted from electronic medical records for all patients who underwent unilateral primary TKA in the year 2013 and 2014. Only those patients who underwent primary TKA under SA using bupivacaine 12.5 mg with ITM 0.2 mg and those who underwent primary TKA under GA with FNB using 20 mL 0.5% bupivacaine at our hospital in 2013 and 2014 were included in this analysis. The case-paper record files were also obtained at this stage and looked into.

In the ITM group, 0.2 mg morphine was mixed with bupivacaine while performing SA. Preservative free morphine is supplied in ampoules of 10 mg in 1 mL. The person performing SA diluted preservative free 10 mg morphine with 9 mL of normal saline to obtain 1 mg/mL under aseptic precautions. From this diluted morphine, 0.2 mL was taken using insulin syringe and mixed with 2.5 mL of isobaric 0.5% bupivacaine. Lumbar puncture was performed under asepsis using either Quincke or Whitacre spinal needle of 25 G and the mixture of bupivacaine and morphine was injected slowly. Only patients who received this dose of morphine and bupivacaine were included in this analysis for uniformity. In the FNB group, FNB was performed before the induction of GA and its effectiveness was confirmed by checking loss of sensation on the medial aspect of leg just below the knee before the start of GA. All FNBs were performed using ultrasound guidance and 22 G Stimuplex needle A50 (by B. Braun Medical Inc. - a stimulating non-echogenic single shot 50 mm needle). GA was induced with appropriate dose of propofol, fentanyl and atracurium and airway maintenance was with laryngeal mask airway. GA was maintained with oxygen, sevoflurane and intermittent doses of morphine. Only patients who received 20 mL of 0.5% bupivacaine for FNB were included in this study for uniformity. Patients who received a different dose of bupivacaine or ropivacaine were not included. Patients who received continuous FNB, FNB plus sciatic block, SA with FNB or any other combination were not included in this analysis.

All patients in both groups had received intra-operative peri-articular infiltration as per the hospital protocol; a mixture of 20 mL of 0.5% bupivacaine with 30 mg ketorolac, and 5 mg morphine plus 20 mL normal saline. In FNB group, the surgeon carried this out at least 120 min after FNB was performed to avoid

Table 1 Demographic data

	ITM (<i>n</i> = 22)	FNB (<i>n</i> = 32)	Statistical significance
Median (IQR) age: Years	69.0 (62.8-74.3)	61.0 (57.0-67)	<i>P</i> = 0.002
Sex: Numbers			
Male	9 (37.5%)	15 (62.5%)	<i>P</i> = 0.665
Female	13 (43.3%)	17 (56.7%)	
Median (IQR) weight: Kg	64.3 (53.2-77.2)	67.3 (61.2-80.2)	<i>P</i> = 0.275
Median (IQR) ASA status	3.0 (2.0-3.0)	2.0 (2.0-3.0)	<i>P</i> = 0.161
Median (IQR) total surgery time in minutes	117.5 (108.8-135.0)	107.5 (86.3-128.8)	<i>P</i> = 0.163

IQR: Interquantile range; *n*: Numbers; ITM: Intrathecal morphine; FNB: Femoral nerve block.

local anesthetic toxicity.

Data for gender, age, weight, total surgical time, ASA status, postoperative pain scores using visual analogue scale (VAS) from 1 to 10 on flexion of the operated knee at 6, 12 and 24 h postoperatively, 24 h opioid consumption, use of oral multimodal analgesia, postoperative high dependency unit (HDU) admission and the time to discharge from the hospital was collected.

All patients had received O₂ 2 lit/min through nasal prongs for the first 12-h after the surgery. Also, we looked for complications such as postoperative nausea and vomiting (PONV), respiratory depression, urinary retention and itching. We defined respiratory depression for this study as respiratory rate < 8/min or SaO₂% < 94%.

Postoperatively, all FNB group patients were prescribed patient controlled analgesia (PCA) with morphine while ITM patients were prescribed intravenous tramadol on as required (PRN) basis. For calculations, tramadol 100 mg was considered equivalent to 10 mg morphine^[3]. Diclofenac, etorocoxib and celecoxib were used orally on PRN basis in both groups. One unit of non-steroidal anti-inflammatory drugs (NSAIDs) was considered as 50 mg diclofenac or 90 mg etorocoxib or 200 mg celecoxib. Patients in both groups were given paracetamol 1 g on PRN basis.

A backward sample size calculation was done for this retrospective study: With a standard deviation (SD) of 10 mg and clinical relevant difference of 10 mg between ITM and FNB (in a ratio of 1:1.5) for the amount of post-operative morphine consumption, the minimum sample size of 20 patients for ITM and 30 patients for FNB were required for a significance level of 5% and power of 90%.

The data was analyzed using Mann-Whitney *U* test for continuous variables and Fisher's Exact test for categorical variables. Patient satisfaction was evaluated from the discharge feedback form.

Ms Carmen Kam Jia Wen, research officer at "Clinical and Trial and Research Unit" (CTRU) at Changi General

Hospital, Singapore helped and reviewed this statistical analysis.

RESULTS

There was no statistically significant difference between two groups as far as the gender, weight, ASA status and total surgery time was concerned (*P* > 0.05). However, median age was significantly older in ITM group than FNB group (69 years vs 61 years, *P* = 0.002) (Table 1). Patients who received additional blocks or continuous femoral block or combined technique were excluded from the analysis. Twenty two patients in ITM group and 32 patients in FNB group were analyzed.

Median pain scores in ITM group were significantly lower at 6 h (0.0 vs 2.0, *P* < 0.001), 12 h (0.0 vs 2.0, *P* < 0.001) and 24 h (0.0 vs 2.0, *P* < 0.001) post-operatively. Also, median of postoperative morphine consumption in ITM group was significantly lower (*P* < 0.001). However, median of NSAID (unit) requirement in 24 h postoperatively was statistically significant higher in ITM compared to FNB group (2.0 vs 1.0, *P* = 0.025). The difference in postoperative paracetamol consumption in 24 h was not statistically significant (*P* = 0.147).

There was no statistically significant difference in the postoperative HDU admission or time to discharge from the hospital.

All patients in ITM group were prescribed antiemetic at regular time interval and hence did not have any incidence of PONV. While the patients in FNB group were prescribed antiemetic on PRN basis; for this reason the incidence of PONV cannot be compared. There were a number of patients who reported PONV in FNB group: 16 patients at 6 h, 11 patients at 12 h and 9 patients at 24 h. Use of sevoflurane and morphine can also cause PONV. Also, a urinary catheter was electively placed for 24 h for all patients in ITM group and hence urinary retention could not be assessed. The results are presented in the Table 2 and Figures 1-3.

DISCUSSION

In this two-year retrospective analysis, patients who received 0.2 mg ITM had much lower pain scores and lower morphine requirement in the first 24 hour postoperatively compared to patients who received FNB using 20 mL of 0.5% bupivacaine.

The pain scores using VAS are recorded by our acute pain service nurses every 6 h for the first 24 hour postoperatively when ITM is given or single shot peripheral or neuraxial blocks are given. Only when the catheters are placed for peripheral or neuraxial blocks or PCA pumps are attached, the acute pain service nurses would evaluate these patients for pain beyond 24 h till the catheters or PCA pumps are removed. For this reason we could not analyze the data for pain beyond 24 h postoperatively.

TKA causes a lot of pain postoperatively. Current trend amongst most surgeons is to mobilize the

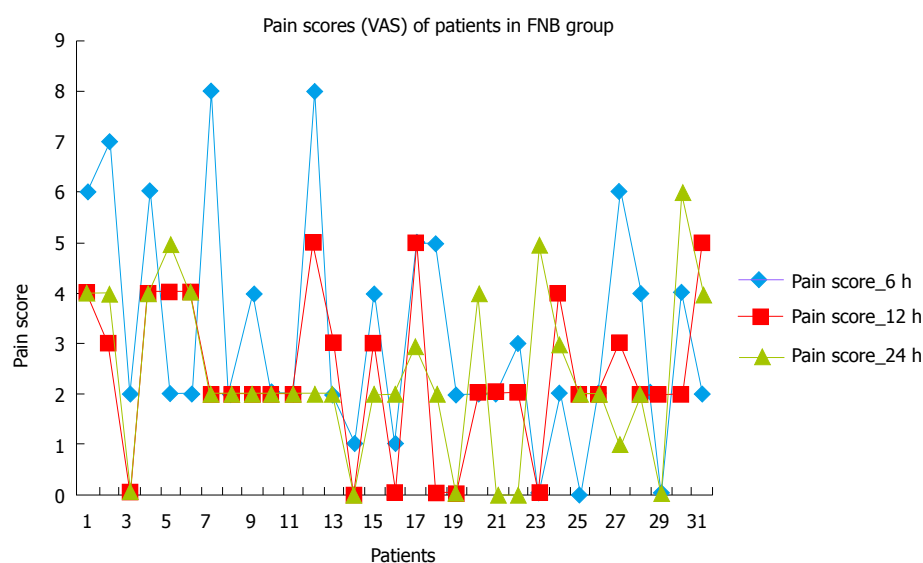


Figure 1 Pain scores at 6, 12 and 24 h in femoral nerve block group. ITM: Intrathecal morphine; FNB: Femoral nerve block; VAS: Visual analogue scale.

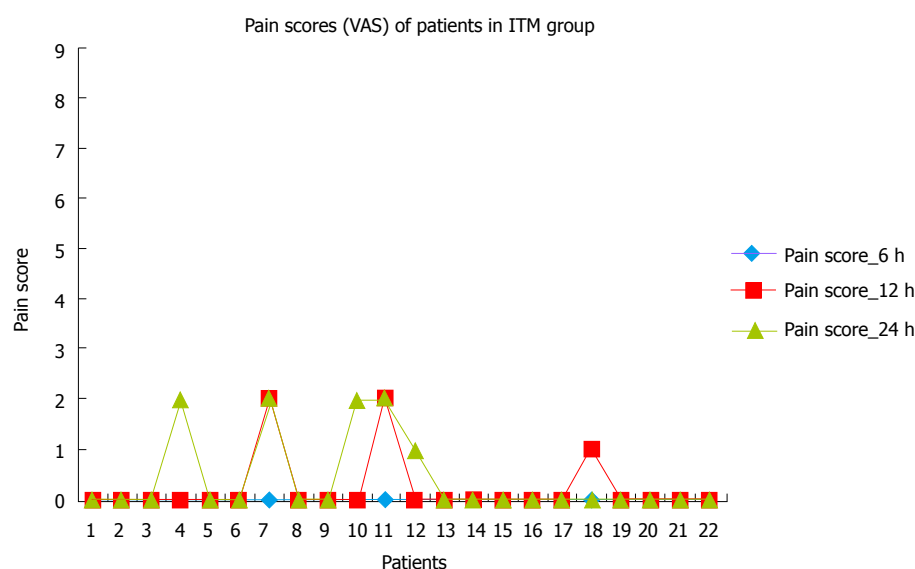


Figure 2 Pain scores at 6, 12 and 24 h in intrathecal morphine group. ITM: Intrathecal morphine; FNB: Femoral nerve block; VAS: Visual analogue scale.

patients early and discharge from the hospital as early as possible. Hence good pain control in immediate postoperative period is imperative for early mobilization and full flexion recovery.

ITM provides excellent post-operative analgesia and with low dosage it gives segmental analgesia, resulting in localized nociception without motor, sensory or autonomic side effects^[4]. Late last century very large dose up to 4 mg ITM was used while today the dose ranges from 0.1-0.5 mg, depending on the type of surgery^[5]. In one meta-analysis, it was shown that the use of ITM at dose < 0.3 mg, the rate of episodes of respiratory depression was not higher compared to the placebo group who received systemic opioids^[6]. In our analysis where 0.2 mg ITM was used, no respiratory depression was recorded. Other undesirable side effects of ITM are itching, urinary retention and PONV. All patients who had received ITM in our analyses had

indwelling urinary catheter for the first 24 h. Also they received round the clock prophylactic antiemetic and hence no patient suffered from PONV.

Regional and peripheral nerve blocks are promising inclusions in multimodal analgesia techniques. According to one study, femoral nerve block is still the gold standard for an effective analgesia approach in knee arthroplasty and should be supplemented (if needed) by oral opioids^[7]. Femoral nerve block is frequently used as a part of multimodal technique for postoperative analgesia after TKA all over the world. In a meta-analysis by Paul *et al*^[8], single shot FNB or continuous FNB plus patient controlled analgesia (PCA) was found to be superior to PCA alone for postoperative analgesia for patients having TKA. The impact of adding a continuous FNB to a single shot FNB was not found to be superior and further investigations were suggested by the authors. The use of single shot FNB was frequent

Table 2 Results

	ITM (n = 22)	FNB (n = 32)
Ease of performance	Very easy, no special training	Expertise and training required, special equipment required
Added cost	Only morphine	Ultrasound machine, special needle and local anesthetic
Median (IQR) pain score at:	Low	High
6 h	0.0 (0.0-0.0)	2.0 (2.0-4.8)
12 h	0.0 (0.0-0.0)	2.0 (2.0-3.8)
24 h	0.0 (0.0-0.3)	2.0 (2.0-4.0)
Median (IQR) of morphine requirement (in mg) in 24 h	Low 5.0 (3.8-10.0)	High 16.5 (8.0-21.5)
Median (IQR) of NSAID unit in 24 h	2.0 (1.0-2.0)	1.0 (0.0-1.3)
Median (IQR) of Paracetamol (G) in 24 h	3.0 (2.0-3.0)	3.0 (2.0-4.0)
Complications	Low	Low
	No PONV since antiemetic prescribed in anticipation	Incidence of PONV was higher since no regular antiemetic given (16 at 6 h, 11 at 12 h and 9 at 24 h)
	No urinary retention since all patients were catheterized	No urine retention
	No respiratory depression	No respiratory depression
	No itching recorded	No itching recorded
Number of elective HDU admission status	3 (15%)	2 (6.5%)
Median (IQR) days to discharge	4.5 (3.0-5.0)	4.0 (3.0-6.0)
Patient satisfaction	18/20 (90.0%) rated good	4/31 (12.9%) rated good

IQR: Interquantile range; n: Numbers; ITM: Intrathecal morphine; FNB: Femoral nerve block; PONV: Post-operative nausea and vomiting; HDU: High dependency unit.

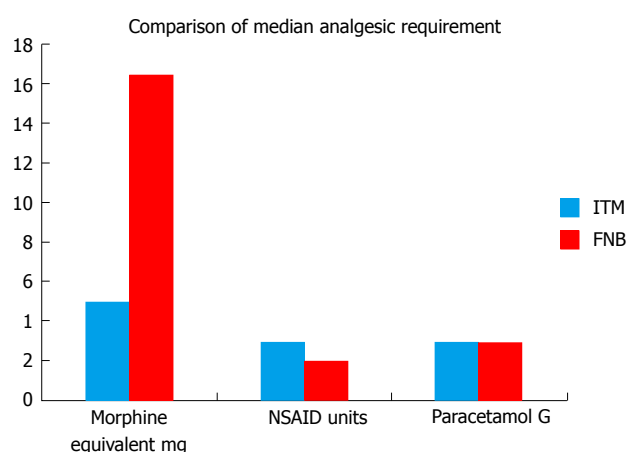


Figure 3 Comparison of median analgesic requirement in 24 h. ITM: Intrathecal morphine; FNB: Femoral nerve block; NSAID: Non-steroid anti-inflammatory drug.

at our hospital in 2013 and 2014. Also, single shot FNB can have analgesic effect from 12 to 24 h^[9,10] and may extend up to 48 h^[11]. Similarly analgesic effect of ITM also lasts for around 24 h and hence it is only fair to compare ITM and single shot FNB for their efficacy for postoperative analgesia.

In a meta-analysis by PROSPECT working group^[1], for joint replacement surgery GA combined with an FNB for surgery and postoperative analgesia, or SA with local anesthetic plus ITM is recommended. The group also recommends cooling and compression techniques, paracetamol and conventional NSAIDs or COX-2-selective inhibitors, plus intravenous strong opioids (high-intensity pain) or weak opioids (moderate- to low-intensity pain) for postoperative analgesia. At our institute we follow these recommendations. In addition,

the surgical team also prefers to use local infiltration technique as described earlier.

FNB requires the use of ultrasound machine and a special needle, which add to the cost. Also, an expertise in performing the FNB is necessary for good outcome. Additional time to perform and to evaluate the block is also required. In addition, there is a possibility of motor weakness which can increase the risk of postoperative fall. ITM is very cost effective, time saving and a relatively simple technique. Having these considerations on our mind we decided to analyze the outcome for these two techniques and found that ITM group had lower pain scores in the first 24 hour after surgery though the number of patients that we could include was small.

We found three more clinical trials in the literature comparing ITM and FNB for primary unilateral TKA but in all three trials both groups had received SA. In the study published by Frassanito *et al*^[2], where SA was used for both ITM and FNB group, the 24 h and 48 h morphine consumption was lower in ITM group though not statistically significant. In this prospective study, a very low dose of ITM of 0.1 mg was used. In another trial by Sites *et al*^[12] there was no statistically significant difference in the morphine consumption or pain scores between ITM and FNB group where SA was used for both groups. This trial reports more adverse effects in ITM group compared to FNB group but a slightly higher dose of ITM 0.25 mg was used. Tarkkila *et al*^[13] compared ITM with continuous 3 in 1 femoral block in primary unilateral TKA patients and reported lower pain scores in ITM group. Our study involved use of 0.2 mg ITM with statistically significant lower pain scores and morphine consumption without any respiratory depression. Perhaps a large prospective trial with standardized drug regime and multivariate analysis may

be needed to prove superiority of ITM over FNB in this particular group of surgical patients.

From our analysis we conclude that 0.2 mg ITM with SA is more effective for first 24 hour postoperatively compared to single shot FNB with GA for primary unilateral TKA. Also, 0.2 mg ITM is safe, time saving and cost effective with better patient satisfaction compared to FNB.

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We thank Ms Carmen Kam Jia Wen, research officer at "Clinical and Trial and Research Unit" (CTRU) at Changi General Hospital, Singapore for her statistical help.

COMMENTS

Background

Total knee arthroplasty (TKA) leads to considerable post-operative pain, which requires optimal control for early mobilization. Till date, varieties of techniques and drugs have been used to achieve this optimal pain control. Use of intrathecal morphine (ITM) with spinal anesthesia (SA) is extremely easy and can be time saving and cost effective. Also, femoral nerve block (FNB) is one of the easiest peripheral nerve blocks. In this study the authors have compared these two easy techniques for postoperative pain management after TKA.

Research frontiers

Regional blocks are commonly used for pain management after TKA. Most recent studies are comparing femoral nerve blocks with adductor canal block and local infiltration techniques. This study compares use of ITM with SA and FNB with GA. In the past only three other studies have compared ITM and FNB, albeit both groups had undergone surgery under SA.

Innovations and breakthroughs

In this study, 0.2 mg ITM with SA was more effective for first 24 hour post-operatively compared to single shot FNB with GA for primary unilateral TKA. In one previous study, which compared 0.1 mg ITM with SA and FNB with SA, pain scores and postoperative opioid consumption were lower in ITM group though statistically not significant. In another similar study, ITM group had more complications when a higher dose of 0.25 mg ITM was used. In their study using 0.2 mg ITM, lower pain scores and opioid consumption were statistically significant. This study also illustrates that use of adequate prophylaxis can prevent known complications of ITM.

Applications

This retrospective analysis shows that 0.2 mg ITM with SA is more effective for first 24 h postoperatively compared to single shot FNB with GA for primary unilateral TKA. Perhaps a prospective trial with standardized drug regime and multivariate analysis in a large group of patients is required to prove their findings.

Terminology

ITM: Intrathecal morphine; FNB: Femoral nerve block; SA: Spinal anesthesia; GA: General anesthesia; PONV: Postoperative nausea and vomiting; PCA: Patient controlled analgesia; NSAIDs: Non-steroidal anti-inflammatory drugs; VAS: Visual analogue scale.

Peer-review

This retrospective analysis is worthy of publishing as it provides value clinical

information for how pre-emptive analgesia could effectively prevent or mitigate postoperative pain.

REFERENCES

- 1 **Fischer HB**, Simanski CJ, Sharp C, Bonnet F, Camu F, Neugebauer EA, Rawal N, Joshi GP, Schug SA, Kehlet H. A procedure-specific systematic review and consensus recommendations for postoperative analgesia following total knee arthroplasty. *Anaesthesia* 2008; **63**: 1105-1123 [PMID: 18627367 DOI: 10.1111/j.1365-2044.2008.05565.x]
- 2 **Frassanito L**, Vergari A, Zanghi F, Messina A, Bitondo M, Antonelli M. Post-operative analgesia following total knee arthroplasty: comparison of low-dose intrathecal morphine and single-shot ultrasound-guided femoral nerve block: a randomized, single blinded, controlled study. *Eur Rev Med Pharmacol Sci* 2010; **14**: 589-596 [PMID: 20707248]
- 3 **Vergnion M**, Degesves S, Garcet L, Magotteaux V. Tramadol, an alternative to morphine for treating posttraumatic pain in the prehospital situation. *Anesth Analg* 2001; **92**: 1543-1546 [PMID: 11375843 DOI: 10.1097/00000539-200106000-00039]
- 4 **DeSousa K**, Chandran R. Intrathecal Morphine for postoperative analgesia: Current trends. *World J Anesthesiol* 2014; **27**: 191-202 [DOI: 10.5313/wja.v3.i3.191]
- 5 **Mugabure Bujedo B**. A clinical approach to neuraxial morphine for the treatment of postoperative pain. *Pain Res Treat* 2012; **2012**: 612145 [PMID: 23002426]
- 6 **Gehling M**, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. *Anaesthesia* 2009; **64**: 643-651 [PMID: 19462494 DOI: 10.1111/j.1365-2044.2008.05817.x]
- 7 **Bauer MC**, Pogatzki-Zahn EM, Zahn PK. Regional analgesia techniques for total knee replacement. *Curr Opin Anaesthesiol* 2014; **27**: 501-506 [PMID: 25111605 DOI: 10.1097/ACO.000-00000000000115]
- 8 **Paul JE**, Arya A, Hurlburt L, Cheng J, Thabane L, Tidy A, Murthy Y. Femoral nerve block improves analgesia outcomes after total knee arthroplasty: a meta-analysis of randomized controlled trials. *Anesthesiology* 2010; **113**: 1144-1162 [PMID: 20966667 DOI: 10.1097/ALN.0b013e3181f4b18]
- 9 **Allen HW**, Liu SS, Ware PD, Nairn CS, Owens BD. Peripheral nerve blocks improve analgesia after total knee replacement surgery. *Anesth Analg* 1998; **87**: 93-97 [PMID: 9661553]
- 10 **Szczukowski MJ**, Hines JA, Snell JA, Sisca TS. Femoral nerve block for total knee arthroplasty patients: a method to control postoperative pain. *J Arthroplasty* 2004; **19**: 720-725 [PMID: 15343531 DOI: 10.1016/j.arth.2004.02.043]
- 11 **Ng HP**, Cheong KF, Lim A, Lim J, Puhaindran ME. Intraoperative single-shot "3-in-1" femoral nerve block with ropivacaine 0.25%, ropivacaine 0.5% or bupivacaine 0.25% provides comparable 48-hr analgesia after unilateral total knee replacement. *Can J Anaesth* 2001; **48**: 1102-1108 [PMID: 11744586 DOI: 10.1007/BF03020376]
- 12 **Sites BD**, Beach M, Gallagher JD, Jarrett RA, Sparks MB, Lundberg CJ. A single injection ultrasound-assisted femoral nerve block provides side effect-sparing analgesia when compared with intrathecal morphine in patients undergoing total knee arthroplasty. *Anesth Analg* 2004; **99**: 1539-1543; table of contents [PMID: 15502061 DOI: 10.1213/01.ANE.0000136470.51029.52]
- 13 **Tarkkila P**, Tuominen M, Huhtala J, Lindgren L. Comparison of intrathecal morphine and continuous femoral 3-in-1 block for pain after major knee surgery under spinal anaesthesia. *Eur J Anaesthesiol* 1998; **15**: 6-9 [PMID: 9522133 DOI: 10.1097/00003643-199801000-00002]

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