A systematic review of graft materials and biological agents for periodontal intraosseous defects

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Authors' objectives
To compare grafting biomaterials or biological agents plus open flap debridement (OFD) with OFD alone for the treatment of deep intraosseous defects.

Searching
MEDLINE and the Cochrane Oral Health Group's Specialised Trials Register were searched to June 2001 for reports published in the English language; the search terms were stated. Unpublished data and 'in press' reports were requested from the Journal of Periodontology, Journal of Clinical Periodontology and the Journal of Periodontal Research. Reference lists in reviews, relevant texts, previous workshops and all primary reports were checked. The authors of eligible studies and experts, groups and companies involved in research were contacted for additional and unpublished studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Case reports, letters and historical reviews were excluded. The included studies used either parallel groups, split-mouth randomisation, or random block designs.

Specific interventions included in the review
Studies that compared grafting biomaterials or biological agents (alone or in combination) plus OFD with OFD alone, or in combination with a placebo treatment, were eligible for inclusion. Studies of any type of grafting biomaterials or biological agents were eligible apart from guided tissue regeneration, either alone or in combination with other biomaterials or biological agents. The types of grafting biomaterials or biological agents used in the included studies were: autogenous bone graft (ABG); bone allograft; dentin allograft; coralline calcium carbonate (CCC); bioactive glass; hydroxyapatite (HA); calcium-layered composite of polymethylmethacrylate and polyhydroxyethyl methacrylate (PMMA-PHEMA); polylactic acid granules; and enamel matrix proteins.

In the included studies, all patients received nonsurgical therapy (including periodontal debridement and instructions about oral hygiene) before the allocated treatment. Some of the studies used antibiotics post-operatively. In all studies, the patients received follow-up periodontal supportive therapy at an interval of 15 days to 6 months after surgery. OFD techniques included open flap curettage, access flap surgery and modified Widmans flap.

Participants included in the review
Studies of patients with at least one intraosseous defect due to destructive periodontal disease were eligible for inclusion. Participants with intraosseous, 1-2-3 walled defects that were diagnosed clinically or radiologically and with defects affecting at least one aspect of the tooth were included. Studies of patients with pure inter-radicular defects were excluded. The included studies were of patients with chronic periodontitis or undefined periodontal disease.

Outcomes assessed in the review
Only studies that reported treatment outcomes assessed clinically and/or radiologically at least 6 months after treatment were eligible for inclusion. The review assessed short-term (6 to 12 months after treatment) outcomes, long-term (at least 13 months post-treatment) clinical outcomes, and patient-centred outcomes (including adverse effects). The primary outcome was the gain in clinical attachment level (CAL). Other outcomes assessed in the review included change in probing pocket depth and extent of intraosseous defect fill.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened titles and abstracts for possible inclusion according to the listed criteria. Any disagreements were resolved by discussion.
Assessment of study quality
Validity was assessed on the basis of randomisation, allocation concealment and blinding of the examiners and therapists. The review also assessed the completeness of follow-up. Two reviewers independently assessed validity and the results were entered onto a specifically designed form. Inter-reviewer agreement was assessed using the kappa statistic.

Data extraction
One reviewer extracted data onto a computer. The variance was estimated for studies that did not report standard deviations. For studies in which inter-radicular defects were combined with intraosseous defect, only data for the intraosseous parts were included in the analysis. Only studies that reported the variance, or that presented adequate data for its estimation, were included in the meta-analysis. Trials with three treatment arms were split and each grafting treatment was compared with the same control group.

Methods of synthesis
How were the studies combined?
The studies were combined in meta-analyses according to the type of biomaterial or biological agent. Weighted mean differences (WMD) and 95% confidence intervals (CIs) were calculated for continuous outcomes. The studies were combined using random-effect models where significant heterogeneity was detected (P<0.05) and fixed-effect models otherwise.

How were differences between studies investigated?
Statistical heterogeneity was assessed and forest plots were presented. Heterogeneity was explored, where appropriate, using Galbraith plots and meta-regression.

Results of the review
Twenty-six RCTs (605 patients with 1,306 intraosseous defects) were included.

Ten RCTs reported adequate methods of randomisation. Five RCTs reported adequate allocation concealment. Seven RCTs reported blinded outcome assessment and two RCTs reported blinding of the therapist. One RCT reported information on all randomised patients.

CAL gain.
ABG (1 RCT): the study showed that ABG increased CAL gain but the increase was not statistically significant, 3.2 mm versus 2.0 mm (P>0.20).

Bone allograft (6 RCTs): the meta-analysis showed that bone allograft increased CAL gain but the increase was not statistically significant; the WMD was 0.36 mm (95% CI: -0.16, 0.87). Significant heterogeneity was detected (P=0.01). The Galbraith plot showed that the results from one RCT differed from the others.

Dentin allograft (1 RCT): the study showed no significant difference in CAL gain between treatments, 2.8 mm with graft versus 2.0 mm with controls (P>0.5).

CCC (4 RCTs): the meta-analysis showed that CCC significantly increased CAL gain; the WMD was 0.90 mm (95% CI: 0.53, 1.27). No significant heterogeneity was detected (P=0.10).

Bioactive glass (4 RCTs): the meta-analysis showed that bioactive glass significantly increased CAL gain; the WMD was 1.04 mm (95% CI: 0.31, 1.76). Significant heterogeneity was detected (P=0.02).

HA (4 RCTs): the meta-analysis showed that HA significantly increased CAL gain; the WMD was 1.40 mm (95% CI: 0.64, 2.16). Significant heterogeneity was detected (P<0.01).
Calcium-layered PMMA-PHEMA (2 RCTs): a meta-analysis was not possible since only one RCT presented adequate data. One RCT showed CAL gain was 3.43 mm with graft versus 2.73 mm with control. The second RCT showed that ABG significantly increased CAL gain, 1.9 mm versus 1.0 mm (P=0.001).

Polyactic acid granules (1 RCT): CAL gain was 1.95 mm with OFD plus polyactic acid granules compared with 0.50 mm with OFD only.

Enamel matrix proteins (5 RCTs): the meta-analysis showed that enamel matrix proteins significantly increased CAL gain; the WMD was 1.33 mm (95% CI: 0.78, 1.88). Significant heterogeneity was detected (P<0.001). The Galbraith plot showed that the results from one RCT differed from the others. The meta-regression showed no influence on the results of initial defect depth.

Probing pocket depth.

The meta-analysis showed that bone allograft, bioactive glass, HA and enamel matrix proteins significantly reduced probing pocket depth compared with OFD: the WMDs were 0.41 mm (95% CI: 0.16, 0.66), 0.60 mm (95% CI: 0.20, 1.00), 0.91 mm (HA non porous; 95% CI: 0.32, 1.50) and 0.98 mm (HA porous; 95% CI: 0.67, 1.29), and 1.60 mm (95% CI: 0.59, 2.62), respectively. Significant heterogeneity was found for enamel matrix proteins and HA non porous only. The meta-analysis found no significant difference using CCC; the WMD was 0.04 mm (95% CI: -1.78, 1.87). Significant heterogeneity was found.

Extent of intraosseous defect fill: a meta-analysis was not performed.

Long-term outcomes: most studies did not report long-term outcomes.

Patient-centred outcomes: 10 of the 16 RCTs that considered adverse effects reported no systemic or local adverse effects in patients who received grafts. The adverse effects reported in the other RCTs included pebbled surface texture of grafted site (1 RCT), transient slight gingival inflammation (1 RCT), delayed soft tissue healing (1 RCT), and exfoliation or shedding of implanted material (3 RCTs).

Authors' conclusions

The overall use of grafting biomaterials or biological agents was more effective than OFD in increasing attachment levels in intraosseous defects, but the significant unexplained heterogeneity among studies means that the results should be interpreted with caution.

CRD commentary

The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched for published and unpublished studies and the search terms were stated. Limiting the included studies to those in the English language may have omitted some relevant studies. Two reviewers independently selected the studies and assessed validity, which reduces the potential for bias and errors, but only one reviewer extracted the data. Validity was assessed using defined criteria and some relevant information on the included studies was tabulated, but validity was not used to weight the study results. The data were combined in a meta-analysis and statistical heterogeneity was assessed. Limited attempts were made to explore potential causes of heterogeneity. In view of the heterogeneity among studies, the authors correctly advised caution when interpreting the results of the review.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice. Research: The authors stated that future studies should aim at determining the reasons for the heterogeneity among studies, and should assess patient-centred outcomes and cost-effectiveness. The authors also stated that authors of future research should adhere to the CONSORT guidelines (www.consort-statement.org; accessed 19/08/04).

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.