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b) Article Title: **Enamel Matrix Derivative Use in Dentistry-an Update**

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Article Title: Enamel Matrix Derivative Use in Dentistry-an Update

Abstract:

Following a review of periodontal wound healing the article will discuss techniques designed to optimise periodontal wound healing including Guided Tissue Regeneration and Periodontal Regeneration using Enamel Matrix derivatives. Enamel matrix derivatives are porcine derived and are thought to stimulate differentiation, proliferation, migration and mineralisation in cells found in periodontal tissues. The paper will chart the development in surgical techniques to optimise outcomes from regenerative techniques in addition to explaining complications and how these can be avoided.

Recent research relating to use of Enamel Matrix Derivatives as an adjunct to non-surgical periodontal therapy will be described and whilst the evidence is limited to a single research study, the paper will discuss potential utilisation of this technique in practice, accepting a cost benefit analysis will be needed for individual patients.

Objective:

The reader will understand the use of Enamel Matrix Derivatives in Dentistry and current proposals relating to their use as a minimally invasive approach as an adjunct to non-surgical Periodontal Therapy

Clinical Relevance:

This will update practitioners on developments in use of Enamel Matrix Derivatives in Dentistry allowing them to make an informed decision on the utility and value of using flapless techniques in their own practice.

Introduction

In the vast majority of cases following non-surgical or surgical periodontal therapy, reparative wound healing occurs with formation of a long junctional epithelium, reduction in inflammation, and maturation of the collagen in the periodontal connective tissue. However, this fails to replicate the previous healthy periodontal architecture and function. Regenerative periodontal techniques aim to replicate the original form and function of the periodontium, by allowing key elements; such as cementum, the periodontal ligament and bony architecture to reform[1].

Background/ History

It is now well understood that periodontal disease is a balance between the microbial biofilm (Figure 1) and the host response which may lead to both hard and soft tissue destruction as a result of a dysbiosis between the two.

In 1976, Melcher suggested that wound healing following periodontal treatment was determined by the first type of cell to repopulate the root surface; this cell type would then determine the nature of the clinical attachment that forms[2]. In a series of studies carried out by Lindhe and Karring on periodontally compromised teeth, it was shown that, if the first cell to populate the root surface was epithelium, reparative healing occurred and a new attachment was formed creating a long junctional epithelium[3] (Figure 1). Nyman expanded on these findings and established that cells from the

periodontal ligament held the key to regeneration of the periodontium [4]. This understanding of periodontal healing methods led in the longer term to the development of surgical periodontal regeneration therapy, where practitioners have explored the use of graft types and inhibition methods, such as guided tissue regeneration (GTR), and the introduction of enamel matrix proteins (Emdogain®), in order to optimise periodontal healing (Figure 2).

Guided Tissue Regeneration

The concept of GTR is based around the idea of limiting the access of epithelial cells to the root surface[5]. This is achieved by placing a physical barrier to ensure cells from the periodontal ligament contact the root surface first, preventing long junctional epithelial formation[5]. The technique involves using a range of barrier membranes, but largely relies upon raising extensive surgical flaps to allow membrane placement (Figure 3); often leading to complications[6]. GTR is shown to have the greatest impact when used in narrow, deep, three walled defects[7] (Figure 4); however, case selection is of paramount importance, and exposure of membranes, alongside other post-operative healing complications are not uncommon (Figure 5).

Enamel Matrix Proteins (Emdogain®)

The biologic concept of using enamel matrix proteins (EMPs) is the hope that they mimic the cells from Hertwig's epithelial root sheath in the formation of the periodontium[8]. EMPs are thought to be deposited onto the root surface and are the prerequisite needed to generate cementum. As cementum production occurs, stimulation of the periodontal ligament follows[9]. For many years, the use of

Emdogain® has been shown to accelerate wound closure, reduce inflammation and increase predictability of healing outcomes[10].

Using EMPs clinically is less technique sensitive, but still relies on the need for good primary closure; leading to a range of surgical flap designs to optimise apposition[11/12/13]. Figure 6 shows an example of a modified papilla preservation flap which allow access to the bony defect, whilst figure 7 provides the radiographic appearance of the clinical bone loss.

Surgical Flap Designs:

Improving surgical flap designs helps to produce predictable results, assisting healing, improved patient comfort and decreased complications. It should be noted however: that when carrying out any surgical techniques, access and vision should be optimal, and an awareness of vital structures is paramount to limit adverse complications. Takei's papilla preservation technique[11] (Figure 8) allows support for clot stabilisation and close apposition of the surgical site, all contributing to primary wound healing. This technique has since been developed into the single flap approach[12] or Modified-minimally invasive papilla preservation surgical flap technique[13]. Surgical papilla preservation flaps rely on not only good magnification but use of microsurgical instruments, a range of which can be seen at figure 9 as used in practice.

GTR vs EMPs

When comparing the use of EMPs to GTR techniques, both produced improvements in wound healing clinical parameters.[14] Figure 10 illustrates the radiographic outcome following use of Emdogain surgically. However, Sanz and colleagues when

investigating healing outcomes of both GTR and EMPs, found that GTR cases had 100% complications, compared to that of only 8% seen when using EMPs[6].

A proposed Flapless Technique using Enamel Matrix Derivatives

Recent work carried out by Graziani and colleagues has suggested that Emdogain® used following non-surgical debridement can improve clinical parameters[15]. Whilst this improvement in clinical parameters has been suggested to reduce the need for future surgery, there is no histological evidence to quantify the type of healing involved. [15].

After appropriate case selection is carried out (Table 1) Emdogain® is applied to clean root surfaces. This single research study suggests the use of Emdogain® flapless can now improve the effectiveness of first phase treatment, in the hope that patients won't advance to needing surgical intervention[16]. Graziani's work shows a reduction in follow up treatment need by 32%[14] which includes surgical therapy. In addition there is a suggestion of less pain and reduction in inflammatory markers which may improve speed of recovery[17/18]. With no initial surgical intervention needed, the manufacturers suggest this method (Table 2) can be incorporated as part of the wider dental team's day-to-day general practice, allowing them to offer more effective phase 1 care[15].

However, this assertion needs to be approached with caution as still limited evidence on outcomes and a cost benefit analysis (a single vial of emdogain flapless costs £109.39 incl VAT at time of writing) may limit utility when similar outcomes may be received with effective non-surgical debridement and optimal patient self-care.

Instruments

To complement the Emdogain® flapless technique, minimally invasive periodontal instruments are available to facilitate the approach, for example micro-mini curettes. Using minimally invasive instruments helps to decrease unwanted iatrogenic damage and facilitate operator ease during the procedure[13]. In addition, Emdogain® flapless uses a thinner canula delivery system (Figure 11) to aid application into the targeted site[15].

Conclusion

With a greater understanding of wound healing within the periodontium, we are now able to offer patients innovative techniques that improve the outcome of the treatment provided. With non-surgical, minimally invasive techniques showing some promise (though significant cost) such techniques may have an increased role in promoting wound healing and improving non-surgical periodontal outcomes [15].

Disclosure

None of the authors have any conflict of interest.

Appropriate consent gained for clinical images and data.

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Figures Captions:

Figure 1: Diagram illustrating a) healthy gingival attachment b) periodontal breakdown mechanisms and c) reparative healing, resulting in long junctional epithelium and clinical attachment loss.

Figure 2: Timeline showing the history of key periodontology discoveries.

Figure 3: Clinical image showing a raised flap and barrier membrane in-situ.

Figure 4: Diagram schematic to illustrate bony defect classifications: a) 1 walled defect b) 2 walled defect c) 3 walled defect.

Figure 5: Clinical image showing unwanted post-operative membrane exposure.

Figure 6: Intra-surgical view of a modified papilla preservation flap exposing a bony defect before being treated with Emdogain®

Figure 7: Radiographic image of the bony defect shown in Figure 6.

Figure 8: Diagram schematic to illustrate papilla preservation flap technique: a & b) Bony defect before Emdogain® Flapless. c & d) Buccal full-thickness flap with the defect-associated papilla still in place. e & f) Papilla elevated along with the full-thickness palatal flap. g & h) Barrier membrane placed following debridement. i & j) Placement of sutures. N.b. left column depicts the buccal view and right column depicts the occlusal view.

Figure 9: An example range of microsurgical instruments

Figure 10: Radiographic evidence of bony infill and improved healing using Emdogain® Surgically.

Figure 11: Emdogain® FL delivery system.

Tables:

Table 1: Indications and Contraindications *(Adapted product instruction manual).*

Table 2: Step-by-step guide of Emdogain® Flapless[15]. *(Adapted Straumann® Guide).*

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