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Periodontal tissue engineering and regeneration: Consensus Report of the Sixth European Workshop on Periodontology

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Abstract

Aim: To review the scientific preclinical background and clinical studies of current methods of periodontal regeneration in the treatment of infrabony defects and soft tissue deficiencies

Method: Five commissioned review papers including two systematic reviews were scrutinized by a group of experts in order to derive consensus conclusions, clinical relevance/implications and to propose future research requirements.

Results: The following five papers were assessed:

1. Biological mediators and periodontal regeneration: a review of enamel matrix proteins at the cellular and molecular levels.
2. Regeneration of periodontal tissues: combination of barrier membranes and grafting materials – Biological foundation and preclinical evidence.
3. Clinical outcomes with bioactive agents alone or in combination with grafting or GTR
4. Treatment of gingival recession with coronally advanced flap procedures. A systematic review.
5. Soft tissue management at implant sites

Key words: enamel matrix proteins; gingival recession; growth factors; guided tissue regeneration; periodontal ligament

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*Bosshardt, D., Cairo, F., Christgau, M., De Sanctis, M., Etienne, D., Fourmousis, I., Hughes, F., Jepsen, S., Sculean, A., Sicilia, A., Trombelli, L., Van der Velden, U., Yilmaz, S.

Regenerative therapy is usually restricted to defined types of periodontal defects. Research is seeking to identify ways to improve predictability and to extend indications. At the present time the generalized use of combinations of existing therapies can sometimes improve clinical outcomes, but current evidence suggests caution is required. Regeneration is not just about clinical improvements but also background biology: we need the foundations from a sound biologic rationale, histologic evidence and predictable significant clinical outcomes.

The existence of a strong biologic rationale and preclinical animal data will not always result in successful clinical application, highlighting the crucial role of properly designed clinical studies. Clinical outcomes do not necessarily reflect true regeneration. In particular with mineralized grafting materials the interpretation of radiographic and probing evidence is difficult.

There is a huge literature on the molecular mechanisms of action of many growth factors, which have been proposed as bioactive agents in periodontal regeneration. However at present there is very limited translation of this knowledge into tested clinical application. In contrast one bioactive agent (cEMD[†]) has been in clinical use for more than 10 years and its clinical efficacy is very well established. However, little is known about the molecular mechanisms of its activities.

Successful application of a bioactive agent requires a vehicle or carrier that may contribute to the healing event. In addition the optimization of concentration and release kinetics will have profound influences on the effectiveness of the agent.

One of the problems of evaluating combination therapy, is the high number of possible combinations that are individually tested fully and this makes it difficult to dissect the role of the different components of the treatment. In addition, in some circumstances, a combination could antagonize the bioactive agent.

[†]cEMD refers to the commercial product Straumann Emdogain which contains enamel matrix derivative (EMD) plus PGA carrier.

Biological mediators and periodontal regeneration: a review of enamel matrix proteins at the cellular and molecular levels (Bosshardt 2008)

Conclusions

1. EMPs increase cell proliferation of PDL and gingival fibroblasts and cells of osteoblast and chondrocyte lineage.
2. EMPs have biological effects on cells of the osteoblast lineage including upregulation of markers of bone formation.
3. Specific small amelogenin polypeptides (5 kDa) have osteoinductive properties when tested in an ectopic bone-forming model.
4. The evidence does not demonstrate an inductive role of EMPs on cementogenesis.

Implications

There is a substantial literature on the activity, targets cells and signalling pathways of many growth factors that are involved in growth, development and wound healing.

Growth factors and other bioactive molecules have marked activities in many biological systems and do have potential therapeutic applications.

EMD and EMPs are bioactive, specifically in wound healing and new tissue formation (hard and soft).

Research Recommendations

However, we need to know the active components, the primary targets, the signalling pathways of EMD and EMPs.

There is a need for preclinical and clinical studies of growth factors and for laboratory studies on EMPs and EMD.

Regeneration of periodontal tissues: combination of barrier membranes and grafting materials – Biological foundation and preclinical evidence (Sculean et al. 2008)

Conclusions

1. The combination of barrier membranes and grafting materials may result in histological evidence of periodontal regeneration, predominantly bone repair.
2. No additional benefits of combination treatments were detected in models of 3-wall infrabony, class 2 furcation or fenestration defects.
3. In supra-alveolar and two wall infrabony (missing buccal wall) defect models of periodontal regeneration the additional use of a grafting material gave superior histological results of bone repair to barrier membranes alone.
4. In one study using a supra-alveolar model, combined graft and barrier membrane gave a superior result to graft alone.

Implications and Research Recommendations

There is limited evidence supporting the potential of combined therapy of barrier membranes and grafting materials in non-containing defects.

Appropriate animal models should be used to evaluate new materials, treatment approaches and procedures for the regenerative potential, side effects and complications. However, the results of animal studies should be extrapolated with caution to human clinical application.

There is the need to use appropriate animal and defect models for focused questions. Discriminating models, such as the supra-alveolar model, appear to have the most potential to evaluate regenerative efficacy.

Clinical outcomes with bioactive agents alone or in combination with grafting or GTR (Trombelli & Farina 2008)

Conclusions

1. There are several bioactive agents that are actually considered potentially beneficial to periodontal regeneration. Some of them have been clinically tested in humans, with varying levels of scientific evidence: rh-PDGF-BB, IGF, FGF, BMP-3, cEMD (commercially available EMD+PGA), PRP, and P-15. Other bioactive agents have been experimentally investigated in vitro and in preclinical models, showing a potential for a clinical application in periodontal regeneration.
2. There is evidence to support the use of cEMD in the treatment of infrabony defects (robust evidence). The magnitude of the adjunctive effect of cEMD as compared with OFD is still unclear (two systematic reviews which show heterogeneity among the results of the studies).

3. In intrabony defects, the clinical combination of autogenous bone particles [one randomized control trial (RCT)], DFDBA (one RCT), BPBM (three RCT) seems to enhance the clinical outcomes of cEMD as compared with cEMD alone. On the other hand, the clinical combination of EMD with alloplastic materials did not show similar outcomes. Three out of four RCTs did not show additional clinical advantage as compared with cEMD alone (3* RCTs using tricalcium phosphate, bioactive glass, biphasic calcium phosphate). Only one study using bioactive glass showed additional benefit.
4. The clinical combination of grafts and cEMD did not show any difference as compared with the grafting alone (BPBM, two RCTs, Bioactive glass one RCT).
5. The clinical combination of cEMD and barrier membranes did not show advantages as compared to either barriers alone (two RCTs) or cEMD alone (four RCTs).
6. Adjunctive benefits have been observed clinically with the use of rh-PDGF-BB (one RCT), P-15 (three RCTs) when combined with a graft as a carrier.
7. Conflicting results have been reported with the combined use of PRP and grafting (three RCTs showing an additional effect of PRP and three RCTs showing no additional benefit).

Clinical Implications

Robust evidence indicates the clinical use of cEMD for periodontal regeneration in infrabony defects.

The additional use of selected grafting materials in combination with cEMD could improve the clinical outcomes over cEMD alone. However, the existing evidence does not provide specific indications in terms of patient and defect characteristics on the advantage of using a combination of cEMD and graft over cEMD alone.

The existing evidence on selected grafting materials does not support the use of cEMD to enhance the clinical outcomes over the grafting materials per se.

Promising results are reported on the use of rh-PDGF-BB in combination with β-tri-calcium phosphate. More studies are required to corroborate the existing data.

The use of P-15 combined with anorganic bovine bone matrix is a well-supported option in the treatment of intrabony defects.

There is no evidence to support the use of PRP alone in the treatment of periodontal defects.

The use of PRP in combination with grafting materials may be affected by both the PRP preparation and the type of grafting material.

There is no evidence to support the use of bioactive agents per se or in combinations with grafting materials in furcations, with the exception of cEMD in mandibular buccal class II furcations.

Clinicians should monitor carefully for potential side effects particularly with new bioactive agents. Risk/benefit ratio should also be carefully considered.

The cost of therapeutic approaches should be compared with the expected clinical benefits. This may be especially true with bioactive agents either alone or in combination with other materials.

Research Recommendations

There is a need for RCTs on non-containing defects to assess the efficacy of combination of grafting materials and bioactive agents.

There is a need for three arm RCTs on efficacy of bioactive agents, with both a carrier/graft and an OFD controls to elucidate both the effect of the treatment as well as the contribution of the bioactive agent.

There is a need for RCTs on fully characterized PRP.

For future clinical studies it is recommended to include the following outcome measures: probing pocket depth, clinical attachment level, bleeding on probing, hard tissue assessment (radiographs and bone sounding). A characterization of the anatomy of the defect should be included, as well as patient characteristics such as full smoking history, medical history, full mouth and site-specific oral hygiene and gingival inflammation.

Patient related outcomes should be reported which include post-operative pain and discomfort, any adverse effect, patient satisfaction.

Clinical attachment level would normally be chosen as the primary outcome variable. Bone sounding, or other reproducible hard tissue measurements, could be a suitable alternative, according to the primary hypothesis of the study.

To allow a clinically meaningful interpretation of the results it is recommended that frequency distribution of outcomes are reported.

It is recommended that subjects should have received adequate non-surgical treatment and maintained low plaque levels for a period of 3 months before regenerative treatment, after which baseline measurements should be recorded.

There is a need for novel technologies to achieve a quantum leap in the application of regenerative procedures.

Treatment of gingival recession with coronally advanced flap procedures. A systematic review (Cairo et al. 2008a)

Conclusions for treatment of single Miller class I and II gingival recession:

Conclusions

1. Coronally advanced flap is a safe and predictable approach to obtain root coverage (11 RCTs).
2. The use of Connective Tissue Graft (two RCTs)(OR = 2.49) or cEMD (four RCTs) (OR = 3.89) with a coronally advanced flap procedure enhances the probability to obtain complete root coverage.
3. Connective tissue graft with a coronally advanced flap shows greater keratinized tissue gain over coronally advanced flap alone (two RCTs).
4. Barrier membranes do not improve the clinical benefits of coronally advanced flap in terms of complete root coverage (one RCT).
5. Contradictory results were associated with the use of Acellular Dermal Matrix with a coronally advanced flap (two RCTs).
6. Scientific data do not support the use of PRP (one RCT) or fibroblast-derived dermal substitute (one RCT) with a coronally advanced flap as a routine root coverage procedure.

Clinical Implications

Elective surgical procedures are chosen with the consent of the patient to improve appearance. There is no data to support the use of these techniques to reduce sensitivity.

Use of cEMD may improve the rate of complete root coverage achieved with a coronally advanced flap.

A connective tissue graft will improve the rate of complete root coverage achieved with a coronally advanced flap.

A connective tissue graft used with a coronally advanced flap will improve the width of keratinised tissue.

Research Recommendations

RCTs of root coverage techniques should include the following:

1. A sample size calculation
2. Appropriate stratification with random assignment to take account of factors such as:

a. Miller classification I and II
b. Width of recession
c. Tissue thickness/morphotype
d. Width of keratinized tissue
e. Amount of recession on adjacent teeth

3. Detailed description of the technique

a. Split/full thickness flap
b. Root preparation

4. Long term results of at least 5 years
5. Patient centred outcomes

Soft Tissue Management at Implant Sites (Cairo et al. 2008b)

Conclusions

1. The existing evidence does not support the importance of keratinized tissue for soft tissue inflammatory status or survival of dental implants.
2. There is no scientific data to recommend a specific technique to preserve or augment keratinized tissue.
3. Factors including bone level, keratinized tissue and implant features have not been shown to be associated with future mucosal recession around dental implants.
4. Although scientific evidence in most part is lacking, soft tissue augmentation may be considered in order to obtain satisfactory aesthetic results.

Clinical Implications

Soft tissue augmentation techniques are used to improve appearance and amount of non-mobile keratinized mucosa around implants. However, the outcomes of these procedures have not been evaluated in studies.

Research Recommendations

Studies are required to evaluate the value and importance of keratinised/non-mobile soft tissue in maintaining peri-implant health.

Studies should include patient centred outcomes on factors such as appearance, comfort and difficulties with oral hygiene.

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