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RESEARCH PROGRESS OF CELL ACTIVE COMPONENT TRANSPLANTATION IN REPAIRING DISTAL BONE DEFECT OF ADJACENT TEETH AFTER EXTRACTION OF MANDIBULAR IMPACTED THIRD MOLARS

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ABSTRACT

Impacted mandibular third molars are very common, and can directly or indirectly cause dental or periodontal damage to adjacent teeth. Clinicians often extract the impacted mandibular third molar, but still, leave problems such as distal bone wall defect of the second molar or aggravation of the defect after extraction. The above further manifestations were the formation of the distal periodontal pocket, distal tilt, distal root resorption and so on. The distal bone wall defect of the second molar is affected by many risk factors, such as the age of the patient, the impacted type of the third molar, and the mode of operation. Cell active ingredient transplantation refers to the technique of extracting various cellular active components in the human body, such as platelet derivatives and bone morphogenetic protein, into tooth extraction to promote bone regeneration and repair bone defects. The extraction of cellular active components is convenient, cheap and safe. Surgery involves medical ethics, which is widely used in the repair of oral soft and hard tissue. The purpose of this paper is to review the influencing factors and cellular active components implantation of distal bone defect of mandibular third molar in the repair and prevention of bone defect, to provide a reference for clinical treatment of mandibular impacted third molar and repair and clinical treatment of the adjacent second molar distal bone defect.

Keywords: Mandibular third molars impacted teeth, alveolar bone resorption, bone regeneration, cellular active components

INTRODUCTION

Due to ethnic evolution and changes in food structure, the volume of the human skull relative to the jaw increased, and unbalanced masticatory organs degenerated, which led to the lack of space for the eruption of the third molar at the end of the dentition and impacted. Because of the existence of mandibular ramus, the impacted mandibular third molar is more common and complex. (Gandevivala et al. 2017) The mesially impacted and horizontally impacted mandibular third molars lose their normal contact with the adjacent second molars, which is most likely to lead to food impaction and plaque accumulation in the distal neck of the adjacent second molars, resulting in dental and periodontal diseases of the second molars. (Nuvvula et al. 2016) Dental caries, pulpitis, periapical periodontitis, inflammatory resorption or retraction of periodontal tissue in impacted third molars and their adjacent teeth are very common.

Some studies have found that more than 60% of impacted mandibular third molars are in close contact with adjacent second molars below the distal enamel bone boundary. (Nakagawa et al. 2007) Therefore, patients are recommended for early extraction of mandibular third molars. There are many ways of impacting mandibular third molars, which means different degrees of difficulty and prognosis of tooth extraction. The extraction of impacted mandibular third molars in close contact with large areas of mandibular second molars usually leads to oblique displacement and periodontal pocket formation due to insufficient distal support of adjacent second molars, resulting in tooth loosening. (F 1990a) This lack of distal support is due to the extraction of adjacent teeth and the defect of distal bone. The position and contact relationship between the impacted mandibular third molar and the adjacent second molar and the time of local lesions caused by the impacted mandibular third molar have a significant effect on the bone quality around the mandibular second molar. Impacted teeth can further affect the periodontal tissue healing of mandibular second molars after extraction of mandibular third molars, (Szalma et al. 2010) resulting in oblique displacement, distal bone defect and root surface exposure of mandibular second molars. (Vignudelli et al. 2017) Therefore, most scholars prefer prophylactic extraction of the impacted mandibular third molar and repair of the distal bone defect of the second molar.

The distal bone defect of the second molar is affected by many factors, and there are many methods to repair or prevent the bone defect, mostly through periodontal surgery, such as guided tissue regeneration (Guided Tissue Regeneration therapy, GTR), bone graft repair, tissue engineering bone technology and so on. (Dongmiao et al. 2017) Cell active ingredient transplantation refers to the technique of extracting all kinds of cellular active components (growth factor, platelet active substance, bone morphogenetic protein, etc.) from the human body into a tooth extraction wound to promote bone regeneration and repair bone defect. (Butcher et al. 2009) At present, a variety of cellular active components, such as platelet-rich fibrin (Platelet Rich Fibrin, PRF) and autologous growth factor-rich fibrin gel (Concentrated growth factor, GCF), have been proven to be effective in inducing bone regeneration, and have been widely used in clinical treatment and basic research of tissue regeneration, and their composition and mechanism tend to be understood. Because of its convenient extraction, low price, low safety risk and no medical ethics, the cellular active component has been recognized by a large number of scholars for repairing soft and hard tissue defects in oral and maxillofacial areas. However, there are still few reports about its application in the repair of a distal bone defect of the second molar caused by impacted mandibular third molars. The purpose of this paper is to review the research status of the influencing factors and cellular active components implanted into the bone defect of the second molar for the repair and prevention of the distal bone defect of the mandibular third molar. To provide a reference for the clinical treatment of mandibular impacted third molars and the repair and clinical treatment of adjacent second molars distal bone defects.

The purpose of this paper is to review the influencing factors of distal bone defect of the second molar when the mandibular third molar is impacted and the research status of bone defect caused by implantation of cellular active components. This provides a reference for the clinical treatment of mandibular impacted third molars and the repair of distal bone defects of adjacent second molars.

1. RISK FACTORS

1.1 Classification of impacted mandibular third molars

When the third molar is mesially impacted, the contact point with the second molar is closer to the root, and the alveolar bone defect is serious. (Quek et al. 2003) In addition, during mesial impaction, a small angular space with large mouth bottom is formed between the mandibular second and third molars, which is conducive to the retention and growth of food residues and bacteria and microorganisms, which not only leads to distal caries of the mandibular second molars but also leads to periodontal tissue inflammation and middle bone resorption of the second molars. In the proximal and low-impacted mandibular third molars, the distal contact area between the mandibular third molars and the second molars is large, which not only occupies the bone space between the two teeth but also increases the difficulty of operation (Marciani 2007). In addition, there is chronic inflammation in the distal periodontal tissue of the second molar before the operation, which greatly affects the level of the distal bone wall(G et al. 2007). According to Kugelberg et al. (Ahmet and Nihat 2019), 2 years after the extraction of impacted third molars, 32.1% of the second molars had a height of distal bone loss above 4mm, especially in proximal or horizontally impacted molars.

1.2 Patient's age

Time plays an important role in the periodontal damage of the second molar caused by the mandibular impacted third molar(F. et al. 1991). With the increase of age, the probability of periodontal tissue inflammation, alveolar bone resorption and distal adjacent surface caries of adjacent second molars increases. Santosh et al. (Santosh 2015) believe that for teeth with periodontal problems, the regeneration of periodontal tissue is more difficult than that of normal teeth. Some studies have shown that the age of [15] 25 is an important time for the extraction of impacted mandibular third molars, and it is better to recover after extraction of impacted third molars before the age of 25 (G 2009). Early preventive extraction of mandibular third molars is recommended. Faria et al. (F 1990b) found that the rate of distal bone wall resorption of adjacent second molars after extraction of mandibular impacted third molars after 25 years old was significantly higher than that before 25 years old. Some studies have found that the distal bone wall of the second molar extracted before 30 years old is better than that after 30 years old (Faria, Gallas-Torreira, and López-Ratón 2012). It can be seen that age can affect the distal bone defect and recovery of adjacent second molars, in which 25-30 years old may be an important age node.

1.3 Other factors

The extraction of the impacted mandibular third molar often includes flap flipping, bone removal, interstitial augmentation, tooth division and so on. At present, there are many styles of flap design, but at the same time, the continuity of periodontal tissue has been destroyed, which will affect the effective blood supply of periodontal tissue during operation and for a long time after the operation. Some scholars have designed a flap-turning method to avoid damage to the distal periodontal tissue of the second molar, but it has no significant effect on the recovery of the distal periodontal tissue of the adjacent second molar, and can not improve the recovery of the distal bone defect of the second molar (MOTAMEDI 1999; Suarez-Cunqueiro et al. 2003). Different types of impacted teeth require different surgical methods (Marciani 2007). Long operation time and large trauma range will affect the recovery of the distal bone wall of the second molar (Ahmet and Nihat 2019). Some studies have found that the third grinding extraction assisted by an ultrasonic bone knife can effectively reduce surgical injury and shorten the operation time, and the postoperative reaction is mild (Brignardello-Petersen 2017; Jiyuan et al. 2018). After the extraction of the mandibular impacted third molar, a local bacterial microorganism retention area will be formed between the distal second molar

and the mandibular ramus, and inadequate plaque control after the operation will affect the recovery of the distal bone wall of the second molar (Kan et al. 2002).

2-CELL ACTIVE INGREDIENT TRANSPLANTATION

2.1 Platelet-rich plasma, PRP

PRP was first isolated from whole blood by Harke et al. (H et al. 1977) in 1977. The platelet concentration in PRP is very high, which is more than 4 times of ordinary whole blood. If the platelet concentration in plasma obtained by centrifugation is less than 4 times, it is called platelet-poor plasma, PPP (Maisel-Campbell et al. 2020). Platelets in PRP can release a variety of bioactive substances, including platelet-derived growth factor, transforming growth factor-B, insulin-like growth factor, bone morphogenetic protein, etc. ('Tissue Engineering; Findings from University of Paris in the Area of Tissue Engineering Reported (An In Vitro Investigation of Platelet-Rich Plasma-Gel as a Cell and Growth Factor Delivery Vehicle for Tissue Engineering)' 2016) These bioactive substances promote the migration, adhesion, proliferation and differentiation of osteoblasts, so PRP can promote bone regeneration and bone development('Tissue Engineering; Findings from University of Paris in the Area of Tissue Engineering Reported (An In Vitro Investigation of Platelet-Rich Plasma-Gel as a Cell and Growth Factor Delivery Vehicle for Tissue Engineering)' 2016). Sammartino et al. (Sammartino et al. 2009) found that simultaneous implantation of PRP after extraction of mandibular impacted third molars could accelerate and induce distal new bone formation and periodontal tissue attachment of adjacent second molars. In addition, PRP combined with bone grafts, such as calcium phosphate cement artificial bone (calcium phosphate cement, CPC) (Hasan, Taz, and Lee 2018) and allogeneic bone (Ashish and Dev 2014), can promote new bone formation, and the long-term effect is good. However, activators such as calcium chloride and bovine thrombin need to be added in the preparation of PRP, and there is a certain risk of coagulation disorder and immune rejection. At present, there is little use of PRP to repair clinical tissue defects.

2.2 Platelet-rich fibrin, PRF

PRF is the second generation of platelet concentrate product discovered after PRP. It is obtained by peripheral blood centrifugation without adding an anticoagulant or activator. It is simpler, safer and more reliable than PRP and has gradually replaced PRP in the clinic. PRF is composed of fibrin and a variety of cells and growth factors, such as platelets, leukocytes, cytokines and circulatory stem cells, which contain about 97% of platelets and more than 50% of leukocytes in centrifuged blood, showing a three-dimensional reticular microstructure in which cells can differentiate(M et al. 2010). In addition, the three-dimensional reticular structure of fibrin can protect the rich platelets from activation [30] and release them gradually with the degradation of PRF, so that platelets can stably release various growth factors, which is more conducive to the promotion and induction of cell proliferation, differentiation and migration(E et al. 1998). In the process of preparation, white blood cells in the reticular structure of PRF are also activated, which is important for local immunity in the process of tissue healing(M et al. 2006). PRP combined with freeze-dried bone can significantly increase the thickness of the maxillary sinus floor (Alain et al. 2011). Placing PRF in a fresh extraction wound of the mandibular impacted tooth, it was found that it can accelerate the healing of the extraction wound, promote periodontal tissue and reduce the depth of the periodontal pocket (Miron et al. 2017). But at present, PRF has some disadvantages, such as poor texture and strength, fast degradation rate and so on (Al-Maawi et al. 2021), and it is still rare to use PRF to repair the distal bone defect of the second molar

caused by mandibular impacted third molar, and whether it can be repaired by PRF to provide enough distal support of the mandibular second molar still needs to be further confirmed.

In addition, as a newer generation of platelet products, advanced- platelet-rich fibrin, A-PRF is also widely used in clinical and basic research of tissue repair. Nishiyama et al. (Kazuhiko et al. 2016) found that A-PRF can induce human periosteal cells to proliferate and differentiate into osteoblasts and show obvious osteogenic. LihongLei et al. (Lei et al. 2020) compared A-PRF and GCF in promoting periodontal tissue repair and regeneration, and do not find there was a significant difference between them. The alveolar bone defect after extraction of mandibular wisdom teeth was repaired with A-PRF, and it was found that the bone mass and bone mineral density could be significantly restored after 4 months (Yewale et al. 2021). However, the sample size of these studies is small, and the observation time is short. Whether A-PRF can repair the defect of the distal bone wall of adjacent teeth caused by mandibular impacted third molars needs further study.

2.3 Bone morphogenetic protein, BMP

BMP is a member of the transforming growth factor-beta, TGF- βfamily. It is essentially a special kind of glycoprotein extracted from human bone tissue, mainly derived from human bone and bone-derived cells, and plays an important role in bone development and remodelling. BMP can induce mesenchymal stem cells to differentiate into osteoblasts, thus promoting the healing of bone defects. At present, it has been confirmed that a variety of BMP can promote the formation of bone and cartilage, among which BMP-2 and BMP-7 have been widely used in the commercial treatment of tissue repair and regeneration(C et al. 2014). Compared with the single use of BMP, the BMP sustained release agent made of fibrin glue, polylactic acid-polyglycolic acid (PLGA), chitosan, bone matrix and BMP prolonged the degradation cycle of BMP, maintained the BMP concentration of local tissue for a long time, and obtained a better effect of bone repair (A et al. 2006). However, some studies have shown that BMP-2 has tumorigenicity, which may be related to the fact that BMP-2 can change the electrostatic charge on the cell surface by binding to the membrane receptors of mesenchymal cells, thus causing DNA variation (Raida et al. 2006; Cicciù et al. 2014; Stok et al. 2015). Therefore, there is still some uncertainty about the long-term effect and safety of BMP-2.

2.4 Concentrated growth factors, GCF

Compared with PRP and PRF, GCF is the third-generation platelet concentrated product. unlike PRF, GCF is prepared by gradient centrifugation. In the process of centrifugation, collagen in blood polymerizes slowly and finally forms a three-dimensional reticular structure. Many platelets, white blood cells and various growth factors are deposited in the three-dimensional structure of concentrated growth factors in GCF. The preparation method of GCF is beneficial to the deposition of platelets and growth factors in the three-dimensional reticular structure of fibrin, and the physical strength of GCF is stronger than that of PRF (Fabrizio et al. 2011). Hyun-ChunPark et al (Hyun-Chun et al. 2016) found that GCF is superior to PRF in repairing peri-implant bone defects in dogs. Using GCF to perform guided bone regeneration surgery, it is found that the ideal bone plate thickness can be obtained and the postoperative swelling can be significantly reduced (Chen et al. 2021). At present, there are still few studies on GCF, and it has not been used to repair the defect of the distal bone wall of adjacent teeth after extraction of mandibular impacted third molars. However, as the third-generation platelet concentrate, GCF has an excellent performance in soft and hard tissue repair (C 1975), which can be used as one of the research directions for the repair of distal

bone wall defects of adjacent teeth after extraction of mandibular impacted third molars.

2.5 Enamel matrix proteins, EMPs

EMPs are a protein mixture extracted from the unmineralized enamel layer of the tooth embryo, which is the general name of the protein contained in the unmineralized matrix of the tooth embryo. EMPs are mainly secreted by the ameloblasts during the development of the tooth crown and can contribute to the mineralization and maturation of the enamel. Slavkin (T et al. 2000) first reported that enamel matrix protein can induce cementum production on the tooth root surface. Vander Pauw et al. (Oscar et al. 2015) proved that EMPS could induce cells with differentiation potential in periodontal tissues to differentiate into osteoblasts by significantly improving the alkaline phosphatase activity of fibroblasts. EMPs show a high degree of homology conservation among different species. Currently, EMPs used in clinical research are mostly extracted from young pig tooth embryos, which are mainly composed of amelogenin protein, amelogenin protein, amelogenin protein and a variety of enzymes. Of these, about 90% is amelogenin protein(Peter et al. 2014). Enamel Matrix Derivatives and EMD were extracted from the main proteins in EMPs. EMD could also induce the regeneration of periodontal soft and hard tissues, and was widely used in periodontal therapy and implantation surgery (Eickholz et al. 2014). In conclusion, EMPS may be used in the study of adjacent bone wall repair after extraction of impacted teeth.

In summary, many active components of cells show superior bone defect repair performance and are widely used in the study and clinical treatment of oral soft and hard tissue defect repair. However, there are still many defects, such as poor physical strength, low plasticity, fast degradation rate, and difficulty to guarantee local concentration and action time, so there are certain limitations. In addition, there are few studies on the repair of distal bone wall defects of adjacent teeth behind impacted mandibular third molars. Searching for ideal materials to repair the soft and hard tissue defects of the oral cavity is still the research direction and hot spot in the future.

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