Regenerative Materials in Furcations of Patients with Periodontitis

Subjects: Dentistry, Oral Surgery & Medicine

Contributor: Sergio Bizzarro, Enrico Marchetti, Gerasimos Odysseas Georgiou, Francesco Tarallo

Periodontitis is a chronic, multi-factorial inflammatory disease, caused by an inflammatory reaction by the host to a dysbiotic subgingival microflora, which can be modified by genetic and lifestyle factors, and it results in the loss of tooth-supporting apparatus, the connective tissue attachment and alveolar bone. Worldwide, periodontitis affects about 20–50% of the global population. Regeneration of lost tissues around the teeth remains a clinical challenge, especially in furcation defects of molar teeth. This research will give an overview of the outcomes of the use of different regenerative materials in the treatment of class II furcation defects in patients with periodontitis.

Keywords: regeneration ; furcation ; periodontitis ; periodontal defects

1. Introduction

When left untreated or not successfully treated, periodontitis can eventually cause the loss of the tooth, gradually leading to a loss of both chewing and aesthetical function. The progression of the bone loss seems to be more prevalent in multi-rooted teeth, particularly the upper and lower molars [1]. The treatment of the furcation regions of the molars is often less effective when compared to the non-molar teeth, because of their complex anatomy and the possible presence of other abnormalities as enamel projections, enamel pearls or grooves [2][3][4][5][6]. A retrospective cohort study reported that 58.1% of the patients lost at least one molar over 10 years of supportive periodontal treatment after active periodontal therapy [7].

To improve both treatment outcomes and the prognosis of the molar teeth, different resective surgical approaches have been proposed—more specifically, root resection, hemi-section or tunnelization. However, these treatments showed a considerable amount of failures (25–58%) and a high level of morbidity and costs [8].

Alternatively, the regeneration of the lost periodontal tissues is also another treatment option. According to the Glossary of Periodontal Terms, regeneration is the “reproduction or reconstitution of a lost or injured part in a manner similar or identical to its original form. In periodontics, it refers to the formation of new bone, cementum, and a functionally-oriented periodontal ligament at a site deprived of its original attachment apparatus” [9]. To achieve this goal, different biomaterials have been investigated.

Guided Tissue Regeneration

In guided tissue regeneration (GTR), the gingival epithelium is excluded from the healing wound in order to allow a selective repopulation of the root surface by cells of the periodontal ligament and alveolar bone. This will prevent the rapid proliferation of the sulcular epithelium and the forming of a long junction epithelium on the root surface [10]. To achieve this, different sorts of barriers (membranes) have been used [10][11][12].

The main characteristics for a GTR membrane should be:

- Biocompatibility to allow integration with the host tissues without eliciting inflammatory responses.
- Proper degradation profile to match with the new tissue formation.
- Adequate mechanical and physical properties to allow its placement in vivo.
- Sufficient sustained strength to avoid membrane collapse and perform their barrier function [13].

A major distinction among membranes is as follows:

- Non-absorbable barriers

The mostly used non-absorbable membranes are made of tetrafluoroethylene or expanded polytetrafluoroethylene. Other materials were rubber dam, resin–ionomer barrier, a barrier made out of knitted nylon fabric mechanically bonded onto a semipermeable silicon membrane and coated with collagen peptides, and Millipore filter [14]. The main issues related to non-absorbable barriers are the high chance of bacterial contamination and the need for a second surgery for removal.

- Absorbable barriers

Absorbable membranes offer better biocompatibility than the non-absorbable ones but low to no control over the regenerative healing. In fact, the degradation process starts immediately after the placement in the tissues and the rate of absorption may vary among patients. Absorbable membranes are made of collagen and various derivates of collagen such as dura mater, cargile membrane, oxidized cellulose, laminar bone, connective tissue graft, polyglycolic acid and polylactic acid [15][16].

Grafts

Graft materials, or bone substitutes, are used mainly to stabilize the blood clot in the alveolar bone defect and allow regeneration of the periodontal tissues. Graft materials should present one of the following characteristics to promote regeneration:

- They contain bone-forming cells (osteogenesis).
- They function as a scaffold for bone formation (osteoconduction).
- They contain biological substances in their matrix that induce bone formation (osteoinduction).

Graft materials can be subdivided in four categories:

- Autogenous: Grafts obtained by the patient, harvested both from intraoral and extraoral sites, consisting of cortical bone or cancellous bone and marrow.
- Allogeneic: Grafts of human origin. Three types of bone allografts are used in periodontics, namely, demineralized freeze-dried bone, non-demineralized freeze-dried bone and frozen iliac cancellous bone.
- Xenogeneic: Graft from a non-human donor, mainly from bovine or porcine origin.
- Alloplastic materials: Synthetic or inorganic implant materials which are used as substitutes for bone grafts [16][17].

Enamel Matrix Derivative

This is a purified fraction derived from the enamel layer of developing porcine teeth. The enamel matrix derivative (EMD) is a gel-like material that consists of enamel matrix proteins, water and propylene glycol alginate, which is used as a carrier. The major enamel matrix proteins in EMD are amelogenins (90%). EMD also contains other proteins such as enamelin, ameloblastin, amelotin and various proteinases in a very low percentage. EMD plays a significant role in wound healing, promoting the formation of new blood vessels as well as collagen fibers in the connective tissue. It also promotes regeneration through the increase in cell attachment, the proliferation of periodontal ligament-fibroblasts and the increase in the expression of growth factors, molecules involved in osteogenesis and molecules involved in the regulation of bone remodeling [18][19].

Blood derivatives

Blood derivatives are materials obtained by the patient's own blood. These materials are not meant to create a mechanical barrier or a stabilization of the blood clot, but rather to induce regeneration by means of a potent production of growth factors by the platelets and other components of the blood clot obtained by the patient's own blood.

Platelet-rich plasma (PRP) was the first generation of blood derivatives, obtained by two cycles of centrifugation and characterized by a short-term release (1–8 days) of growth factors. Within 10 min, 70% of growth factors are already released, and within the first hour, almost 100% are released [20][21][22]. Nowadays the PRP has been replaced by platelet-rich fibrin (PRF), which needs a much simpler preparation without any use of anticoagulants. PRF provides a more stable material with a higher concentration of growth factors, as platelet-derived growth factor aa (PDGFaa), PDGFbb, PDGFab,

transforming growth factor beta1 (TGF-b1), TGF-b2, vascular endothelial growth factor and epithelial growth factor. Additionally, T-lymphocytes, B-lymphocytes and monocytes are found within the first 25–30% proximal part of the clot and increase anti-bacterial and angiogenetic properties [23][24][25].

Blood derivatives have the advantage of being an attractive alternative option for patients who do not accept materials from allogenic or xenogeneic origin and at the same time reduce the risks of possible foreign body reactions. However, retrieving blood can cause additional local pain and discomfort and it may not be suitable in patients with a high hemorrhagic diathesis. Moreover, additional training is needed for clinical staff to learn the blood sampling procedure and the preparation of the material.

In the literature, there is a great variety of clinical studies and few meta-analyses that have investigated the effect of the above-described materials, alone or combined, in the regeneration of molars with affected furcation sites, but the majority of them focus on a limited amount of materials. One recent review presented meta-analyses of different materials, but it did not include blood derivatives [26]. Therefore, this research is to propose an overview of the clinical effects of different regenerative materials when applied in periodontal surgical regeneration of molars affected by class II furcation defects.

2. Current Insights

In the researchers' search, only RCTs with open flap debridement (OFD) as control group were included. In a previous meta-analysis, OFD has shown to provide clinical improvement, although limited, in mandibular class II furcations [27] with relatively low cost and morbidity. The question is whether the additional costs for the adjunct of regeneration materials are justified by the additional clinical improvements.

The results from the studies included in the present research suggest that surgical therapy combined with regenerative materials can lead to mildly to moderately better clinical outcomes, particularly for VCAL and VPD, in mandibular buccal class II furcations when compared to OFD alone. Less consistent results have been reported for maxillary and lingual mandibular class II furcation defects. No conclusions can be made for class III furcations because of the very limited data available.

These conclusions are supported by a number of meta-analyses already available in the literature, which assessed the use of blood derivatives, EMD, absorbable and non-absorbable membranes and bone graft substitutes [26][28][29][30][31][32]. More specifically, the meta-analysis by Jepsen et al. [26] is one of the most complete available. In their Bayesan network analyses, the authors showed a mean treatment improvement of a 1.6 mm gain in HCAL and a 1.3 mm reduction in VPD and VCAL in comparison with OFD. In addition, the authors suggested that the treatments with a bone graft alone or combined with an absorbable barrier seemed to show the highest chance of achieving the treatment outcome for mandibular class II furcations, followed by the use of EMD alone. On the other side, the authors reported higher incidence of post-operative complications when barriers were used, particularly non-absorbable, in comparison with EMD. This can be due not only to the biological characteristics of the materials, but also to the differences in the need for high technical skills required in order to apply barriers in comparison with EMD. In this research, one study which used EMD combined with an absorbable barrier and bone graft was included and it showed some better results than the combination of the biomaterials alone or the OFD. However, the results of this RCT are not corroborated by a recent meta-analysis, which could not show statistically significant differences between EMD alone or combined with a bone substitute [29].

Although very extensive, the review of Jepsen et al. did not include blood derivatives [26]. These materials have been introduced in relatively more recent times in comparison with the others. In the past 15 years, the enthusiasm about the clinical and histological potential of blood derivatives elicited the initiation of several RCTs in different oral applications [33]. The RCTs included in the current research also showed the highest quality assessment when compared with the other trials. A meta-analysis by Troiano et al. [32] analyzed the additional effect of blood derivatives as the only material in comparison to OFD. The authors reported an additional improvement of 1.8 mm for VPD, 1.5 mm for VCAL and 1.4 mm for HCAL. However, the authors noticed that the three studies included in the meta-analysis were all performed in the same country. This may make an extrapolation of the results to other cultural situations more difficult. A more recent meta-analysis from Tarallo et al. [31] confirmed these findings and further investigated the possible additional effect of the combination of blood derivatives with bone graft materials. They concluded that the additional use of a bone graft yielded only an additional statistically significant improvement of 0.7 mm in VCAL in comparison with the blood derivative alone. No patient-centered outcomes were reported by any of the studies included.

The current research includes a wide palette of treatment options. However, a meta-analysis to compare all materials was not implemented. The main reasons were the large heterogeneity of the research populations, the differences in the

designs, treatment protocols and primary outcomes, the low to moderate quality of the majority of the studies resulting from the quality assessment (the main exceptions were the studies which used blood derivatives) and the scarce availability of multi-armed randomized control trials that compare different materials with each other and with the OFD. In addition, the majority of studies have a small sample size, a relatively short follow-up (6 to 12 months) and no reported long-term data on the stability of the clinical results or tooth loss. These limitations are also often reported the other previous reviews.

With the available scientific evidence, the choice of a single specific material or a combination of multiple materials still remains a challenge. Although the use of a bone graft alone or combined with other materials seems to be more promising, in clinical settings, other parameters should be considered rather than the mere mean data reported. In the available trials, there is a lack of detailed analyses of the anatomy and morphology of the bone defects. These factors may play a role in the final clinical outcome, and they can be important to assess the choice of the most compatible material in terms of biological and mechanic characteristics. Future RCTs should record in detail the anatomical configurations of the furcations and of the relative bony defects, and these data should be taken into account in the final statistical analyses of the clinical results. In addition, there is a lack of information about the quality of the regeneration achievable in the furcation areas with the different materials. The non-absorbable membranes offer the opportunity to assess the bone growth at the re-entry surgery, necessary to remove the barrier. This would not be the case for the other materials. In future trials, assessing the amount of regeneration through histological or radiographic analyses would be suitable, but it can be ethically challenging. Alternatively, investigators may consider a clinical assessment of the change in the bone level through the bone sounding as a relatively non-invasive surrogate measure of bone healing.

Another important point of discussion is the limited availability of patient-centered outcomes, e.g., pain experienced during the post-operative healing, clinical complications, patient's satisfaction and acceptance of the treatment. Moreover, the costs of the use of the xenografts, allografts and alloplastic materials, and the invasiveness of the procedures required to harvest autologous materials, together with the risks of post-surgical complications and morbidity should be weighted with clinical significance of the benefit. All these factors should be critically evaluated in every specific clinical situation.

References

1. Salvi, G.E.; Mischler, D.C.; Schmidlin, K.; Matuliene, G.; Pjetursson, B.E.; Brägger, U.; Lang, N.P. Risk factors associated with the longevity of multi-rooted teeth. Long-term outcomes after active and supportive periodontal therapy. J. Clin. Periodontol. 2014, 41, 701–707.
2. Swan, R.H.; Hurt, W.C. Cervical enamel projections as an etiologic factor in furcation involvement. J. Am. Dent. Assoc. 1976, 93, 342–345.
3. Vandersall, D.C. Pearls, grooves, and projections. J. Am. Dent. Assoc. 1979, 99, 794.
4. Hou, G.L.; Tsai, C.C. Cervical enamel projection and intermediate bifurcational ridge correlated with molar furcation involvements. J. Periodontol. 1997, 68, 687–693.
5. Loos, B.; Claffey, N.; Egelberg, J. Clinical and microbiological effects of root debridement in periodontal furcation pockets. J. Clin. Periodontol. 1988, 15, 453–463.
6. Kalkwarf, K.L.; Kaldahl, W.B.; Patil, K.D. Evaluation of furcation region response to periodontal therapy. J. Periodontol. 1988, 59, 794–804.
7. Dannewitz, B.; Zeidler, A.; Husing, J.; Saure, D.; Pfefferle, T.; Eickholz, P.; Pretzl, B. Loss of molars in periodontally treated patients: Results 10 years and more after active periodontal therapy. J. Clin. Periodontol. 2016, 43, 53–62.
8. Huynh-Ba, G.; Kuonen, P.; Hofer, D.; Schmid, J.; Lang, N.P.; Salvi, G.E. The effect of periodontal therapy on the survival rate and incidence of complications of multirooted teeth with furcation involvement after an observation period of at least 5 years: A systematic review. J. Clin. Periodontol. 2009, 36, 164–176.
9. American Academy of Periodontology. Glossary of Periodontal Terms, 3rd ed.; American Academy of Periodontology: Chicago, IL, USA, 1992; p. 50.
10. Melcher, A.H. On the repair potential of periodontal tissues. J. Periodontol. 1976, 47, 256–260.
11. Nyman, S.; Gottlow, J.; Lindhe, J.; Karring, T.; Wennstrom, J. New attachment formation by guided tissue regeneration. J. Periodontal. Res. 1987, 22, 252–254.
12. Caton, J.G.; DeFuria, E.L.; Polson, A.M.; Nyman, S. Periodontal regeneration via selective cell repopulation. J. Periodontol. 1987, 58, 546–552.

13. Bottino, M.C.; Thomas, V.; Schmidt, G.; Vohra, Y.K.; Chu, T.M.; Kowolik, M.J.; Janowski, G.M. Recent advances in the development of GTR/GBR membranes for periodontal regeneration—A materials perspective. Dent. Mater. 2012, 28, 703–721.
14. Nyman, S.; Gottlow, J.; Karring, T.; Lindhe, J. The regenerative potential of the periodontal ligament. An experimental study in the monkey. J. Clin. Periodontol. 1982, 9, 257–265.
15. Tatakis, D.N.; Promsudthi, A.; Wikesjo, U.M. Devices for periodontal regeneration. Periodontology 2000 1999, 19, 59–73.
16. Lindhe, J.; Lang, N.P.; Berglundh, T.; Giannobile, W.V.; Sanz, M. Clinical Periodontology and Implant Dentistry, 6th ed.; John Wiley and Sons, Inc.: Chichester, UK; Ames, IA, USA, 2015; p. 1.
17. Brunsvold, M.A.; Mellonig, J.T. Bone grafts and periodontal regeneration. Periodontology 2000 1993, 1, 80–91.
18. Miron, R.J.; Sculean, A.; Cochran, D.L.; Froum, S.; Zucchelli, G.; Nemcovsky, C.; Donos, N.; Lyngstadaas, S.P.; Deschner, J.; Dard, M.; et al. Twenty years of enamel matrix derivative: The past, the present and the future. J. Clin. Periodontol. 2016, 43, 668–683.
19. Sculean, A.; Alessandri, R.; Miron, R.; Salvi, G.E.; Bosshardt, D.D. Enamel Matrix Proteins and Periodontal Wound Healing and Regeneration. Clin. Adv. Periodontics 2011, 1, 101–117.
20. Marx, R.E. Platelet-rich plasma (PRP): What is PRP and what is not PRP? Implant Dent. 2001, 10, 225–228.
21. Marx, R.E.; Carlson, E.R.; Eichstaedt, R.M.; Schimmele, S.R.; Strauss, J.E.; Georgeff, K.R. Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 1998, 85, 638–646.
22. DeLong, J.M.; Russell, R.P.; Mazzocca, A.D. Platelet-rich plasma: The PAW classification system. Arthroscopy 2012, 28, 998–1009.
23. Dohan Ehrenfest, D.M.; Rasmusson, L.; Albrektsson, T. Classification of platelet concentrates: From pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol. 2009, 27, 158–167.
24. Ghanaati, S.; Booms, P.; Orlowska, A.; Kubesch, A.; Lorenz, J.; Rutkowski, J.; Landes, C.; Sader, R.; Kirkpatrick, C.; Choukroun, J. Advanced platelet-rich fibrin: A new concept for cell-based tissue engineering by means of inflammatory cells. J. Oral Implantol. 2014, 40, 679–689.
25. Kobayashi, E.; Fluckiger, L.; Fujioka-Kobayashi, M.; Sawada, K.; Sculean, A.; Schaller, B.; Miron, R.J. Comparative release of growth factors from PRP, PRF, and advanced-PRF. Clin. Oral Investig. 2016, 20, 2353–2360.
26. Jepsen, S.; Gennai, S.; Hirschfeld, J.; Kalemaj, Z.; Buti, J.; Graziani, F. Regenerative surgical treatment of furcation defects: A systematic review and Bayesian network meta-analysis of randomized clinical trials. J. Clin. Periodontol. 2020, 47 (Suppl. S22), 352–374.
27. Graziani, F.; Gennai, S.; Karapetsa, D.; Rosini, S.; Filice, N.; Gabriele, M.; Tonetti, M. Clinical performance of access flap in the treatment of class II furcation defects. A systematic review and meta-analysis of randomized clinical trials. J. Clin. Periodontol. 2015, 42, 169–181.
28. Panda, S.; Karanxha, L.; Goker, F.; Satpathy, A.; Taschieri, S.; Francetti, L.; Das, A.C.; Kumar, M.; Panda, S.; Fabbro, M.D. Autologous Platelet Concentrates in Treatment of Furcation Defects-A Systematic Review and Meta-Analysis. Int. J. Mol. Sci. 2019, 20, 1347.
29. Soares, D.M.; de Melo, J.G.A.; Barboza, C.A.G.; Alves, R.V. The use of enamel matrix derivative in the treatment of class II furcation defects: Systematic review and meta-analysis. Aust. Dent. J. 2020, 65, 241–251.
30. Swami, R.K.; Kolte, A.P.; Bodhare, G.H.; Kolte, R.A. Bone replacement grafts with guided tissue regeneration in treatment of grade II furcation defects: A systematic review and meta-analysis. Clin. Oral Investig. 2021, 25, 807–821.
31. Tarallo, F.; Mancini, L.; Pitzurra, L.; Bizzarro, S.; Tepedino, M.; Marchetti, E. Use of Platelet-Rich Fibrin in the Treatment of Grade 2 Furcation Defects: Systematic Review and Meta-Analysis. J. Clin. Med. 2020, 9, 2104.
32. Troiano, G.; Laino, L.; Dioguardi, M.; Giannatempo, G.; Lo Muzio, L.; Lo Russo, L. Mandibular Class II Furcation Defect Treatment: Effects of the Addition of Platelet Concentrates to Open Flap: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. J. Periodontol. 2016, 87, 1030–1038.
33. Tavelli, L.; Ravidà, A.; Barootchi, S.; Chambrone, L.; Giannobile, W.V. Recombinant Human Platelet-Derived Growth Factor: A Systematic Review of Clinical Findings in Oral Regenerative Procedures. JDR Clin. Trans. Res. 2021, 6, 161–173.