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ABOUT COVER

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MINIREVIEWS

Minireview of the clinical efficacy of platelet-rich plasma, platelet-rich fibrin and blood-clot revascularization for the regeneration of immature permanent teeth

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Abstract

The aim of this mini-review was to investigate and compare the clinical efficacy of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF), *vs* blood clot revascularization (BCR) for the regeneration of immature permanent teeth. The clinical efficacy of PRP, PRF, and BCR to regenerate 90 immature permanent teeth after one year, were compared for their ability to accomplish apical closure, a periapical lesion healing response, root lengthening, and dentinal wall thickening. The 90 cases were published in three different articles**.** The mean success rate for apical closure after one year was: PRP (89.2%) PRF (80%), and BCR (75.6%). The mean success rate for root lengthening after one year was: BCR (88.9%), PRP (68.2%), and PRF (65%). The periapical lesion healing response was 100% for BCR and 100% for PRP. Dentinal wall thickening was 100% for BCR, and 100% for PRP. All the PRP, PRF, and BCR treatments appeared to be effective. The published clinical results for PRP, PRF, and BCR indicate that these treatments are effective for the regeneration of immature permanent teeth.

Key words: Saving immature teeth; Regenerative endodontics; Dental pulp; Revascularization; Apical closure

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Core tip: The fractured or decayed immature permanent teeth of children and young adults aged 6 years to 28 which have a restorable crown, but thin dentinal walls may be regenerated by using a revascularization procedure which draws blood and stem cells into a disinfected root canal space. This study has shown that in addition to the most common method of using a blood clot revascularization technique, a platelet-rich plasma and a platelet-rich fibrin technique may also be used as alternatives.

Murray PE. Minireview of the clinical efficacy of platelet-rich plasma, platelet-rich fibrin and blood-clot revascularization for the regeneration of immature permanent teeth. *World J Stomatol* 2018; 6(1): 1-5 Available from: URL: http://www.wjgnet.com/2218-6263/full/v6/i1/1.htm DOI: http://dx.doi.org/10.5321/wjs.v6.i1.1

INTRODUCTION

Millions of mature teeth are saved by root canal therapy. The overall success rates for endodontic treatment after an average of 22 mo was 99.3%[1] and the success rate remains above 83.34% after eight years[2], and 86.02% after ten years[3]. It is the endodontic management of permanent incompletely developed teeth, after a traumatic injury, which have a poor prognosis when treated by conventional root canal therapy[4]. A common problem with incompletely developed teeth is that the dentinal walls are thin and weak, and are prone to stress fracture[5]. The long-term use of calcium hydroxide as a root canal dressing may increase risk of root fracture[6]. Immature teeth that have open and often divergent apices are not suitable for complete cleaning and obturation with traditional techniques and materials[7]. Ideally incompletely developed teeth require a "regenerative endodontic procedure" (REP) to thicken the dentinal walls to help prevent the subsequent fracture of the tooth[8]. REPs might not always result in complete root formation, and may not completely reduce the chances of root fracture[9], more successful REPs need to be investigated.

Regenerative endodontic therapies began around 1952, when a German dentist called: Dr. Hermann advocated the use of calcium hydroxide as a dressing for after a vital pulp amputation[10]. Today, many dentists still use calcium hydroxide, mainly for apexification[11], although MTA has overtaken calcium hydroxide to become the most popular pulp repair material[12]. Subsequent regenerative dental procedures include the development of guided tissue or bone regeneration procedures and distraction osteogenesis[13]; the application of platelet rich plasma (PRP) for bone augmentation[14]; the use of platelet rich fibrin (PRF) for periodontal wound healing[15]; and blood clot revascularization (BCR) by a Norwegian dentist called Dr. Nygaard-Ostby for the regeneration of tissues within the root canals of pulpotimized teeth[16,17]. There maybe a resistance among clinicians to use PRP and PRF instead of BCR, because PRP and PRF requires a venous blood draw from the arm of the patient at the time of treatment, and this adds time and complexicity to the tasks necessary to deliver the dental treatments, in addition to the added cost of the PRP and PRF kits[18].

The efficacy of BCR, or PRP or PRF has proved controversial for the regeneration of teeth: A randomized clinical trial which compared PRP, RPF and BCR concluded that BCR was the standard procedure for revascularization of non-vital permanent immature teeth[19]. Meanwhile another clinical case series of BCR and PRP, concluded that PRP was the most successful therapy[20]. Another clinical study, concluded that the regenerative effects of PRP and BCR were similar, except that PRP could increase the root length of immature teeth[21]. Further research is needed to determine if BCR, or PRP or PRF can give improved treatment outcomes, to guide clinicians to deliver the most effective treatment to benefit patients.

The successful outcome of the REP is commonly measured as; the ability to accomplish apical closure of the tooth root, a periapical lesion healing response, root lengthening, and dentinal wall thickening, because these indicate the regeneration of tissues[19-21].

The aim of this study was to compare the clinical efficacy of PRP and PRF, *vs* BCR for the regeneration of 90 immature permanent teeth after one year, compared using a meta-analysis for their ability to accomplish apical closure, a periapical lesion healing response, root lengthening, and dentinal wall thickening. The diverse treatment outcomes of the 90 treated teeth had been published in three different articles[19-21].

EXISTING RESEARCH

The clinical efficacy of PRP, PRF, and BCR to regenerate 90 immature permanent teeth after one year from three articles[19-21], were compared using a meta-analysis for their ability to accomplish apical closure, a periapical lesion healing response, root lengthening, and dentinal wall thickening.

This study did not require ethical approval from the Institutional Review Board because it used a publically available data. The de-identified data was previously published in three articles[19-21]. The three articles were selected from Medline following the search terms "immature permanent teeth,clinical, platelet rich plasma (PRP), revascularization, and clinical." This search returned one article which was excluded, because it investigated replanted teeth. Two articles were excluded because they were a case report of one tooth. The three articles were included in this mini-review because they were clinical trials of permanent immature teeth treated with PRP revascularization treatments, which measured the outcomes of treatment radiographically for more than one year.

The clinical criteria selected for evaluating the success of PRP, PRF, and BCR was apical closure of the tooth root, a periapical lesion healing response, root lengthening, and dentinal wall thickening[19-21].

SUCCESS RATE FOR ROOT LENGTHENING

The mean success rate for apical closure after one year

Table 1 Meta-analysis data of blood clot revascularization, platelet-rich plasma and platelet-rich fibrin for the regenerative endodontic treatment of immature teeth following trauma a one year follow-up

Article	Procedure (PRP, PRF or BCR)?	Apical closure?	Periapical lesion healing response	Root lengthening	Dentinal wall thickening
Jadhav *et al*[20], 2013	PRP	3/3 (100%) Satisfactory, good and excellent)	3/3 (100%) (Satisfactory, good and excellent)	3/3 (100%) (Satisfactory, good and excellent)	3/3 (100%) (Satisfactory, good and excellent)
Jadhav *et al*[20], 2013	BCR	3/3 (100%) (Satisfactory, good and excellent)	3/3 (100%) (Satisfactory, good and excellent)	3/3 (100%) (Satisfactory, good and excellent)	3/3 (100%) (Satisfactory, good and excellent)
Alagl *et al*[21], 2017	PRP	14/15 (93.3%) (Complete closure)	15/15 (100%) (All lesions healed)	NA	NA
Alagl A *et al*[21], 2017	BCR	8/15 (53.3%) (Complete closure)	15/15 (100%) (All lesions healed)	NA	NA
Shivashankar *et al*[19], 2017	PRF	16/20 (80%) (Apical foramen response *vs* no response)	NA	13/20 (65%)	NA
Shivashankar *et al*[19], 2017	BCR	14/15 (93.3%) (Apical foramen response *vs* no response)	NA	13/15 (86.7%)	NA
Shivashankar *et al*[19], 2017	PRP	16/19 (84.2%) (Apical foramen response *vs* no response)	NA	12/19 (73.70%)	NA
Mean for all publications	PRF	16/20 (80%)	18/18 (100%)	13/20 (65%)	NA
Mean for all publications	BCR	25/33 (75.6%)	18/18 (100%)	16/18 (88.90%)	3/3 (100%)
Mean for all publications	PRP	33/37 (89.2%)	NA	15/22 (68.20%)	3/3 (100%)

BCR: Blood clot revascularization; PRF: Platelet-rich fibrin; PRP: Platelet-rich plasma.

was: PRP (89.2%) PRF (80%), and BCR (75.6%). The mean success rate for root lengthening after one year was: BCR (88.9%), PRP (68.2%), and PRF (65%). The periapical lesion healing response was 100% for BCR and 100% for PRP. Dentinal wall thickening was 100% for BCR, and 100% for PRP. All the PRP, PRF, and BCR prcedures were similarly effective ($P > 0.05$). The individual and mean results for the PRP, PRF, and BCR procedures are summarized in Table 1.

Traumatic injuries to incompletely-developed permanent teeth affect 22% of children[22]. Despite this high demand for RETs to save teeth following trauma and caries, the use of endodontic treatments or RET has proved to be controversial[8]. A survey found that 55.1% of dentists were unsure whether RETs would be successful[23]. The failure to use RETs to save immature traumatized due to a lack of training or confidence in the outcome, may cause millions of children to grow up with missing natural teeth that could have been saved. To change clinician opinions and to gain a wider acceptance of RETs to be used to help save childrens traumatized teeth it was necessary to determine if the PRP, PRF, and BCR prcedures could make RET more successful or if they were similarly effective.

This present study calculated the mean success rate for apical closure after one year was: PRP (89.2%) PRF (80%), and BCR (75.6%). PRP was at least 9% to 13.6% more effective at inducing apical closure in comparison to PRF and BCR. PRP, PRF, and BCR were similarly effective at inducing apical closure in traumatized immature teeth, however, clinicians who treat hundreds of traumatized immature teeth with REPs, may find that using PRP will slightly increase the rate of procedure success. Potential disadvantages of the use of PRP *vs* BCR is the increased cost and time needed to prepare the PRP. Clearly, a child who has trypanophobia (a fear of needles) or hemophobia (a fear of the sight of blood) and do not allow veinous blood to be drawn from their arm is not a suitable candidate for PRP or PRF procedures.

The mean success rate for root lengthening after one year in this present study was: BCR (88.9%), PRP (68.2%), and PRF (65%). Although, BCR was at least 20.6% to 23.9% more effective at inducing root lengthening in comparison to PRF and PRP. The superior effectiveness of BCR, supports the theory that blood revascularization through the root apex brings mesenchymal stem cells into the root canal space to help accomplish dentinal regeneration[24].

The periapical lesion healing response was 100% for BCR and 100% for PRP. These findings are very good news for patients. It suggests that REPs are very successful at the disinfection of bacteria from the periapical region, which helps to heal loalized lesions, and avoid the need for complex apical surgery[25].

An essential requirement for REPs is to accomplish dentinal wall thickening to strengthen the immature teeth and to help prevent them from suffering a fracture[26]. The amount of remaining tooth structure is the most critical factor for the fracture resistance of endodontically

treated teeth[27]. Immature teeth can have very thin dentin walls. The thicker the dentin wall, the less likely that the tooth will fracture, once the thickness exceeds 1.5 mm, the tooth will have an improved fracture resistance. Only six cases measured the dentinal wall thickness, and no difference was found between the use of PRP and BCR procedure, which were similarly effective.

CONCLUSION

The published clinical results for PRP, PRF, and BCR indicate that these treatments are similarly effective for the regeneration of immature permanent teeth. The fractured or decayed immature permanent teeth of children and young adults aged 6 years to 28 which have a restorable crown, but thin dentinal walls may be regenerated by using a revascularization procedure which draws blood and stem cells into a disinfected root canal space. This study has shown that in addition to the most common method of using a BCR technique, a PRP and PRF technique may also be used as alternatives. A drawback of the PRP and PRF techniques is extra time needed to draw blood and centrifuge it prior to insertion into the root canals.

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EDITORIAL

Next generation sequencing in oral disease diagnostics

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Abstract

DNA sequencing is the method of identifying the precise order of DNA nucleotides within a molecule. The information of DNA sequencing is of prime requisite for basic biological research as well as in various clinical specialties. They can be used to determine the individual genetic sequence, larger genetic regions, chromosomes as well as to sequence RNA and proteins. Since the first DNA sequencing in 1970s, there has been tremendous advancements in the technologies aimed to determine the entire human genome. The need for rapid and accurate sequencing of human genome has resulted in the introduction of next generation sequencing (NGS) technology. NGS refers to the second-generation DNA sequencing technologies where millions of DNA can be sequenced simultaneously. Some of the next gen sequencing methods employed are Roche/454 life science, Illumina/Solexa, SOLiD system and HeliScope. Application of NGS in decoding the genomic database of various oral diseases may possess therapeutic and prognostic value. This presentation provides an overview of the basics of NGS and their potential applications in oral disease diagnostics.

Key words: Molecular diagnostics; Next generation sequencing; Illumina; Oral diseases; Oral cancer

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Core tip: Advancements in molecular biology has progressed exponentially in the past decade enabling the diagnosis and treatment of various oral and maxillofacial diseases including cancer. Next generation sequencing is one such tool which is used to determine the genetic make up of an individual as well as in identification of various genetic imbalances that occur in human diseases. Knowledge of the various sequencing methods and the genetic abnormalities may aid in its clinical application for overall improvement in disease diagnosis and prognosis.

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INTRODUCTION

Molecular diagnostics aimed at determining the alterations occurring at the genetic levels is an important factor in disease diagnosis as well as in the treatment planning or various human diseases including cancer. The availability of advanced technologies has enabled the identification and characterization of human genome, epigenome, proteome, transcriptome and metabolome. Whole genome sequencing determines the entire genomic DNA of an individual at a single time[1]. Whole genome data is considered the unbiased gold standard for obtaining sequencing data because intra- and inter-genic regions are revealed entirely[2]. The first accomplishment in DNA sequencing was obtained in 1977 with the introduction of Sanger sequencing wherein Sanger *et al*[3] and colleagues described the use of chain-terminating dideoxynucleotide analogs that caused base-specific termination of primed DNA synthesis. This was the first DNA sequencing method used to sequence human and microbial DNA based on the chain elongation using modified nucleotides and DNA polymerase[4]. Based on the sanger sequencing methods the first human genome project was completed in 2003. However, this method was disadvantageous in that it was time consuming, difficult to perform and error-prone owing to its manual laboratory-based methods and data entry. Additionally, traditional Sanger sequencing was mainly used to discover DNA substitutions, insertions and deletions [5]. The year 2005, witnessed a shift in whole genome sequencing technology with the arrival of second and third generation sequencing methods. The newer technologies employed for DNA sequencing were together referred to as second generation or next generation sequencing (NGS) methods.

The NGS methods is advantageous in that it helps in routinely extracting DNA, perform large-scale sequence data acquisition within a day[6]. They provide a valuable insight regarding the genomic pathways and thus may contribute to our understanding on disease development and subsequent progression. Various NGS techniques for DNA sequencing, characterization of the coding genome, the whole genome, copy number alterations, assessment of mRNA abundance and translocation detection exist for practical use.

Several NGS platforms are commercially available for DNA sequencing which includes the Roche/454 FLX, the Illumina/Solexa Genome Analyzer, the Applied Biosystems SOLiDTM System, the Helicos HeliscopeTM, complete Genomics, Pacific Biosciences PacBio and Life Technologies Ion Torrent[7]. Recently, single molecule real-time system from Oxford Nanopore is being developed as a third generation sequencing platform[8].

The feasibility of utilizing NGS in DNA sequencing has resulted in its application in various clinical diseases[8]. In addition to DNA sequencing, NGS is also useful in transcriptomics by detecting mRNA expression, discovering non-coding RNAs, microRNAs and metagenomics[7]. This article aims to highlight the various aspects of NGS platforms and its utility in oral disease diagnostics with emphasis on oral cancer.

NGS

The NGS was introduced in the year 2005 consisting of four main technologies. Each of these technologies is characterized by a interaction of high-resolution optics, hardware, and software engineering which allows streamlined sample preparation steps before DNA sequencing[7]. The various NGS platforms are similar in that the massively parallel sequencing of single DNA molecules are separated in a flow cell and the sequencing is performed by repeated cycles of nucleotide extensions or oligonucleotide ligation. This is different from that of Sanger sequencing, which is based on the electrophoretic separation of chain-termination products produced in individual sequencing reactions[3].

The advantages of NGS is that to obtain a higher and accurate sequence yield in shorter time while also being cost effective[8]. In general, these platforms have a high throughput, long read with short time and high coverage[4]. The main disadvantage of NGS is the requirement of infrastructure and personnel expertise to analyze and interpret the data. Also, the enormous volume of data generated by NGS should be skillfully used to extract clinically relevant information[5].

The NGS system of DNA sequencing has been used in various ways. Some of the important methods of sequencing performed with NGS include whole genome sequencing, exome sequencing, targeted sequencing, transcriptomics for total and mRNA sequencing, epigenomics and metagenomics[9,10]. One of the important utility of NGS is in the identification of non-coding and microRNAs in different organisms. The assessment of mutation in non-coding and microRNAs has helped in understanding and treatment of various diseases including cancer[11].

The different NGS platforms include Roche 454, Illumina, SOLiD systems and Ion personal Genome Machine (PGM™). The first commercially available NGS was the Roche 454 system which had a long hand on time and high error rate. Nevertheless, this platform is employed for *de novo* whole sequencing of microbes and exome sequencing[4]. The most commonly used NGS platform is the Illumina system (Illumina Hi Seq™) which are based on a sequencing by synthesis approach and is applicable for human whole genome sequencing, exome sequencing, RNA-seq and methylation[12]. The SOLiD System 2.0 platform, which is distributed by Applied Biosystems is a short-read sequencing technology based on ligation[3]. This platform is useful for human whole genome sequencing, exome sequencing, RNA-seq and methylation[4].

The method of DNA sequencing is similar among various NGS platforms in that the procedure is common for template preparation, nucleic acid sequencing, imaging and data analysis. The first step in NGS involves the preparation of the template or library. It involves preparation of library of nucleic acid by fragmentation of the DNA or cDNA sample and 5′ and 3′ adapter ligation[13]. Once constructed the library is amplified for sequencing. Nucleic acid sequencing from the amplified library is obtained through sequencing by synthesis[14]. The next step involves the data analysis of the sequences. The raw sequence data are then aliged to a known reference sequence by *de novo* assembly[15]. Following the alignment, many forms of analyses are possible using various online tools and software packages. The next crucial step is the visualization of the data obtained by the sequencing procedure. Considering the enormous amount of data obtained, it is mandatory to use a bioinformatics tool to simplify the datasets for genome resolution. While there are many commercially available software packages for enabling data visualization, constant effort in improvising the bioinformatics tool is required to support the NGS applications and help in decoding the obtained data.

CLINICAL APPLICATIONS OF NGS

Whole genome sequencing platforms have wide applications in human pathology. The application of NGS has been attempted in identifying the genomic alterations in various types of cancers including oral cancer, to determine the genetic abnormalities in hereditary conditions like cleft lip and palate as well as in various microbial infections.

The role of NGS in general microbiology is to obtain a genomic definition of pathogens which may harbor information about drug sensitivity and the inter-relationship of the various pathogens which can be used to detect infection outbreaks[5]. The oral microflora is composed of numerous microorganisms which are normal commensals of the oral cavity. While some of them are harmless, certain microorganisms are known to be pathogenic and responsible for commonly occurring oral infections. Usually, the focus of dental research was restricted to a small fraction of oral microbes especially the opportunistic pathogens. The advent of sequencing methods like next-generation sequencing has enabled newer avenues in microbiome studies thereby providing information on the broad diversity of microbial taxa regardless of their cultivability[16].

The use of NGS has made tremendous progress in identification of genetic variation in diseases with underlying genetic disorder. Prior to the use of NGS, it was not possible to identify the entire sequence of genetic alterations. NGS has enabled new the identification of the complete complement of DNA variants, *de novo* mutations and the genes underlying Mendelian forms of disease and characterization of important structural variation that may contribute to diseases like cleft lip and palate[17].

Oral squamous cell carcinoma is a common epithelial malignancy known for its heterogenous nature. The complexity of the lesion has result in the inability to accurately diagnose and manage them thereby resulting in poor prognosis. The use of NGS has enabled researchers to identify the genomic alterations evident in oral squamous cell carcinoma (OSCC). Whole exome sequencing studies have identification alterations with TP53, CDKN2A, PIK3CA and HRAS genes[18]. Another

important alteration which was identified using NGS is the NOTCH1 gene which is involved in regulating squamous differentiation[19]. Other observed alterations include EGFR, STAT3, JAK kinases, transforming growth factor-α and FBKW7 among others[20]. Evaluation of miRNA in oral squamous cell carcinoma has revealed a differential expression of miR-204-5p, miR-370, miR-1307, miR-193b-3p, and miR-144-5p, miR-30a-5p and miR-769-5p[21]. In another study three miRNAs (miR-222-3p, miR-150-5p, and miR-423-5p) were altered in oral leukoplakia and oral squamous cell carcinoma thereby suggesting their utility in early detection and to monitor the progression of oral leukoplakia to OSCC[22]. The role of miRNA in metastasis of oral squamous cell carcinoma has also been analyzed. Literature data has reported significant upregulation of 45 miRNAs in OSCC tissues than the normal controls. Further analysis of miR-21-3p suggests that they may have a potential role in cell metastasis in OSCC progression. Thus targeted therapy aimed at inhibiting the action of miR-21-3p may possess clinical utility and improve prognosis[23]. Other potential biomarkers that were analyzed in OSCC using NGS includes TP53, MDM2, CDKN2A/p16 and TNF- alpha. TP53 mutations were found to be the most frequent alteration in OSCC and hence could be used as a diagnostic marker[24]. Alteration in CDKN2A/p16, a tumor suppressor gene, aids in several molecular events responsible for the malignant transformation as well as in disease progression[25]. MDM2 amplification can promote tumorigenesis and possess increasing clinical relevance because inhibitors are under evaluation in clinical trials. Assessment of MDM2 regulation in various cancers has found that a majority of tumor type has a subset of patients with MDM2 amplification thereby suggesting its role in tumor progression[26]. The role of inflammation in OSCC has garnered renewed interest owing to the advent of NGS. Analysis of tumor necrosis factor-α in OSCC tissues has shown that they promote pro-inflammatory and pro-invasive phenotype and increased expression of TNF-α leads to tumor invasion and thereby associated with poor prognosis. Targeted therapy aimed at nullifying the effect of this gene may aid in the treatment of oral cancer[27].

CONCLUSION

NGS is being developed as an important research means in assessment of genomic alterations in various human diseases. The advantage is that most of the available NGS platforms share a common parallel sequencing process of clonally amplified DNA molecules. With ever improving knowledge regarding its utility, NGS can have a wider role in clinical practice provided some of the limitations are addressed. The need of the hour is to educate the current and future clinicians regarding its applications, the availability of accurate bioinformatics tool to assess the enormous data generated; and to improvise the technical skill and expertise of the laboratory operators. Overall, NGS is a significant discovery to help in disease diagnosis and implementation of appropriate therapy with minimal complications.

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MINIREVIEWS

Autism spectrum disorder: Review of literature and dental management

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Abstract

With an increase in the number of cases of autism spectrum disorder (ASD), dental professionals need to be aware of the different techniques required to ensure safe dental treatments for affected patients. The concerns and preferences of the parents and the medical and dental history of each patient should be considered. The aim of this article was to provide a comprehensive update on the medical and dental health of patients with ASD. A detailed search of the electronic database PubMed/Medline/Lilacs was performed for the terms "Autism", "Autistic", "Autism Spectrum Disorder", "ASD", "Dentistry" and "Dentist", in the period between 2006 and 2017. Systemic reviews, research articles, and literature reviews were included. Expert opinions, case series, and case reports were excluded from the search. A detailed family-centered approach based on the preferences and concerns of parents is an important foundation for appropriate individualized dental treatment of patients with ASD. In addition, the knowledge of disruptive behaviors and patient´s challenges may guide dental practitioners in improving treatment planning, oral management, and the overall oral health of patients with ASD.

Key words: Autism; Autism spectrum disorder; Autistic; Dentistry; Dental management

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Core tip: The number of patients diagnosed with autism spectrum disorder is increasing and the behavioral disorders of these patients can prove challenging during dental treatment. This literature review concluded that desensitization techniques and a patient-centered individual approach with the support of family could make dental treatments less stressful, less time consuming, and more successful.

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INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) published in 2013[1], provides the most current diagnostic criteria for individuals with autism spectrum disorder (ASD). The term is used to describe neurodevelopmental disorders that were previously classified as autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive neurodevelopmental disorder not otherwise specified[2].

The term spectrum represents a group of disorders with symptoms that are seen on a continuum, which ranges from mild to severe expression[2]. All of them are related to difficulties due to deficits in social and emotional reciprocity, the ability to start and maintain relationships, and the use of non-verbal communication; marked by stereotyped and repetitive behaviors, with restricted interests, and allied to hyper and/or hypo sensorial hyposensitivity[1].

According to Bernier *et al*[3] the disorder affects between 1 in 68 and 1 in 50 American children in all racial, ethnic, and socioeconomic groups, and it is almost five times more likely to occur in boys than girls.

Current evidence suggests that dental treatment under general anesthesia in children with special needs, especially individuals with ASD, are performed majorly due to uncooperative behavior and the extensiveness of the dental treatment, both of which are judged objectively[4,5].

The objective of this study was to conduct a review of the literature illustrating the important aspects of dental management in patients with ASD.

In order to conduct the proposed literature review, a bibliographic research was conducted in the database PubMed/MEDLINE/Lilacs with the following descriptors: "Autism", "Autistic", "Autism Spectrum Disorder", "ASD", "Dentistry", and "Dentist". The article search was restricted to the years 2006-2017. Systematic and non-systematic reviews and research articles were considered in this study. Articles such as expert opinions, case series, and case reports were disregarded for this review.

The initial search provided 358 articles from which 119 were selected based on their titles. This was further reduced to a final sample of 46 articles, after the main researcher perused the abstracts. Flow Diagram of Literature Search and Selection Criteria is available in Figure 1.

DIAGNOSIS AND CLASSIFICATION BY DSM-5

According to DSM-5 the ASD is classified into 3 levels of severity based on social interaction, communication, restricted interests, and repetitive behaviors[1].

Level 1 (Requiring support): Deficit in social communication capacity, difficulty in social interaction, and an apparent lack of interest in social relations. There is resistance in attempts to change or redirect interests[1].

Level 2 (Requiring substantial support): Greater deficit in the capacity of social communication both verbal and nonverbal, limited social initiation of interaction, and reduced or anomalous responses to social interactions. Individual become distressed or frustrated when their routine has changed[1].

Level 3 (Requiring very substantial support): Serious lack of social communication both verbal and nonverbal, very limited social initiation, and minimal responses to other people's social proposals. Restricted interests and repetitive behaviors interfere significantly in other contexts. Individuals demonstrate high level of suffering when their routine has been altered[1].

Currently, there are no biological markers that are specific to children with the disorder, and diagnosis is based on observation of patient interaction, and detailed information from interviews (anamnesis) with parents and/or caregivers, observations made by the medical team, and a neurological exam to exclude medical comorbidities and/or psychiatric disorders[1,6].

The Autism Diagnostic Interview-Revised (ADR-I) is considered the gold standard for ASD diagnosis. It is a questionnaire of 90 questions, which can be administered to

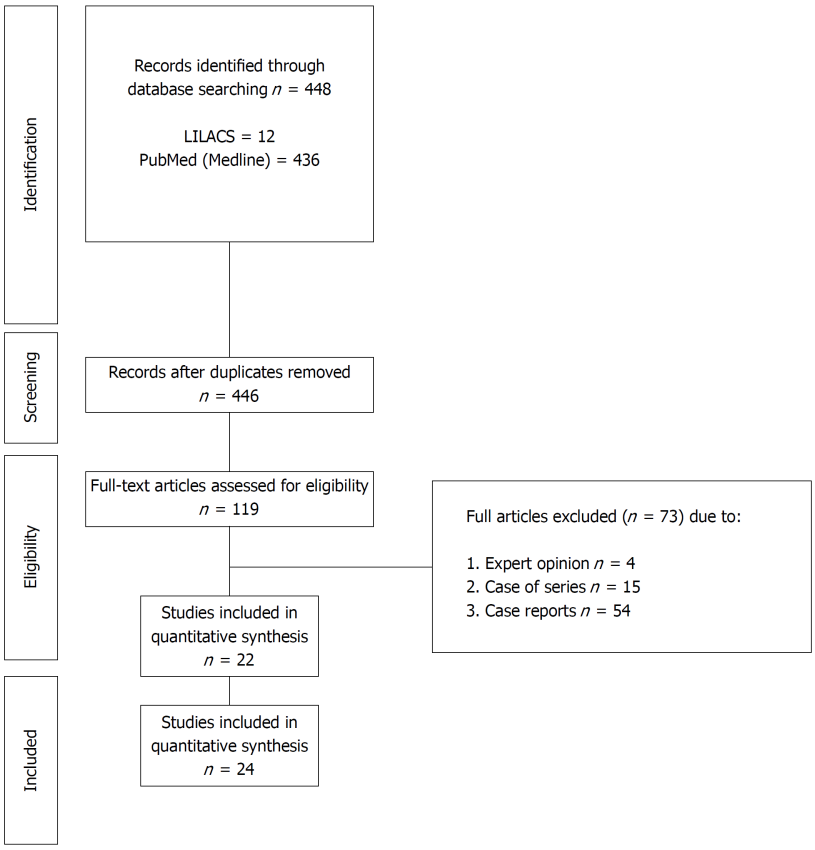


Figure 1 Flow diagram of literature search and selection criteria. Adapted from PRISMA REF.

parents and/or caregivers, by experts from different areas such as psychiatrists, neurologists and psychologists. Despite these advances, the mean age of diagnosis is still 4-5 years[7].

ETIOLOGY

No specific etiology for ASD has been identified; therefore, there is a general tendency to credit multiple etiologies to the disorder[8,9]. Several hypotheses have been considered reduction in the number of Purkinje cells of the cerebellum[10], reduction in the connectivity between specialized local neural networks in the brain and possibly over connectivity within the isolated individual neural assemblies[11], mutations of the PTEN gene[12], contact with pesticides during pregnancy[13], paternal age above 35 years[14], and altered levels of chemokines and specific cytokines during pregnancy[15].

In the past, exposure to mercury and thimerosal present in vaccines represented an important etiological factor for the development of ASD[16]. However, in 1999, the American Academy of Pediatrics reduced the exposure to these substances, culminating in a significant reduction in the number of cases.

SENSORY PROCESSING

Individuals with ASD may face significant challenges in sensory processing and sensory integration (nervous system processes and response to information obtained through the five senses), displaying socially disruptive behaviors externalized in form of aggressiveness, or self-mutilation, and hyperactivity when exposed to sensations like noises or lights, contact with strangers, and taste of unknown foods, among other stimuli that overwhelm them[4,17,18]. According to researchers, 80%-100% of individuals have a differentiated way of processing information, actions, and stimuli from the social context. This difficulty in interpretation is attributed to the presence of eidetic memory, which results in the individual´s inability to extract the implicit context in everyday situations and actions[19]. Summary data are presented in Table 1.

It is extremely important to highlight that each individual is unique, with different

Table 1 Type of sensory and behavioral difficulties associated with autism

Type of sensory and behavioral difficulties	Description
Visuals	Interest in rotating, colored or moving objects;
Auditory	Changes in sensory processing manifested as hypo or hypersensitivity;
Tactile	Reactions exacerbated by textures, touches, clothes, shoes and difficulty performing daily activities such as brushing teeth, cutting nails and cutting hair;
Proprioceptive	Difficulties in feeling their body in space
Gustatory	In form of refusal of food;
Flapping	Enjoy hitting their arms excessively against some specific surface
Rocking	Enjoy hitting their whole body against some specific surface
Spinning	Enjoy spinning excessively
Excessive ordering and stiffness	Difficulty performing actions and activities outside of your routine
Escape, avoidance or isolation behavior	It is usually related to auditory hypersensitivity and stimulus overload;
Aggressiveness	Caused by or as a reflex of sensory overload;
Hyperfocus	The child usually has a deep concentration, observing only some details in the environment;
Difficulties of attention	It is believed that more than half of the children with autism spectrum disorder have behaviors compatible with attention deficit disorder and/ or hyperactivity.
Eidetic memory	The person has a mental photograph of an event in their memory
Dyspraxia	Difficulty in planning, sequencing and performing motor actions due to sensory problems

characteristics and specificities; therefore, all possible stimuli and behaviors listed above must be relativized and individualized. Besides, the observation of a specific behavior only makes sense in a social context, and not in isolation[19].

THERAPEUTIC APPROACH

Currently, there isn't a single best treatment for ASD[20]. However, there is a diversity of drugs commonly prescribed for associated conditions, such as sleep disorders, epilepsy, gastrointestinal problems, and hyperactivity, amongst others[21].

It is very crucial that the dentist knows the medications prescribed by the medical team and studies the possible drug interactions with drugs commonly prescribed in dentistry[4].

Other therapeutic strategies consist of intensive and early behavioral intervention programs, applied with different techniques jointly or individually[22].

Desensitization consists of a series of procedures that are performed to repeatedly expose children with ASD to a controlled environment in order to promote their confidence and increase their adaptation, thus increasing their cooperation. The process begins with parents/caregivers using techniques of positive reinforcement, such as the use of a reward at the end of the consultation, and validating appropriate behavior[23].

The Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) is still widely used in many parts of the world, since the 1960s. The program is based on the organization of the physical environment through pre-established routines, in which the use of pictures, panels, or agendas systematize daily tasks or work systems in order to facilitate the understanding of the environment[24]. The method promotes the independence of the child while simultaneously assisting parents/caregivers and teachers[24].

The analytical behavior treatment (ABA) aims to develop skills and abilities that are acquired in stages, by means of instructions or indications that predict the events or stimuli that precede a daily activity and its consequences. It is important that learning is pleasant and helps children to identify different stimuli. When necessary, additional support is offered, this should be removed as soon as possible, so as not to make children dependent on it. As an appropriate response is obtained, the child will receive a reward as a positive reinforcement. Repetition is an important factor in this type of approach, as is the exhaustive record of all trials and their results[25].

Social histories present a short description of a specific event, which combines descriptive and visual resources, and promotes appropriate behavior within the situation addressed[26]. The elaboration of a social history should begin with the

selection of a specific theme, like a dental appointment, and should be explained using photos, figures, or drawings with short descriptive sentences mixed with phrases that indicate the desired behavior. An atmosphere of positivity is important for the success of therapy, and it is important to avoid negative phrases. Adequate social behavior can be attained by the reading frequency of the story[27].

Regardless of the technique used, the time required for the application of desensitization techniques represents the most difficult factor for professionals, since it requires both professional and family availability. Multi-professional work with occupational therapy, and simulated visits to the dentist, can minimize this disadvantage[28].

All of the above interventions are aimed at developing language, physical, and intellectual skills, and should consider the type of patient's communication. It is important that the strategies be carried out on a continuous basis, often with a mix of therapies, taking into consideration, the maximum number of people who are part of the children's routine[25].

ASD AND DENTISTRY

The dental treatment of individuals with ASD has been a challenge for dental professionals. Barriers to dental treatment include difficulties in access to the health care system, uncooperative patient behavior, cost and lack of insurance[29,30].

A questionnaire administered to parents/caregivers of children with ASD recorded the most common complains as difficulty in getting to the dental office and increased waiting time in the waiting room for dental appointments[31]. The environment of the dental office and the care itself, acts as triggers for different sensory processing in some patients leading to possible socially disruptive behaviors. Materials commonly used in clinical practice, temperature variations, different smells, direct light on the eyes, physical exam, noisy environment, or a combination of different factors, can be stressful as well[28].

Moreover, the feeling of anxiety is often exacerbated by routine changes, such as going to the dental office, and could be expressed as social phobias or specific phobias (excessive fear of a noise, for example). Together, all these factors may result in difficulties in dental management, resulting in a frustrating and inefficient appointment for professionals, patients and family[28].

Difficulty in dental care management results in poor oral hygiene which is the main risk factor implicated in the development of oral diseases, such as caries and gingivitis[20,32,33].

A systematic review conducted by Bartolomé-Villar *et al*[34] shows that children with ASD and other sensory disturbances present with poor oral hygiene, with an increase in plaque and bleeding indexes as a result of poor hygiene. However, the study was not conclusive regarding the prevalence of caries and malocclusions.

Data about the prevalence of caries in ASD patients are divergent in the literature, and no correlation with comparatively worse oral hygiene was directly established[33]. The evaluation of the buffer capacity and the salivary flow rate were evaluated, and no correlation was verified[35]. On the other hand, high prevalence of caries in ASD patients was observed by Jabar[32]; DeMattei *et al*[36]; and Vishnu *et al*[37]. After reviewing 385 records of patients with ASD, Loo *et al*[38], observed a lower prevalence of dental caries in individuals with ASD.

DENTAL MANAGEMENT

In the first appointment to the dental clinic, the patient and parents/caregivers must discuss the future therapeutic approach with the dental team. Data collection in the form of communication, medical history, associated conditions, sensory triggers, oral hygiene habits, inappropriate social behaviors, and dental history including patient's reaction to previous treatments, should be done. Consequently, the child's strengths and potential obstacles to dental intervention will be discovered[4].

In some cases, it eventually becomes necessary to use general anesthesia to carry out dental treatment for individuals with ASD. General anesthesia can assist in providing quality dental care in many patients who cannot be treated otherwise[28,39,40]. In these situations, the systemic health conditions should be evaluated in conjunction with the anesthesiology team, and the cost/benefit issues of the therapy must be discussed with family and or caregivers[41].

It is important to highlight that the hospital environment may produce hypersensitive responses which can lead to a complicated period of hospitalization,

thereby increasing the family's and patient's stress levels[42].

For families who are not comfortable with general anesthesia, the pharmacological sedation with benzodiazepines such as midazolam or diazepam can be used as an alternative since they it represents a good choice to achieve conscious sedation in dentistry, with low incidence of adverse reactions, and low costs[43].

Both techniques, conscious sedation and general anesthesia, do not promote the acceptance of dental interventions. Besides, they are associated with an increased risk of physical and psychological impairment; therefore, they should be reserved for cases where no other behavior orientation options are possible[5].

If an intervention program it is the best choice for a patient, it should be individualized to suit the individual´s characteristics, based on the professional experience and the resources available in the dental clinic. Therapy should be centered on family involvement[24], and the form of communication - verbal or non-verbal - must be considered.

According to Ferreira *et al*[44] and Chandrashekhar *et al*[45], the delay in language acquisition is an important marker of psychomotor development that is reflected in adults as lower intellectual development (intelligence quotient), lower cognition, and adaptive behavior. The form of communication may interfere with the processing of this information, and the professional should pay attention to facial expressions, body expressions, and gestures. If the patient can verbally communicate, it is important for the professional to have an idea of the amount of words he or she knows, in order to correlate the complexity of the subjects and activities that the patient can narrate or interact with during a conversation. The technique of voice control (a technique that uses different word intonations relating to the context and its meanings) can and should be attempted, but its real impact on behavioral improvement is uncertain, considering that some patients do not perceive the meaning of different voice intonations and facial expressions[4]. For patients who do not have verbal communication skills, communication strategies based on the application of symbols, images, and gestures can help in the understanding of potential sensory processing difficulties[4]. The dental team should be organized for changeable and atypical responses to sensory stimuli, as these patients dislike even minute changes in their surroundings and distractions must be avoided[45].

The primary objective of the dental surgeon should be to consider the patient's autonomy and independence training in order to perform his/her daily routine of oral hygiene. The analysis of the type of communication - verbal or non-verbal - is essential for the individual work itself or together with parents/caregivers[34].

For the first non-invasive dental procedure some strategies may be tried in the pursuit of increased patient cooperation. The main objective should be to transform the dental clinic into a less aggressive place and depict the dental visits as part of routine life as well. Some suggested strategies may be[28,46]: (1) To value care and forms of communication provided by the patient, family and caregivers; (2) establish communication strategies that facilitate the dental treatment. The strategy must be family-centered; (3) use simple, short, and clear statements-avoid jargon, language figures, and metaphors, as ASD patients tend to be literal thinkers and have a hard time understanding symbolic language and language figures. Use a calm voice, with detailed explanations of each procedure, and minimize body contact; (4) teaching skills should be one of the objectives of dental treatment. For example, following the professional's commands, testing different brushing techniques, using a hand or electric brush, and choosing a toothpaste with a tolerable taste; (5) be alert during the consultation in identification of trigger points for inappropriate behaviors; (6) mark the appointments in the first hour to reduce the risk of delays, as well as decrease the waiting room time; (7) avoid the use of flavored polish and fluoride pastes for patients extremely sensitive to taste; (8) patients can wear sunglasses to decrease light stimulation and/or earphones with portable music devices to decrease sensory stimuli during procedures; (9) promote familiarization with waiting room, dental clinic, and dental instruments. Personalized photographs or toys may be used as a desensitization strategy.

CONCLUSION

The dental treatment of patients with ASD requires knowledge of the individual's behavioral profile. When commencing dental treatment, it is important that the professional collects data on the patient's medical and dental history, as well as possible comorbidities and medications in use. Behavioral and emotional difficulties should be discussed with family and/or caregivers, and the dental treatment plan must be supported by the family and caregivers.

Making the dental appointment less aggressive for the patient with ASD should be the primary goal of the dentist. The professional should adopt a sensitive approach, and try to understand the world from the perspective of the individual, minimizing possible environmental triggers of disruptive behaviors, as well as knowing how to use different desensitization techniques in order to adapt the dental treatment to the individual needs of the patient, and always guided by family.

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