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**ORIGINAL ARTICLE****Retrospective Study**

- 1 Change in management of predicted difficult airways following introduction of video laryngoscopes
Jarzebowski M, Rajagopal A, Austell B, Moric M, Buvanendran A

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Retrospective Study

Change in management of predicted difficult airways following introduction of video laryngoscopes

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Abstract

AIM

To determine if video laryngoscopy (VL) has significantly impacted management of difficult airways by decreasing the rate of awake fiberoptic intubation (FOI).

METHODS

Anesthetic records of 3723 patients who underwent general anesthesia at Rush University Medical Center were reviewed over a 2-mo period prior to the introduction of VLs in 2009 ("pre-VL" group) and over the same 2-mo period after the introduction of VLs in 2012 ("post-VL" group). Patient records with predicted difficult airways based on pre-operative airway examination were analyzed. The primary outcome was rate of awake FOI.

RESULTS

To control for possible factors that may influence the FOI rate, a logistic regression was performed with these factors included as covariates. The rate of awake FOI was 13.1% in pre-VL group compared to 9.0% in post-VL group. Although this decrease was not statistically significant individually ($P = 0.1768$), it showed a trend toward significance when covariates were accounted for ($P = 0.0910$). Several factors predicting a higher

likelihood of awake FOI were found to be statistically significant: Morbid obesity (larger BMI $P = 0.0154$, OR = 1.5 per 10 point BMI increase), male gender ($P = 0.0026$, OR = 3.0) and a higher el-Ganzouri airway score ($P = 0.0007$, OR = 1.5). Although VLs were seen to be used to intubate 51% of predicted difficult airways, the rate of awake FOI has not significantly changed.

CONCLUSION

Although VL may continue to grow in popularity, the most difficult airways are still managed using awake FOI.

Key words: Difficult airway; Video laryngoscope; Awake fiberoptic intubation

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Core tip: This study shows that the introduction of video laryngoscopes has not significantly impacted the management of predicted difficult airways in the operating room; specifically, that the rate of awake fiberoptic intubation (FOI), the previous gold standard for intubating a predicted difficult airway, has not decreased. Although video laryngoscopy (VL) has clear advantages compared to direct laryngoscopy and has been proven to have increased in popularity in the operating room for non-difficult airways, we postulate that the anesthesiologist's assessment of the ability to mask ventilate is likely a key factor in the choice of awake FOI vs VL.

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INTRODUCTION

Tracheal intubation in patients with predicted difficult airways often requires advanced techniques and equipment, much of which is changing as technology advances. As anesthesiologists, we often turn to difficult airway algorithms such as those published by the American Society of Anesthesiologists to offer guidance^[1]. One of the newest and most commonly used tools is the video laryngoscope (VL). Introduced into practice around 2001, VLs have gained widespread use in the operating room. Multiple studies have compared VL to direct laryngoscopy in patients with at least one predictor of a difficult airway and found increased success in first-attempt intubations^[2-5], improved Cormack Lehane view obtained^[4-7] and decreased time to intubation^[4,5,7]. The data from these studies

are difficult to compare, with wide variances in patient populations, level of experience and specialty of the physician performing the intubation, differences in location of airway management, and multiple different VLs available for use. Despite such encouraging outcomes, data on how anesthesiologists are using VL for predicted difficult intubations is lacking.

The previous gold standard technique for tracheal intubation in patients with predicted difficult airways has been flexible bronchoscopy. This is either done following induction of general anesthesia or awake, while maintaining spontaneous ventilation, in patients assessed to be difficult to mask ventilate or who require a neurological exam post intubation (awake fiberoptic intubation or FOI). By maintaining spontaneous ventilation, one eliminates the risk of the much feared "can't intubate, can't ventilate"^[1] scenario. The ASA difficult airway algorithm^[1] recommends assessment of the merits of awake intubation and preservation of spontaneous ventilation in all patients. Although the success rate of awake FOI is reported to be high (ranging from 88%-100%^[8-10]), this technique requires considerably more skill and time than direct laryngoscopy. There is also potentially more discomfort for the patient. At Rush University Medical Center, attending and resident physicians are encouraged and trained to adhere to the ASA difficult airway algorithm for securing difficult airways. If VL is deemed appropriate by an attending for a difficult airway then this method is employed by the attending and resident. With the logistical challenges of awake FOI and the advent of the newer, faster and simpler VL, we hypothesize that the number of awake FOI has decreased for predicted difficult airways.

MATERIALS AND METHODS

Following institutional IRB approval, we collected data for a 2-mo period (November and December of 2009) before the introduction of VL at our hospital (the "pre-VL" group) and for a 2-mo period (November and December of 2012) after the introduction of VLs (the "post-VL" group). We reviewed anesthetic records of patients undergoing general anesthesia both before and after the introduction of VLs at a major academic medical center in order to assess any change in airway techniques used to intubate the trachea. VLs were first introduced at the institution in May, 2010. Given this information, we collected patient-level data for each surgical encounter 6 mo before and then three years after their introduction. The gap allows for familiarization of anesthesia personnel with the new VLs, as well as time for the equipment to become more readily available. Using electronic medical records, all patients over the age of 18 years who received general anesthesia during those time periods were identified and their anesthetic record for that encounter reviewed.

From the pre-anesthetic evaluation, we reviewed each patient's modified el-Ganzouri airway score (Table

Table 1 El-ganzouri airway assessment score

Score	0	1	2
Interincisor gap	> 4 cm	< 4 cm	Cannot open mouth
Head/neck movement	> 90 degrees	90 degrees	< 90 degrees
Buck teeth	Can prognath edentulous	Can approximate teeth only	Cannot approximate teeth
Thyromental distance	> 6.5 cm	6.0-6.5 cm	< 6.5 cm
Body weight	< 90 kg	90-110 kg	> 110 kg
Hx of difficult intubation	None	Questionable	Definite
Mallampati classification	I	II	III

1)^[11]. This validated score for predicting difficult airways includes the following criteria: interincisor gap, head and neck movement, ability to prognath, thyromental distance, body weight, history of difficult intubation and Mallampati classification. Based on this scale, patients with a score of 4 or greater have a significant likelihood of difficult intubation and alternative methods to direct laryngoscopy should be considered. Therefore, only patients with a modified el-Ganzouri score of 4 or greater were included in our study.

We excluded patients who underwent monitored anesthesia care (MAC) and regional or neuraxial anesthesia as their primary anesthetic. We also excluded patients undergoing cardiac surgery, as these patients are frequently left intubated post-operatively (one of our measured secondary outcomes). We excluded patients undergoing thoracic surgery, as their airway management is frequently different to accommodate single-lung ventilation. We also excluded obstetric patients from our data set as the vast majority of patients have neuraxial anesthesia. Patients who had been intubated prior to the operating room were also excluded.

Data collected included age, gender, American Society of Anesthesiologists (ASA) status, body mass index (BMI), and el-Ganzouri airway score with individual components (weight, Mallampati Score, thyromental distance, previous difficult intubation, neck range of motion and ability to prognath the teeth). Airway management data collected included awake FOI vs asleep endotracheal intubation (primary outcome), Cormack-Lehane view obtained, number of attempts at intubation prior to securing endotracheal intubation, method used to secure airway (direct laryngoscopy vs VL vs fiberoptic bronchoscope), if rapid sequence intubation (RSI) was used, if rescue laryngeal mask airway was used, and if the patient was left intubated after surgery.

Power analysis is based on the primary outcome of a reduction in rate of awake vs asleep intubations. Assuming a base rate of 15% awake intubations prior to introduction of the VL and a 50% reduction to 7.5% after introduction, at 80% power to detect a reduction, 219 subjects per group (438 total) are required, using standard parameters of 5% alpha for a one-sided test of proportions.

All patient data was de-identified prior to analysis and stored on password-protected laptops belonging to study personnel. In total, 3723 patient records were

reviewed. 461 patients met the inclusion and exclusion criteria and were analyzed. Their characteristics can be seen in Table 2. The primary outcome was rate of awake FOI. To control for possible factors that may influence the FOI rate, a logistic regression was performed with these factors included as covariates. Various models including models with interaction terms were constructed and evaluated using fit indices. Differences between time periods were also compared using Student's *t*-test (with appropriate adjustment for violations of homoscedasticity), Mantel-Haenszel, χ^2 and Fisher's exact tests. All analyses were performed using SAS version 9.2 (SAS Institute. Cary, NC, United States). Significance threshold was set at $\alpha = 0.05$. Model based assumptions were evaluated for violations using descriptive methods.

The statistical methods of this study were reviewed by Mario Moric, MS from Rush University Medical Center.

RESULTS

Most demographics were similar between both groups but several were found to have significant differences. BMI (and correspondingly weight) was significantly lower in the post-VL patient population. Additionally, the post-VL group had significantly more patients with higher Mallampati scores. Neck range of motion was also significantly less in the post-VL patient population. The final model included age, BMI, time period (pre-VL/post-VL), gender, ASA status, composite airway score, neck range of motion, Mallampati score and surgery type (based on significant univariate differences at baseline and need for control due to possible confounding).

The rate of awake FOI was 13.1% in the pre-VL group compared to 9.0% in post-VL group (Figure 1), although this decrease was not statistically significant ($P = 0.1768$). Due to differences in demographics between the two time periods, we included these and other factors (listed above) that may impact the primary outcome in the logistic model, to account for these effects. Controlling for the covariates did not change the significance of the effect over time ($P = 0.0910$) but does indicate a trend toward significance.

Method of intubation for patients with predicted difficult airways was significantly different after the introduction of VLs (Figure 2). In the post-VL group, VLs

Table 2 Patient characteristics *n* (%)

	Pre-VL Mean $\pm$ SD	Post-VL Mean $\pm$ SD	<i>P</i> value
Age	55 $\pm$ 14	57 $\pm$ 14	0.2435
Height (m)	1.71 $\pm$ 0.11	1.69 $\pm$ 0.11	0.0658
Weight (kg)	108 $\pm$ 30	97 $\pm$ 26	0.0001 ¹
BMI	37 $\pm$ 10	34 $\pm$ 9	0.0014 ¹
ASA Status	2.67 $\pm$ 0.62	2.73 $\pm$ 0.67	0.3145
Composite Airway Score	4.83 $\pm$ 1.21	4.79 $\pm$ 1.22	0.7711
	Count (%)	Count (%)	
Gender			0.4546
Female	105 (51)	139 (55)	
Male	101 (49)	116 (45)	
Mallampati score			0.0481 ¹
1	5 (2)	6 (2)	
2	89 (43)	85 (33)	
3	112 (54)	164 (64)	
Interincisor gap			0.9033
> 4 cm	142 (69)	180 (71)	
< 4 cm	63 (31)	73 (29)	
Cannot open mouth	0 (0)	2 (1)	
Neck range of motion			0.0084 ¹
> 90°	149 (73)	152 (60)	
90°	37 (18)	69 (27)	
< 90°	19 (9)	34 (13)	
Ability to prognath			0.3058
Can prognath	157 (77)	187 (73)	
Can approximate teeth	46 (22)	62 (24)	
Cannot approximate teeth	2 (1)	6 (3)	
Thyromental distance (cm)			0.6811
> 6.5	60 (29)	69 (27)	
6.0 – 6.5	128 (62)	162 (64)	
< 6.0	18 (8)	24 (9)	
Known previous difficult intubation			0.1740
None	162 (79)	213 (84)	
Questionable	24 (12)	26 (10)	
Definite	19 (9)	16 (6)	
Surgery type			0.0085 ¹
General	64 (31)	55 (22)	
Gynecologic	24 (12)	27 (11)	
Neurosurgery	20 (10)	56 (22)	
Orthopedic	15 (7)	16 (6)	
Other	37 (18)	47 (19)	
Spine	38 (18)	36 (14)	
Vascular	8 (4)	16 (6)	

¹Significantly different between Pre-VL and Post-VL groups. *P*-value and odd ratio calculated with χ^2 test and Mantel-Haenszel χ^2 test. SD: Standard deviation; VL: Video laryngoscope; FOI: Fiberoptic intubation; DL: Direct laryngoscopy.

were used to intubate 51% of predicted difficult airways ($P < 0.0001$, Table 3). The overall rate of FOI (both awake and asleep) decreased from 37% to 19% ($P = 0.0093$) in patients with predicted difficult airways. The use of direct laryngoscopy decreased from 61% in the pre-VL group to 30% in the post-VL group ($P = 0.0005$).

Potential risk factors, determined prior to study initiation, and significant demographic variables, were entered into the logistic regression predicting likelihood

of awake FOI. After model fit and selection, the resulting odds ratios are shown in Figure 3. Several statistically significant factors predicting a higher likelihood of awake FOI were found: morbid obesity determined by BMI ($P = 0.0154$, OR = 1.5 per 10-point BMI increase), male gender ($P = 0.0026$, OR = 3.0) and a higher el-Ganzouri airway score ($P = 0.0007$, OR = 1.5 per point above 4). Neck range of motion ($P = 0.0582$, OR = 1.6) verged on significant but was not. Neither ASA

Table 3 Airway management *n* (%)

	Pre-VL Count (%)	Post-VL Count (%)	<i>P</i> value
Grade (Cormack-Lehane view obtained)			0.014 ¹
1	86 (57)	149 (75)	
2	43 (29)	28 (14)	
3	19 (13)	16 (8)	
4	2 (13)	5 (3)	
Intubation method			< 0.0001 ¹
FOI	72 (37)	44 (19)	0.0093 ¹
VL	4 (2)	119 (51)	< 0.0001 ¹
DL	118 (2)	70 (30)	0.0005 ¹
Rapid sequence induction			0.1489
RSI	30 (17)	27 (12)	
Rescue LMA used			0.7055
Yes	4 (17)	3 (1)	
Patient left intubated			0.5467
Yes	24 (12)	25 (12)	

¹Significantly different between Pre-VL and Post-VL groups. *P* value and odd ratio calculated with χ^2 test and Mantel-Haenszel χ^2 test. SD: Standard deviation; VL: Video laryngoscope; FOI: Fiberoptic Intubation; DL: Direct laryngoscopy; LMA: Laryngeal mask airway.

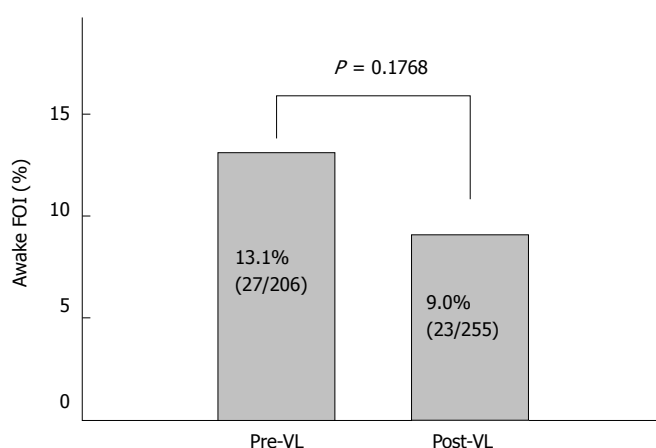


Figure 1 Awake fiberoptic intubation rate in the pre- video laryngoscope group and post video group. *P* value calculated with Fisher's exact test. VL: Video laryngoscope; FOI: Fiberoptic intubation.

status ($P = 0.1869$), Mallampati score ($P = 0.2278$), age ($P = 0.3598$) nor surgery type ($P = 0.5437$) was significantly predictive. The BMI and age variables were scaled so that the odds ratio refers to 10-point change instead of one-point changes. So, a 10-point increase in BMI is associated with 1.5 the odds of an awake FOI. Additionally, surgery type within three categories (general, neurologic, and other) was included in the model as a covariate, since the parameterization with the full seven categories was not estimable.

To evaluate the risk factors independent of the time period, another model with time period removed was run and produced similar results indicating that these risk factors are independent of the time period.

To evaluate possible relationships among the predictors/covariates models, the interactions among them were tested. There were no interactions that appreciably

improved the fit of the model or the overall significance of the primary contrast. Although the primary outcome was not statistically significant it trended towards significance with a *P*-value of 0.0910. The decrease in awake FOI, from 13.1% to 9.0% represents a reduction of 4.1%. Our power analysis was based on the assumption of a larger effect size (7.5%), so if the true effect is smaller, we may be underpowered to test the hypothesis.

DISCUSSION

Our results suggest that the proportion of patients with predicted difficult airways who receive awake FOI has not changed significantly following the introduction of VLs at the magnitude we had postulated. However, there was a trend toward a reduction in the

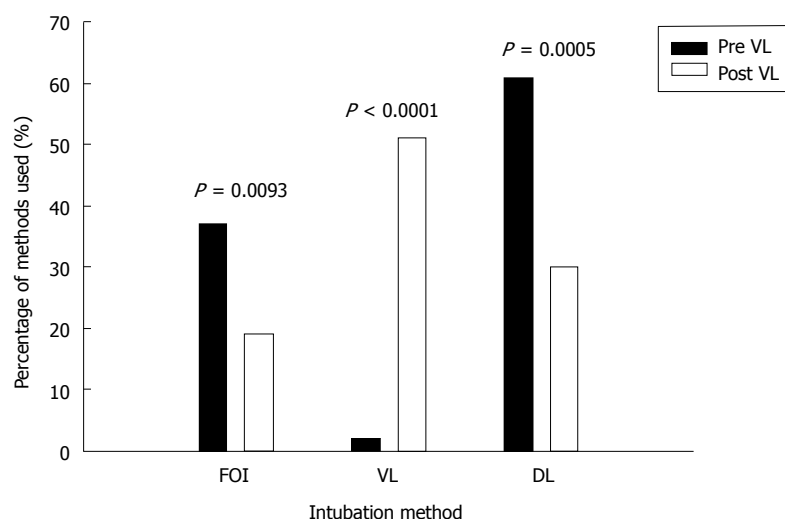


Figure 2 Change in intubation method of predicted difficult airways before and after introduction of video laryngoscopes. P value calculated with χ^2 test of equal proportion. VL: Video laryngoscope; FOI: Fiberoptic intubation; DL: Direct laryngoscopy.

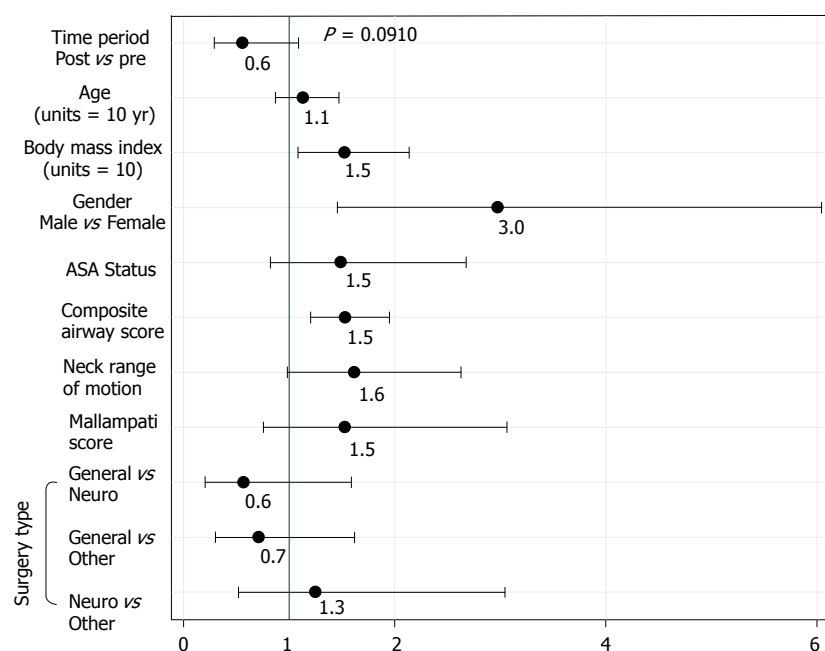


Figure 3 Plot of odds ratio with 95% wald confidence limits of various predictive factors for awake fiberoptic intubation. Statistics calculated with logistic regression.

rate of awake FOI in patients with difficult airways. Overall, the method used to intubate patients with predicted difficult airways changed significantly, with significantly fewer FOI (awake and asleep) and direct laryngoscopies and significantly more VL. Similar results were obtained by Law *et al.*^[12], who noted a steady incidence of awake FOI each year from 2002 to 2013, despite a significant increase in the use of VL over the same time period. The trend toward a reduction in awake FOI (although not statistically seen in our data) has received commentary in recent publications^[13,14], with attention drawn to lack of training in awake FOI, to advances in VL and supraglottic airway devices (SAD), and to pharmacologic advances

in reversal of neuromuscular blockade as possible explanations.

Others disagree with the continued use of awake FOI. A recent editorial^[13] suggests that the practice of awake FOI should be abandoned as our gold standard for airway management in predicted difficult airways. They cite a relative paucity of training in fiberoptic intubations with trainees preferring the latest technological advances in video laryngoscopy. One must also consider the array of SAD that now provides a useful rescue airway for the "can't intubate, can't ventilate" scenario when laryngoscopy fails. Many of these SAD's provide a conduit for intubation. The introduction of sugammadex into clinical practice may also have

influenced the management of difficult airways. A case report of its utility in a “can’t intubate, can’t ventilate” scenario was illustrated recently^[14,15] in a patient who had failed previous attempts at awake FOI. With the continued advances in VL, SAD’s and emergency reversal of neuromuscular blockade, perhaps the need for awake FOI is further decreasing.

Patients with cervical myelopathy also warrant consideration. In the past, fear of exacerbating their myelopathy led most anesthesiologists to perform awake FOI with a confirmatory neurologic exam after intubation and before induction of general anesthesia. Studies looking at cervical spine motion during intubation with VLs show mixed results, with one reporting no difference in cervical spine movement between direct laryngoscopy and VL^[16] and another showing significantly less cervical spine movement between direct laryngoscopy and VL^[17]. However, when directly compared, asleep FOI yielded significantly less cervical spine motion than intubation by VL^[18]. It seems reasonable, therefore, to conclude that fiberoptic bronchoscopy may be a safer technique for intubation in patients with critical cervical myelopathy; however, outcomes data remains lacking.

In its relative infancy as a technique, VL will also have its limitations. A retrospective analysis of intubations using VL found the most likely predictors of failed VL were the presence of a surgical scar in the oropharynx, history of neck irradiation, or presence of a neck mass^[19]. Interestingly, these are also predictors of difficult mask ventilation, based on a retrospective analysis by Kheterpal *et al*^[20]. It seems likely, therefore, that we are accepting a certain amount of risk by inducing general anesthesia and relying on VL without fully understanding who is most at risk of failed airway management with this technique.

Data from the National Audit Project (NAP4) of the Royal College of Anaesthetists looking into complications of airway management in the United Kingdom makes some pertinent points concerning the implications of difficult awake FOI^[21]. The authors present data of unsuccessful awake FOI. Difficulties encountered were because of lack of patient cooperation, anatomical airway obstruction and obscuration of visualization by blood or secretions. However, the reviewers of the NAP4 data did caution that the failure to consider or employ awake FOI when clinically indicated provided the largest cohort of cases of failed airway management that they reviewed. Based on this, they recommend that “all anaesthetic departments should provide a service where the skills and equipment are available to deliver awake fiberoptic intubation whenever it is indicated”. Notably, they also recommend that “where FOI is considered the optimal method of securing the airway, an awake technique should be considered unless contraindicated”^[21].

The strengths of our project lie in defining potential trends in airway management with the advent of new technology. There will likely always be a subset of patients

who, despite advances in SAD’s, VL and pharmacologic reversal of neuromuscular blockade, cannot be intubated or ventilated. Therefore, we posit the need for awake FOI will remain for the future. Our commitment as a specialty to patient safety mandates approaching predicted difficult airways with the same caution as in the past, despite advances in technology, as the outcomes of failed airway management remain devastating. Our study also emphasizes the implications for training of future anesthesiologists to foster proficiency at awake FOI. Familiarity with awake FOI is necessary if we are to continue to consider it a viable option in patients with predicted difficult airways.

The limitations of our study are several. First, as it is retrospective data, the possibility of confounding variables is always present. Our two groups had some differing baseline characteristics, which we attempted to control for using logistic regression. However, prospective data would be more valuable. Second, our sample size was relatively small. With advances in electronic anesthetic records, a larger review of anesthetic data may hold more statistical power to observe these trends over time. In conclusion, our data demonstrate a trend, although not significant, toward a decrease in awake FOI in patients with predicted difficult airways, although at a smaller effect size than expected. This trend has been noted at other institutions and highlights potential risks to patient safety in patients with difficult airways. Our data also demonstrate a reduction in the use of asleep FOI and direct laryngoscopy for the intubation of predicted difficult airways, with > 50% of these patients receiving VL. We believe awake FOI continues to remain the gold standard for managing the predicted difficult airway, despite new technology. As such, we advocate for a specialty-wide commitment to train future physician anesthesiologists to be ready to manage the most difficult of airways safely.

ARTICLE HIGHLIGHTS

Research background

Advanced techniques and equipment are often needed for tracheal intubation in patients with difficult airways. New technology has brought about video laryngoscopes (VLs). Multiple studies have compared VL to direct laryngoscopy and the effects on success rates and factors surrounding intubation. However, in this study we aim to investigate the influence of VL on fiberoptic intubation, the previous gold standard for difficult airways.

Research motivation

Management of the difficult airway has traditionally relied on the difficult airway algorithm published by the American Society of Anesthesiologists. Given the ever-increasing clinical use of VL, it is important to assess if their introduction has affected the clinical practice of managing difficult airways, specifically in regards to awake fiberoptic intubation, part of the difficult airway algorithm.

Research objectives

In light of the introduction of VL, this study investigates whether or not the rate of awake fiberoptic intubation has decreased in the management of difficult airway. It is important to recognize the trends surrounding VL given that the frequency of use and level of training that anesthesiologists have with fiberoptic intubation may be influenced. If this were the case it would be important to

acknowledge and address in the future.

Research methods

Anesthetic records were reviewed at Rush University Medical Center before and after the introduction of video laryngoscopes to analyze the effects on awake fiberoptic intubation (FOI).

Research results

Awake FOI decreased from 13.1% before VL to 9% after video laryngoscopy ($P = 0.1768$ but trended toward significance). Morbid obesity (larger BMI $P = 0.0154$, OR = 1.5 per 10-point BMI increase), male gender ($P = 0.0026$, OR = 3.0), and higher el-Ganzouri score ($P = 0.0007$, OR = 1.5) predicted higher rates of awake FOI. VL was used to intubate 51% of predicted difficult airways, while use of direct laryngoscopy significantly decreased.

Research conclusions

In light of increasing use of VL, fiberoptic intubation remains the gold standard for difficult airway intubation. It is important for patient safety that our specialty commit to train on multiple modalities of tracheal intubation in order to be prepared for the most difficult of airways. Continued study is required to assess trends in regards to VL vs fiberoptic intubation in difficult airways.

Research perspectives

While a retrospective study has shed light on the fact that the rate of VL is clearly increasing, a randomized clinical trial could provide greater data on the outcomes of difficult airways given varying tracheal intubation methods. In addition, continual readdressing of VL use in difficult airways will aid in assessing whether or not it should be introduced into the difficult airway algorithm.

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REVIEW

- 10 Targeting tumor necrosis factor in the brain relieves neuropathic pain

Ignatowski TA, Spengler RN

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Targeting tumor necrosis factor in the brain relieves neuropathic pain

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Abstract

Neuropathic pain is a chronic syndrome caused by direct damage to or disease of the somatosensory nervous system. The lack of safe, adequate and sustained pain relief offered by present analgesic treatments is most alarming. While many treatment options are available to manage chronic pain, such as antidepressants, non-steroidal anti-inflammatory agents, opioids, and anti-convulsants, chronic neuropathic pain remains largely unmanaged. Compounding the dilemma of ineffective chronic pain treatments is the need to provide relief from suffering and yet not contribute to the scourge of drug abuse. A recent epidemic of addiction and accidental drug prescription overdoses parallel the increased use of opioid treatment, even though opioids are rarely an effective treatment of relieving chronic pain. To make matters worse, opioids may contribute to exacerbating pain, and side-effects such as cognitive impairment, nausea, constipation, development of tolerance, as well as their potential for addiction and overdose deaths exist. Clearly, there is an urgent need for alternative, non-opiate treatment of chronic pain. Innovative discoveries of pertinent brain mechanisms and functions are key to developing effective, safe treatments. Pioneering work has revealed the essential effects of the pleiotropic mediator tumor necrosis factor (TNF) on brain functioning. These studies establish that TNF inhibits norepinephrine

release from hippocampal neurons, and show that excess TNF production within the hippocampus occurs during neuropathic pain, which mobilizes additional mechanisms that further inhibit norepinephrine release. Significantly, it has been verified that elevated levels of TNF in the brain are actually required for neuropathic pain development. Since TNF decreases norepinephrine release in the brain, enhanced TNF levels would prevent engagement of the norepinephrine descending inhibitory neuronal pain pathways. Increased levels of TNF in the brain are therefore critical to the development of neuropathic pain. Therefore, strategies that decrease this enhanced TNF expression in the brain will have superior analgesic efficacy. We propose this novel approach of targeting the pathologically high levels of brain TNF as an effective strategy in the treatment of the devastating syndrome of chronic pain.

Key words: Neuropathic pain; Tumor necrosis factor; Brain; Norepinephrine; Analgesia

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Core tip: Chronic pain is a widespread health problem. Current treatments, including opioids or non-steroidal anti-inflammatory drugs are inadequate as they lack sufficient efficacy, produce numerous side effects and hold the potential for addiction. Preclinical studies show that elevated brain tumor necrosis factor (TNF) levels during chronic pain are a novel target for producing analgesia. TNF can be practically targeted by non-invasive delivery of anti-TNF biologics directly to the ventricles of the brain *via* a peripheral perispinal injection. Herein we discuss decreasing TNF activity in the brain as a treatment to provide a superior analgesic strategy. Animal study results indicate potential benefit for patients with treatment-resistant pain.

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INTRODUCTION

Neuropathic pain is a prevalent, chronic disease syndrome caused by injury to peripheral nerves, the spinal cord, or the brain. It affects over 20 million people and costs in excess of \$500 billion per year in lost productivity and expenses^[1,2]. In addition, it inflicts a tremendous amount of suffering and devastating effects on both the patient and loved ones. For those reasons, innovative breakthroughs are very much needed to replace current treatments, which have proven ineffective in treating this devastating health dilemma. The present therapeutic management of

neuropathic pain with medications including opioids, non-steroidal anti-inflammatory drugs, antidepressants, and anticonvulsants is often ineffective in providing adequate as well as sustained pain relief. The next generation of analgesics (anti-pain medications) will be developed by exploiting the current knowledge of chronic inflammation, a pathophysiological response now known to direct fundamental mechanisms involved in the perception of pain. Novel treatment design will selectively target brain-mediators that are directly enhanced by nerve injury, are involved with the chronic inflammation, and very importantly are also localized to the brain regions associated with the perception of pain. Crucial to the understanding of the etiology of neuropathic pain is that many inflammatory mediators are also neuromodulators. A peripheral insult with its accompanying local inflammation produces an associated expression of inflammatory cytokines (inflammatory mediator proteins) in the brain, which subsequently directs profound neuromodulatory mechanisms that ultimately modify neurotransmitter release. It is becoming apparent that the effective treatment of neuropathic pain requires targeting the production of those brain (central nervous system, CNS) pleiotropic inflammatory cytokines. A particularly important cytokine that is also a neuromodulator target within the brain is tumor necrosis factor (TNF), because of its proximal function. In fact, TNF is often referred to as a pro-inflammatory cytokine; this implies that this protein mediator is a marker for inflammation since it sets into motion a myriad of events crucial in the inflammatory response. However, this pleiotropic mediator is involved in a myriad of physiologic processes including modifying release of neurotransmitters^[3-7] and homeostatic regulation of the blood-brain barrier^[8]. Yet, when it is increased in the level of expression or enhanced for an extended duration of time, TNF can instigate pathophysiologic changes; this is the case during neuropathic pain conditions. As a neuromodulator, TNF modifies both the perception of pain as well as brain-body communication directing the peripheral inflammatory loci^[9,10]. Preclinical investigation and clinical case studies involving blocking the responses of this brain-derived protein and its mechanisms of action during neuropathic pain show great efficacy, with minimal side-effects, and has decreased or no apparent potential for drug abuse^[9,11,12]. Accordingly, cutting-edge investigations into the role of brain-derived TNF in chronic pain etiology indicate that pioneering therapeutic approaches are on the horizon, and urgency in their development is paramount based on the rising epidemic of prescription opioid drug abuse and resurgence in heroin use by desperate and hopeless individuals. Current preclinical studies reveal an advanced breakthrough in treatment efficacy for the debilitating and life-threatening illness of neuropathic pain, by blocking the higher levels of TNF that are specifically within the brain during the onset, development and maintenance of this devastating disease^[9,10,12-14].

THERAPEUTIC TARGET LOCATED WITHIN THE BRAIN DURING THE ONSET AND DEVELOPMENT OF NEUROPATHIC PAIN

Improved therapeutic approaches require a greater understanding of the pathogenic mechanisms that create, develop, and propagate neuropathic pain. The perception and experience of pain manifests in select brain loci *via* molecular signaling; therefore, brain-derived protein mediators, such as pro-inflammatory cytokines (neuromodulators), along with neurotransmitters that are linked to neuropathic pain pose novel targets for analgesia. The functional interactive and mechanistic relationships that exist between the classical neurotransmitters and these protein neuromodulators (mediators) are being realized. In particular, how these relationships direct both normal as well as pathological brain functions is offering new insights into etiologies of disease syndromes. For instance, TNF produced either in the CNS or systemically has been implicated or has been shown to play a key role in the onset, development and maintenance of neuropathic pain. This is because increases in inflammatory cytokines occur rapidly after injury, and TNF as a proximal mediator initiates the cytokine cascade^[15,16]. In fact, TNF drives the release of inflammatory cytokines, including IL-1 β , IL-6, and itself, all of which are involved in chronic pain, and it robustly alters neurotransmission (glutamate and norepinephrine) in the CNS^[5,13]. TNF levels rise locally and centrally after peripheral nerve injury^[13,14,17-21]. Substantial data reveal pro-nociceptive roles for TNF in chronic pain^[22-24], and increases in levels of TNF in the brain impact peripheral hypersensitivity^[9,14,25,26]. Thus, whether the increase is central, peripheral or both, TNF facilitates pain^[27,28], and lowering of TNF is antinociceptive^[12,14,29-34]. Spread of inflammation occurs along the neuroaxis (CNS and peripheral nervous system, PNS) during neuropathic pain, providing an explanation for its chronicity^[35]. The chronic pain state may exist from signal-induced TNF, IL-1 β , and IL-6 production distant from the injury or from transport of cytokines to the CNS from the periphery. These cytokines induce neuroplasticity leading to chronicity of pain. In fact, chronic pain is centralized by maladaptive CNS functions that greatly alter brain systems, whether started in the PNS or CNS^[36]. The enhanced production of TNF in the region of the brain known as the hippocampus, which is involved in memory formation and learning, is observed during sciatic nerve constriction-induced pain behavior^[9,12-14]. In fact, it is now evident that enhanced TNF expression in specific brain regions is sufficient as well as necessary for the expression of pain behaviors. Ectopically enhanced expression of TNF (nanoparticle-bound TNF-expression plasmids) that is solely administered into and thus only found within the hippocampus generates a pain response that mirrors the hyperalgesia and allodynia that is normally associated with neuropathic pain^[26]. This experimental study thus mimics the overexpression

of brain TNF that occurs during the evolution of chronic pain, and results in peripheral hypersensitivity in the absence of nerve injury^[9,13,14,26]. Based on these findings, it may be concluded that a treatment that exclusively or directly targets this increased production of TNF in the brain during neuropathic pain onset and development should provide greater therapeutic efficacy against this chronic disease syndrome. In addition, targeting CNS TNF activity would avoid the deleterious side effects associated with peripheral targets. In support of this therapeutic paradigm, alleviation of hyperalgesia occurs following intra-hippocampal injection of TNF-siRNA-complexed (bound) nanoparticles that prevent translation of TNF gene expression that is solely found within this brain region^[12]. Thus, the therapeutic prevention of TNF expression that is specifically located in the hippocampus prevents the onset and development of peripheral hypersensitivity associated with peripheral nerve injury. These studies confirm that the overexpressed TNF that occurs in the hippocampus during the onset, development and maintenance of neuropathic pain is pathogenic and is a promising putative target for antinociceptive therapy^[12,14,26].

NEUROTOXICITY MEDIATED BY TNF CONTRIBUTES TO THE CHRONIC PAIN PHENOTYPE

Patients with diverse chronic pain states have reduced brain region volumes, which highlights the linkage of the brain to chronic pain. The volume of the hippocampus is reduced with back pain, osteoarthritis, or complex regional pain syndrome. Similarly, mice with neuropathic pain have decreased hippocampal neurogenesis^[37]. Prolonged, elevated TNF may reduce gray matter volume, since increased TNF appears to decrease neurogenesis in a neuropathic pain model^[38] and enhances production of glutamate, which is neurotoxic when in excess^[6,39]. Of note, even chronic low back pain patients treated with morphine show reduced gray matter volume^[40]. Thus, ample evidence indicates TNF as a novel, non-opioid associated key mediator of chronic pain, and its dysregulated production in the CNS as vital to pain chronicity.

TNF is produced not only by immune/inflammatory cells, but also by brain neurons and glial cells^[41]. Since microglia and neurons express both TNF receptor-1 (p55) and TNF receptor-2 (p75) (TNFR1 and TNFR2), and neuropathic pain development and maintenance is linked to signaling through TNFR1^[38,42], it is likely that microglial activation by TNF through TNFR1 mediates persistent TNF production that contributes to the ongoing neuroinflammation and neuropathological consequences including synaptic transmission deficits and decreased neurogenesis^[13,43-46]. Since the initial characterization of the roles of TNF in both normal physiology as well as in pathological settings as a pro-inflammatory mediator, TNF was labeled as functioning as a double-edged sword.

Quite interesting, this also holds true with its role now as a neuromodulator. Physiologic levels of brain TNF control proliferation and are neuroprotective; conversely, at high pathologic levels, TNF creates neuron dysfunction and disorder^[41]. Thus, much attention is directed toward TNF as it drives the production/release of cytokines, directly causes nociception, and regulates neurotransmission.

INHIBITS NOREPINEPHRINE RELEASE FROM BRAIN NORADRENERGIC NEURONS

Neuromodulation is the process whereby autocrine, paracrine or hormonal mediators will control the ability of a neuron to release its neurotransmitter; thus, the physiological levels of classic neurotransmitters are regulated by such neuromodulators and accordingly modify the function of neurons. This is, in fact, a classic neuro-immune response, showing how immune effector cells orchestrate the nervous system. Neuromodulators, including cytokines, function as a paracrine by diffusing through large regional areas of the brain (CNS), affecting multiple neurons and glial cells and consequently are a communication signal between the nervous and immune system. This neuro-immune communication has a major impact on brain function. Unlike the specific targeting of an individual neuron by its own neurotransmitter, which is rapidly degraded or reabsorbed, a neuromodulator controls the neuronal circuitry of an entire brain region. The neuro-immune mediator, TNF, and its communication network have a major impact on brain function, and the elevated levels of brain-TNF during neuropathologies provide a therapeutic target. Targeting these elevated levels of TNF within the brain, and thus its impact on numerous neurotransmitter systems, will revolutionize medicine by treating numerous disorders as an aberrant inflammatory response of the brain.

One of the neuromodulator functions of TNF is to inhibit the release of the neuron-derived monoamine neurotransmitter, norepinephrine, as shown in the isolated median eminence^[47]. TNF also inhibits the release of norepinephrine from field-stimulated tissue slices of the hippocampus, a region rich in noradrenergic nerve terminals^[3,4]. Neuropathic pain, while directed by enhanced TNF production in the hippocampus, is also associated with reduced norepinephrine release within the brain^[9,13,48]. Thus, this finding offers credibility to propose that a mechanism by which TNF directs neuropathic pain is through its enhanced and profound inhibitory effect on norepinephrine release. Overproduction of TNF in the hippocampus during neuropathic pain modifies signaling pathways to overwhelmingly inhibit norepinephrine release. Since supra-spinal descending noradrenergic inhibition of pain (endogenous analgesic pathway) occurs when norepinephrine is released in the brain^[49,50], the overproduction of TNF during neuropathic pain, with its enhanced inhibition of norepinephrine release, would

elevate pain to a chronic state by reducing central inhibition, thereby establishing a central component^[9,13,48]. This mechanism explains how engagement of the descending inhibitory neuronal pain pathways is prevented as shown within the hippocampus. In fact, due to its direct sensory input from the spinal cord, indirect sensory input from other brain regions, and complex network connections to thalamic and parabrachial regions, the hippocampus is well-situated to participate in both pain processing and modulation^[51]. Hence, the development of neuropathic pain is dependent upon the neuromodulatory role of the pathologically elevated levels of TNF in the hippocampus. In fact, the therapeutic mechanism by which antidepressant drugs provide analgesia during neuropathic pain is most possibly due to their ability to inhibit TNF production in the brain, and in particular in the hippocampus^[10], as they do for the alleviation of depressive behaviors^[52,53]. It follows then, strategies that decrease TNF expression in the hippocampus would be expected to produce greater therapeutic efficacy. It is becoming increasingly evident that there are clear functional links between brain production of TNF and the development of neuropathic pain^[51]. More importantly, it is imperative to elucidate the mechanisms that are involved in the pathogenesis of neuropathic pain and which are secondary to the enhanced expression of TNF in the hippocampus. The development of novel therapeutic approaches that specifically target the increased levels of TNF in the brain of patients promises superior treatments for hard-to-treat chronic pain, such as neuropathic pain.

TRICYCLIC ANTIDEPRESSANT DRUG ANALGESIC MECHANISM OF ACTION

Of the millions of patients who suffer from devastating chronic pain, many are additionally diagnosed with neuropathic pain that is mediated by peripheral nerve injury^[54,55]. Unlike acute pain, effective safe treatment for neuropathic pain has been elusive. Morphine derivatives are often prescribed for treatment of chronic pain conditions, including neuropathic pain. However, it has been shown that morphine repeatedly given to rats increases TNF expression in microglia, resident macrophage cells of the brain^[56,57]. This finding explains morphine-induced hyperalgesia and/or tolerance that develops during chronic pain treatment, since TNF contributes to the chronic pain state^[58]. Of interest, etanercept, a TNF blocker (a human TNFR2 fusion protein that blocks activity of TNF), when given intrathecally to morphine-tolerant rats decreased spinal TNF, IL-1 β , IL-6 production and restored the antinociceptive effect of morphine^[56]. This effect supports the contraindication of morphine as a chronic pain therapeutic.

We reported clinical benefit from perioperative clonidine use; clonidine lowered TNF levels in the cerebrospinal fluid, lowered patient VAS pain scores, and reduced postoperative morphine need^[59,60]. Clonidine

manages pain mediated from elevated brain TNF, which causes neuroplasticity, that allows for transient pain relief^[9,13,61]. Yet, as with most drugs, clonidine has adverse side-effects limiting its use. Despite its benefits in pain management, this drug is mostly used as an adjunct to other analgesics (opioids, nonsteroidal anti-inflammatory drugs).

Tricyclic antidepressant drugs as well as anti-convulsant drugs are first-line remedies for neuropathic pain^[62-66], yet neither class of drugs effectively treats all patients. While tricyclic antidepressant drugs are employed as a treatment practice, they are only moderately effective largely due to their various additional side-effects, and these multiple, unwanted side-effects limit their use^[67,68]. The tricyclic antidepressant drug analgesic mechanism of action is proposed to involve various neurotransmitter effectors (norepinephrine, serotonin, dopamine, and acetylcholine), which are dysregulated (both at their release as well as at receptor response) during neuropathic pain. Studies suggest that the tricyclic antidepressant drug analgesic mechanism involves their capacity to increase monoamines (NE, serotonin) in the synaptic cleft (at the varicosities) of neurons within the brain. Therefore, as proposed above, enhanced synaptic levels of monoamines activate the descending inhibitory pain pathway, which is compromised during neuropathic pain^[64]. In fact, tricyclic antidepressants and norepinephrine reuptake inhibitors (duloxetine, milnacipran) are better for neuropathic pain than SSRIs (Prozac, fluoxetine)^[69,70]. This may occur because, although each monoamine can activate both descending pain inhibitory and facilitatory pathways^[71,72], brain norepinephrine preferentially activates descending pain inhibitory pathways^[73], whereas serotonin promotes descending pain facilitation^[74]. At the same time, tricyclic antidepressant drug-mediated increase of peripheral-monoamines would enhance afferent pain signal transmission; therefore, tricyclic antidepressant drug analgesic action must occur specifically within the brain to be the most efficacious. In support, during chronic constriction injury (CCI)-induced neuropathic pain, increases in TNF levels occur in the periphery (injured sciatic nerve) as well as in the brain; yet, treatment with amitriptyline (tricyclic antidepressant drug, intraperitoneal injection) only decreased TNF production in the brain (hippocampus) and not in the spinal cord concomitant with alleviation of pain^[10]. Thus, the reduction of peripheral TNF production can be an unwarranted side-effect, where inflammatory responses may be necessary for healing or to combat associated infections. Specifically, we found that chronic treatment with amitriptyline, when initiated early after peripheral injury, reduced brain TNF and alleviated CCI-induced peripheral hypersensitivity^[10]. In contrast, we showed that acute amitriptyline treatment, at peak hyperalgesia, only briefly blocked CCI-induced hyperalgesia, but enhanced total brain TNF level^[48]. Thus, increased brain norepinephrine release is required for antinociception. Amitriptyline increases brain norepinephrine release (through reuptake

inhibition and, as an additional effect, adjusting TNF production), which may be antinociceptive by increasing the activity of the descending inhibitory bulbospinal pathway (inactive during neuropathic pain)^[75]. This acute, transient antinociceptive effect of amitriptyline is most likely explained by norepinephrine activation of presynaptic- α_2 -adrenergic autoreceptor-coupled-G α proteins that inhibit norepinephrine release. Of particular interest, their sensitivity to inhibit norepinephrine release is enhanced by TNF, thereby maintaining a chronic pain state due to preventing engagement of the descending inhibitory pain pathway^[10]. While the α_2 -adrenergic agonist clonidine normally inhibits TNF production^[61], the transient analgesic effect by clonidine in the CCI model of neuropathic pain occurs at the time when we have established that the presynaptic- α_2 -adrenergic receptor response to TNF actually switches from inhibiting to facilitating norepinephrine release^[61]. We propose that while this plays a role in the natural dissipation of CCI-induced thermal hyperalgesia, it can be provoked by blocking TNF production and can be involved in resolving neuropathic pain in humans^[48,61].

The reduction in levels of TNF in the brain elicited by tricyclic antidepressant drugs appears to be the likely mechanism of action directing their off-label analgesic drug use. Since the perception of pain is a product of the brain, and brain synthesized TNF is a key factor in neuropathic pain development, the elevated amounts of TNF in the brain of neuropathic pain patients could profoundly influence various neurotransmitter effectors. It follows therefore, that brain-TNF production when selectively targeted would create a potent and efficacious therapy. As previously stated, while TNF is increased in the brain during animal neuropathic pain models^[9,10,13,14], TNF regulates norepinephrine release from noradrenergic nerve terminals, and norepinephrine release in the brain is decreased at the same time^[13,14,48], which supports a role for TNF in the neuroplasticity associated with the development and maintenance of neuropathic pain. Not only does TNF directly inhibit norepinephrine release, but TNF also modifies the response of the presynaptic α_2 -adrenergic autoinhibitory receptor, a principal inhibitor of norepinephrine release^[3,4]. The presynaptic α_2 -adrenergic autoinhibitory receptor is activated by the release of norepinephrine in the synaptic cleft, as an inhibitory feedback mechanism having a primary effect on norepinephrine release. When activated, the presynaptic α_2 -adrenergic autoinhibitory receptor decreases further release of norepinephrine upon depolarization. Of particular interest, not only do tricyclic antidepressant drugs decrease TNF production, but they are also known to down regulate and desensitize the presynaptic α_2 -adrenergic autoinhibitory receptor^[76,77]. This simultaneous double-hit response by tricyclic antidepressant drugs on TNF production and on the presynaptic α_2 -adrenergic autoinhibitory receptor would have a profound response on depolarized release of norepinephrine culminating with analgesic functioning. It follows that the analgesic mechanism of tricyclic antidepressant drugs is likely the

result of their effect on TNF levels. Thus, the increased expression and levels of brain-TNF that are mediated by peripheral nerve injury is a viable therapeutic target^[3,10].

Founded on the fact that TNF regulates (inhibits) norepinephrine release in the brain both directly as well as indirectly by its effect on presynaptic α_2 -adrenergic autoinhibitory receptors, a pathologic increased level of TNF in the brain, and in particular, in the hippocampus, would be a key nociceptive target affecting norepinephrine bioavailability in the brain. Therefore, it follows that utilizing the inhibition of TNF activity as an antidepressant mechanism supports the monoamine theory of depression as well as the role of norepinephrine in the etiology of chronic pain. This current and comprehensive knowledge of inflammatory mediators such as TNF in chronic pain etiology will allow for the ushering in of new therapeutics that apply these mechanisms to direct the efficacy of new tricyclic antidepressant drug formulations or any other new therapies. Medicine that specifically reduces TNF levels in the brain are effective in animal models of neuropathic pain^[29,30,78]. Unfortunately, FDA-approved anti-TNF drugs are designed to target peripheral TNF and not brain TNF (*i.e.*, Infliximab) and, therefore, have very limited access to the brain; this could explain conflicting clinical reports^[11,79-81]. For instance, not all patients with sciatica receive benefit with peripherally administered TNF blockers^[80,81]. Meanwhile, tricyclic antidepressant drugs that can alleviate pain do in fact decrease the production of TNF in the brain^[10], however, due to their mode of delivery, they produce significant side-effects that confound their efficacy^[67,68]. Therefore, targeting the pathophysiologic levels of TNF that are specifically found within the brain, and in particular within the hippocampus, may be required to efficaciously alleviate pain. This premise is often incorrectly challenged by researchers/clinicians who administer anti-inflammatory drugs peripherally instead of through means that adequately target CNS-TNF alone. This is because when administered peripherally, a drug must distribute throughout the entire body where it is accessible and undergo metabolism through the liver, leaving significantly less unmetabolized drug to reach vital brain targets. Since very little drug reaches the brain when it is delivered peripherally, the (drug) effect on this organ would be minimal^[82]. Even drug delivery *via* intrathecal injection, which delivers more drug to the brain than intravenous injection, is quite limited. Non-invasive drug administration that targets brain effectors would be a pioneering discovery with wide ranging potential for numerous brain disorders.

Blockade of TNF activity specifically in the brain is difficult due to the large size and structure of anti-TNF biologics such that they do not easily cross the blood-brain barrier. Therefore, a new pioneering breakthrough is underway. Perispinal injection is a subcutaneous, peri-venous route for delivery to the brain that is less invasive than epidural or intrathecal

routes^[83]. Drugs injected outside and posterior to the spine (ligamentum flavum and spinal canal) are absorbed by the external vertebral venous plexus, part of the cerebrospinal venous system, which is a direct pathway to the brain^[84]. Perispinal etanercept injection immediately followed with head-down positioning (Trendelenburg positioning) delivers the TNF fusion protein into the choroid plexus and cerebral ventricles in minutes, as shown by PET scan^[85]. In fact, discogenic back pain patients that received perispinal etanercept delivery reported substantial, sustained recovery that was verified by reduction in Oswestry scores^[11]. Also, patients reduced significantly or completely discontinued analgesic medication after perispinal etanercept. This included 11 of 20 patients requiring chronic opioids^[11]. More recently, we reported a case study whereby perispinal injection of etanercept was performed to treat neurological dysfunction, including pain, induced by a traumatic brain injury suffered several years prior^[86]. The results from this case indicate that even years after an acute brain injury, the pathologic levels of TNF induced by the injury may provide a feasible therapeutic target. Taken together, these case reports provide compelling evidence that the specific targeting of brain-TNF is superior and thus an effective analgesic.

ROLES FOR TNF IN NEUROPATHIC PAIN ETIOLOGY

There are multiple roles for TNF in the development and maintenance of neuropathic pain. While many animal model studies show that systemic levels of TNF increase during neuropathic pain and contribute to its pathology^[19,87,88], increased TNF levels specifically in select brain regions alone enhance or initiate peripheral hyperalgesia (increased noxious sensitivity), which is a typical neuropathic pain response^[26]. The increased levels of TNF within the brain direct neuropathic pain onset^[9,13,14,48], as shown in the sciatic nerve CCI model^[9,61,89]. Likewise, the neuropathic pain that develops during diabetes, diabetic neuropathy, is accompanied by high serum TNF levels^[90-92]. High peripheral TNF levels in diabetes are associated with and possibly trigger peripheral nerve dysfunction and death^[93,94]. Interestingly, TNF directs neuron responsiveness, similar to the immune effector cell, the macrophages, and thus TNF stimulates neurons to produce more TNF^[4,61,95,96]. This creates a perpetuating feed-forward cycle, whereby inflammatory mediators released from damaged neurons stimulate cells and result in further production of TNF^[97]. This perpetual cycle may ultimately result in neuronal death, causing atrophy, which is an effect of TNF that may contribute to the decrease in brain gray matter experienced by chronic pain patients^[98]. This atrophy effect may be due to increased glutamate release by TNF, since excessive glutamate is neurotoxic^[39]. However, this effect, one of the many pleiotropic responses to TNF, may reflect the originally defined function of TNF as a TNF or

agent of cachexia or wasting syndrome. Moreover, the blockade of TNF activity by peripherally administered infliximab in rodent diabetes models restores glucose homeostasis^[99], but only reduces diabetic neuropathy^[30]. This inefficient effect by peripheral TNF blockade is in contrast to the complete alleviation of neuropathic pain observed in the CCI model, when TNF was specifically blocked in the brain^[9,12]. Mice deficient in TNF production (TNF α ^{-/-} mice) do not develop diabetic neuropathic pain following injection of streptozotocin (STZ), an antibiotic toxic to pancreatic β -islet cells and used to induce diabetes^[30]. Thus, it is apparent that TNF has a pivotal role in neuropathic pain, and therapies that decrease systemic, but more importantly, brain levels of TNF will provide greater efficacious neuropathic pain treatment, and most importantly, with fewer side effects.

CONCLUSION

In order to design novel therapies to treat neuropathic pain, it is necessary to use our current and comprehensive knowledge of biochemical mechanisms occurring specifically within the brain that elicit the development as well as the maintenance of neuropathic pain. An increased hippocampal TNF level plays a key role in the propagation and perception of neuropathic pain^[9,13,14,26,48,61,89]. Since brain synthesized TNF modifies adrenergic neuron activity, it follows that sympathetic output is altered, and consequently, has profound effects on descending inhibitory pain pathways that normally provide endogenous analgesia. The limited success in treating neuropathic pain with current agents stems from lack of specific and selective targeting of a fundamental mechanism associated with pain perception such as the pathologically overexpressed TNF in the brain and in particular in the hippocampus^[10,12,21,37]. In conclusion, elevated brain TNF levels drive the pathogenesis of neuropathic pain, and therapies that specifically lower this pathologic level of brain TNF may provide more efficacious chronic pain treatment, with fewer side effects and negligible abuse potential.

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- 20 Current challenges in diagnosis of lumbar radiculopathy

Lin JH, Chen CC

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Current challenges in diagnosis of lumbar radiculopathy

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Abstract

Lumbar radiculopathy (LR) is a term used to describe a pain syndrome caused by compression or irritation of nerve roots in the lower back. The surgery cost for LR increased by 23% annually during 1992-2003 in the developed country. Although it is one of most common complaints in clinical practice, the diagnosis for LR is still very challenging. Here we discuss the current tools of LR diagnosis and highlight the needs to develop new diagnosis tools for LR.

Key words: Magnetic resonance imaging; Nerve root; Pain; Lumbar radiculopathy; Lateral stenosis

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Core tip: Lumbar radiculopathy (LR) is a pain syndrome caused by the compression or irritation of nerve roots in the lower back. Because the diagnosis of LR remains challenging, the development of new diagnostic tools is urged.

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INTRODUCTION

Lumbar radiculopathy (LR) is a term used to describe a pain syndrome caused by the compression or irritation

Table 1 Agreement and prediction accuracy between diagnosis tools for detecting the involvement of the nerve root

	Agreement			Prediction		
	Clinical findings	MRI	MRI and clinical findings	Pain relief after surgical decompression	MRI	Clinical findings
Electrophysiology	52.0% ^[2] 89.5% ^[6]	59.6% ^[2] 54.0% ^[6] 60.0% ^[8]	25.0% ^[9]		Sen: 68.90% Sen: 86.3% ^[26]	
MRI	58.6% ^[6] 30.0% ^[7] 16.3%-64.9% ^[4] 3.0%-22.0% ^[5]	N/A	N/A	N/A	N/A	Spe: 16.0%-37.0% Spe: 61.0%-77.0% ^[27]
SNB	N/A	N/A	N/A	Sen: 85.40% Spe: 16.7% ^[10] Sen: 93.00% Spe: 26.0% ^[11] Sen: 96.00% Spe: 56.0% ^[12]		

MRI: Magnetic resonance imaging; SNB: Selective nerve block; N/A: Not available; Sen: Sensitivity; Spe: Specificity.

of nerve roots in the lower back. The cost of surgery for LR increased by 23% annually from 1992 to 2003 in the developed world^[1]. Although it is among the commonest complaints in clinical practice, diagnosing it remains challenging. Here, we discuss the current tools for LR diagnosis and highlight the need to develop new diagnostic tools for LR.

Requirements for an accurate diagnosis of LR

Accurate diagnosis is advantageous for treatment outcomes, with the ultimate aim of post-treatment pain relief. For the successful operative treatment of LR, a surgeon must identify the location that causes pain.

Inconsistency between diagnostic tools for anatomical localization

No gold standard exists for detecting the involved nerve root of LR. The diagnostic tools include symptomatology, physical examinations, electrodiagnostic study (EDX), magnetic resonance imaging (MRI), and selective nerve block (SNB). Currently, a combination of 2 or more of these techniques is generally used to obtain a diagnosis. However, inconsistency between these diagnostic tools is common and may cause confusion^[2,3]. Dermatome pain distribution is generally regarded as the first indication that the nerve root is involved. However, this indication is unreliable; only 16.3% of patients with L5 radiculopathy report a corresponding dermatome pain distribution^[4]. Moreover, only 3%-22% of patients with nerve root compression confirmed through intraoperative exposure had a corresponding dermatome pain distribution^[5]. Although physical examinations enhance LR diagnosis efficacy, conclusions of symptomatology and physical examination are consistent with MRI findings in only 16%-58% of patients with LR^[4,6,7]. Greater consistency could be obtained by combining clinical findings and EDX^[2,6], but abnormalities in EDX were observed in fewer than 50% of patients with LR^[3]. For determining nerve root involvement, MRI is markedly sensitive but exhibits a low specificity. By contrast, EDX

is markedly specific but has a low sensitivity. Therefore, MRI and EDX are currently considered complementary tools for identifying which nerve root is involved in LR. However, inconsistent findings from MRI and EDX are common, with an agreement rate of between 25% and 60%^[2,6,8,9]. SNB is usually employed as a diagnostic tool in patients with inconsistent findings to predict postoperative outcome. The sensitivity of SNB for a favorable postoperative outcome may reach 85%-96%, but it has a specificity of 16%-56%^[10-12] (Table 1).

These inconsistencies reflect the limitations of each diagnostic tool. Crucially, these tools do not directly evaluate pain or nociception. The conventional sensory test elucidates patients' perception of peripheral sensations, but it does not evaluate nociception. Although an MRI may provide anatomical evidence of nerve compression, the compression of a nerve root does not necessarily cause pain. An EDX can detect denervation or regeneration of the involved nerve root, but it provides limited information on nociception. To overcome the difficulty in determining nerve root involvement in patients with LR, a prediction model combining 2 or more of these diagnostic tools may provide more accurate results^[13,14]. A prediction model that included findings from MRI, symptomatology, physical examination, and SNB was developed and validated to predict the likelihood of a favorable 2-year outcome after decompression surgery^[15]. Notably, this prediction model did not include EDX and emphasized the role of the pain visual analog scale (VAS) and its response after SNB. Although the pain VAS is objective, it directly reflects a patient's response to nociception. The advantage of this prediction model is that it treats a favorable 2-year outcome as the gold standard. Nevertheless, a favorable outcome is the goal of any diagnostic tool.

Development of tools for the detection of dorsal root ganglion involvement

The dorsal root ganglion or its surrounding nerve tissue is involved in lateral spinal canal stenosis (also known

as lateral stenosis). An accurate diagnosis should not only reveal which root is involved but also identify the segment (e.g., postganglionic or postganglionic) of the nerve root that is compressed. Currently, sensory nerve action potential (SNAP) and the standardized qualitative sensory test (SQST) are diagnostic tools for detecting lateral stenosis. A 50% decrease in SNAP amplitude of the superficial peroneal nerve on the affected side (compared with the unaffected side) has a sensitivity of 91.3% with a specificity of 85.7% for detecting lateral canal stenosis^[16]. The SQST combined with an MRI is also a valuable tool for diagnosing lateral stenosis and identifying the compressed segment of the back^[17]. SNAP and SQST appear to be promising for discriminating between lateral stenosis and central stenosis in patients with LR. However, SNAP abnormality was observed in only 2% of patients with LR^[18]; SQST requires the full cooperation of patients and is validated only in patients with L5 radiculopathy^[17]. Additional studies are required to optimize these diagnostic tools to enhance their efficacy or develop novel tools.

Lack of mechanism-based diagnostic tools

Pain is the most disturbing symptom in patients with LR. Determining the mechanism by which pain is generated in patients with LR is critical for choosing treatment options. Different types of pain require different treatments. Persistent pain after an accurate diagnosis and even adequate surgical decompression is not uncommon^[19,20]. Some types of LR-associated pain (e.g., neuropathic pain) do not respond to surgical decompression^[20]. Substantial evidence from animal studies has shown that simply touching the nucleus pulposus without applying any pressure on the nerve root can cause pain-like behaviors in rodents^[21-23]. Thus, optimal diagnosis tools should not only reveal the exact anatomical location of the pathology but also the pain mechanism for patients with LR. The types of LR-associated pain include mechanical, ischemic, inflammatory, and neuropathic pain^[24]. Current diagnostic tools are insufficiently sensitive to distinguish between specific pain phenotypes.

Diagnostic tools that directly evaluate nociceptive pathways or pain phenotypes

Currently, few tools address pain phenotypes associated with LR. Interview questionnaires (e.g., neuropathic pain questionnaires, ID pain, and Pain DETECT) are used to detect neuropathic pain components. Allodynia and windup phenomena in quantitative sensory tests are markers of neuropathic pain^[25]. A positive straight leg raise test may be used to identify the mechanical or ischemic pain components^[26]. In older adults with low back pain, inflammatory biomarkers are associated with pain intensity and could thus play a role in detecting inflammatory pain in patients with LR^[27]. However, the diagnostic accuracy of the aforementioned tools has not yet been validated, thus undermining their potential for determining treatment options for patients with

LR. Future studies should examine the mechanisms underlying pain associated with LR. Based on the understanding of pain mechanisms, an ideal diagnostic tool can be developed to evaluate nociception or determine specific pain phenotypes.

CONCLUSION

Diagnosing LR is challenging for surgeons due to the inconsistencies between diagnosis tools and the limited availability of tools for pain phenotyping. It is hoped that further research will be conducted to develop diagnostic tools specifically for LR and associated pain phenotypes.

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