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Prognostic factors for alveolar regeneration: effect of space provision

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***Abstract*:**
Objectives: The role of space provision as an independent prognostic factor for periodontal regeneration remains to be established. The objective of this study was to evaluate the role of space provision on alveolar bone regeneration in periodontal sites.
Methods: Critical size, supra-alveolar, periodontal defects were created in 11 young adult Beagle dogs. Six animals received a porous ePTFE device to provide for space provision. Five animals received sham surgery. The animals were euthanized at 8 weeks post-surgery. A histometric analysis assessed vertical regeneration of alveolar bone and the width of the alveolar crest at the base of the defect. Because of the correlation of within-dog measurements, a mixed model ANOVA/ANCOVA was used to analyse the data.
Results: A significant relationship between the width of the alveolar crest at the base of the defect and bone regeneration was observed with no significant difference between sites receiving the different treatments ($p = 0.84$). Bone regeneration at sites treated with the space-providing device was significantly greater compared with that at sites treated with sham surgery ($p = 0.0003$), and the difference remained significant after adjusting for bone width ($p = 0.0001$).
Conclusions: Space provision has a significant effect on alveolar bone regeneration in periodontal sites. The width of the alveolar bone appears to influence space provision effectively supporting bone regeneration.

Key words: periodontal/bone/guided tissue regeneration; alveolar bone; ePTFE; dogs.

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One significant objective of periodontal therapy is regeneration of periodontal structures including cementum, periodontal ligament, alveolar bone, and gingiva lost to periodontal disease. It has been suggested that tissue resources originating from the periodontal ligament are essential for this process (Melcher et al. 1976). Indeed, preclinical and clinical studies attempting to favour migration and proliferation of tissue resources from the periodontal ligament while isolating the wound site from gingival connective tissue and epithelium have shown that periodontal regeneration is a biologic and clinical possibility (for a review see Karring et al. 1993, Karring & Cortellini 1999).

Others have shown that space provision is a critical factor for periodontal regeneration including alveolar bone (Karaki et al. 1984, Haney et al. 1993, Sigurdsson et al. 1994, Polimeni et al. 2004a–c). Sites providing small wound areas exhibited limited bone formation while sites providing large wound areas showed enhanced bone formation. Tissue separation using occlusive devices has also been considered critical for periodontal regeneration (Scantlebury 1993). However, a recent report evaluating regeneration in an experimental dog model has shown that periodontal regeneration can predictably be obtained in the absence of tissue occlusion (Wikesjö et al. 2003). A subsequent analysis has shown that although tissue occlusion does not appear to be an absolute prerequisite for alveolar bone regeneration in periodontal sites, the extent of regeneration appears greater in the presence of tissue occlusion (Polimeni et al. 2004b). As interaction between tissue occlusion and space provision may affect the outcome of regeneration, the objective of this study was to evaluate, using histometric parameters, the role of space provision as an independent prognostic factor on alveolar bone regeneration in periodontal sites.

Materials and Methods

This study used histologic specimens from two previously published studies

(Sigurdsson et al. 1994, Wikesjö et al. 2003). Detailed information on animal management and specific experimental protocol has been described in these publications. In brief, 11 young adult male Beagle dogs obtained from a USDA approved dealer were used. Animal selection, management, and experimental protocol were approved by the Animal Care and Use Committee, Loma Linda University, Loma Linda, CA, USA and W.L. Gore & Associates Inc., Flagstaff, AZ, USA.

Supra-alveolar, 5–6 mm periodontal defects (Fig. 1) were surgically created around the third and fourth mandibular pre-molar teeth in left and right jaw quadrants in six animals (Wikesjö et al. 2003). Defect preparation in this animal model includes removal of the periodontal attachment and cementum (by root planing) from the cemento-enamel junction to the surgical reduction of the alveolar bone. The crowns of the teeth were reduced to approximately 2 mm coronal to the cemento–enamel junction and exposed pulpal tissues sealed. A space-providing porous ePTFE device (Reinforced GORE-TEX® ePTFE, W.L. Gore & Associates Inc., Flagstaff, AZ, USA) was placed to cover the teeth in one jaw quadrant in each of the animals and was fixed to the alveolar process using medical grade stainless-steel tacks (Fig. 1). This device is reinforced with a laminated polypropylene mesh and exhibits laser-etched 300 μm pores at 0.8 mm (centre to centre) intervals allowing full penetration of the gingival connective tissue (Wikesjö et al. 2003). Autologous blood was drawn using an IV catheter and aspirated blood was expelled underneath the ePTFE device to ensure adequate clot formation. The periostea were then fenestrated at the base of the gingival flaps to allow tension-free flap apposition. The flaps were advanced and the flap margins adapted 3–4 mm coronal to the ePTFE device and sutured. In the maxilla, the first, second, and third pre-molar teeth were surgically extracted, and the fourth pre-molars were reduced in height and exposed pulpal tissues sealed, this to prevent potential trauma from the maxillary teeth to the mandibular experimental sites. The remaining five animals received the identical surgical protocol without an ePTFE device (Sigurdsson et al. 1994).

The animals were anaesthetized and euthanized at 8 weeks when the experimental teeth including surrounding soft

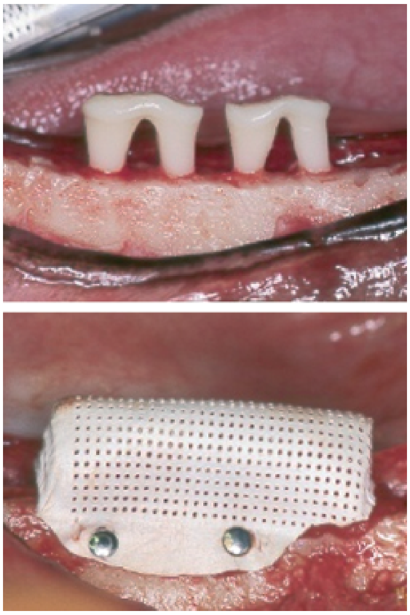

Fig 1. Clinical presentation of the critical size supra-alveolar periodontal defect model, defect preparation includes circumferential surgical reduction of the alveolar bone to a level 5–6 mm apical to the cemento-enamel junction at the mandibular third and fourth pre-molar teeth. The periodontal attachment including the cementum is then removed by root planing leaving a distinct landmark for histometric measurements at the surgically reduced alveolar crest. The lower illustration shows installation of the space-providing, porous ePTFE device used in this study.

and hard tissues were removed en bloc. ePTFE devices were not removed during the healing interval. The tissue blocks were fixed in 10% buffered formalin for 3–5 days, decalcified in 5% formic acid for 8–10 weeks, trimmed, dehydrated, and embedded in paraffin. Serial sections (7 μm) were produced in a buccal-lingual plane throughout the mesial-distal extension of the teeth. Every 14th section was stained with haematoxylin or Ladewig's connective tissue stain modified by Mallory for observations at 100 μm intervals.

One calibrated examiner (G. P.) performed the histometric analysis using incandescent and polarized light microscopy (BX 60, Olympus America Inc. Melville, NY, USA), a microscope digital camera system (DP10, Olympus America Inc.), and a PC-based image analysis system (Image-Pro Plus™, Media Cybernetic, Silver Springs, MD, USA). The most central stained section of each root of the third and fourth pre-molar teeth was identified by the size of the root canal. This section was used for

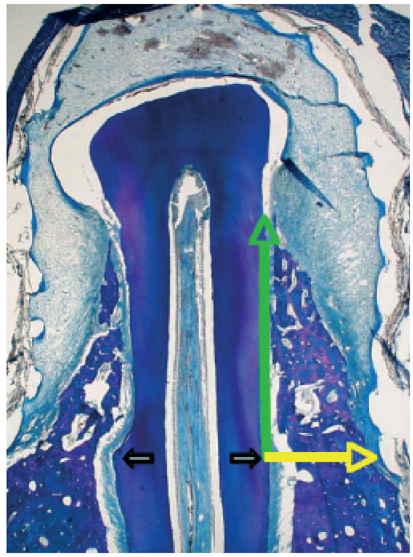

Fig 2. Photomicrograph of the critical size supra-alveolar periodontal defect model depicting the histometric parameters evaluated including the height of new bone formation (green arrow) and the width of the alveolar bone (yellow arrow) at the level of the surgically reduced alveolar crest (black arrows).

the histometric analysis. The following histometric parameters (Fig. 2) were recorded for the buccal and the lingual surfaces for each section:

- *Bone regeneration*: distance between the apical extension of the root planing and the coronal extension of alveolar bone regeneration along the planed root.
- *Bone width*: the width of the resident bone at the apical extension of root planing.

The examiner had performed repeated assessments of the histometric measurements of bone regeneration and bone width 3 months apart. The intra-examiner reproducibility, as assessed by the intra-class correlation coefficient was 0.984.

Data analysis

Analysis of variance was used for comparison of the marginal (unadjusted) means between the groups. The analysis then compared the bivariate means after adjusting for the effect of alveolar bone width. Linear regression assessed the linear relationships between variables, and the analysis of covariance was used for the comparison of slopes. These analyses used the Mixed Models approach (SAS V8.1, SAS Institute Inc., Cary, NC, USA) designed for the analysis of correlated data (sites within animals) and modelling of random effects (Littell et al. 1996).

Results

There was a statistically significant relationship ($p < 0.0001$) between alveolar bone width and bone regeneration, with no significant difference in this relationship between sites receiving the space-providing porous ePTFE device and sham surgery ($p = 0.84$; Fig. 3).

Mean bone regeneration in animals receiving the space-providing porous ePTFE device was significantly greater compared with that at sites receiving sham surgery ($p = 0.0003$; Table 1). After adjusting for alveolar bone width, the mean bone regeneration remained significantly greater at sites treated with the ePTFE device compared with sham surgery ($p = 0.0001$; Table 2). Comparison of the mean bone width showed no statistically significant difference between sites treated with either of the treatments ($p = 0.6$; Table 3).

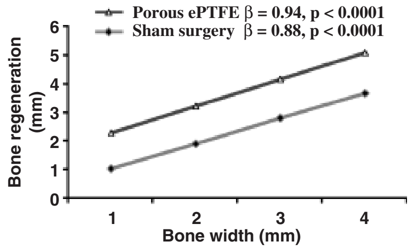

Fig 3. Relationship between bone width and bone regeneration at defect sites receiving the porous space-providing ePTFE device or sham surgery. There was no significant difference between the two slopes ($p = 0.84$).

Table 1. Mean bone height for defect sites receiving the porous space-providing ePTFE device or sham surgery

	Mean	SE	*p*
ePTFE device	2.27	0.24	0.0003
Sham surgery	0.93	0.26	

Table 2. Adjusted* mean bone height for defect sites receiving the porous space-providing ePTFE device or sham surgery

	Mean	SE	*p*
ePTFE device	2.20	0.17	0.0001
Sham surgery	0.95	0.18	

*Controlled for bone width.

Table 3. Mean bone width for defect sites receiving the porous space-providing ePTFE device or sham surgery

	Mean	SE	*p*
ePTFE device	0.97	0.15	0.6
Sham surgery	0.87	0.16	

Discussion

The objective of this study was to evaluate the role of space provision as an independent prognostic factor on alveolar bone regeneration in periodontal sites. For this purpose, critical size, supra-alveolar, periodontal defects from 11 young adult Beagle dogs were analysed. Six animals had received a space-providing porous ePTFE device. Five animals had received sham surgery. The animals were euthanized at 8 weeks post-surgery. Histometric analysis assessed the vertical regeneration of alveolar bone and the width of the alveolar crest at the base of the defect. The results suggest that space provision has a significant effect on bone regeneration in periodontal sites and that the width of the alveolar crest appears to influence space provision effectively supporting bone formation at sites implanted with the space-providing device as well as sites receiving sham surgery.

This study used an experimental model including critical size, supra-alveolar periodontal defects in dogs. The supra-alveolar periodontal defect model has been shown to be a valuable tool to evaluate the regenerative potential of alveolar bone and the periodontal attachment in the assessment of candidate therapies prior to clinical application (Wikesjö & Selvig 1999). The defect dimensions provide for clinically relevant regeneration of alveolar bone and cementum. The defect morphology allows an unbiased, highly reproducible strategy of analysis of various covariates and treatment outcomes (Koo et al. 2004a, b). Alveolar bone and cementum regeneration in sham-operated controls has been shown not to exceed 15% of the defect height over an 8-week healing interval (Wikesjö et al. 1994).

Previous studies have suggested that space provision is important for alveolar bone regeneration (Polimeni et al. 2004a–c). In these studies, space provision showed a direct relationship with bone formation under various experimental conditions. Polimeni et al. (2003c) showed that space provision by tissue/cell occlusive and porous ePTFE devices exhibited a positive correlation to new bone formation. Furthermore, the results showed a significantly enhanced bone formation at sites treated with the occlusive device compared with sites treated with porous device when adjusted for space provision. It was also shown that the width of the alveolar ridge at the base of the defect influenced space provision provided by the membrane, thus providing an indirect effect on alveolar bone regeneration. Although the study demonstrated the efficacy of space provision as a prognostic factor for alveolar bone regeneration, the biological potential of space provision as an independent prognostic factor remained unclear.

In the present study, bone regeneration at sites receiving the space-providing porous ePTFE device was compared with sham surgery. Experimental conditions for both groups were performed in *absence of tissue occlusion*. The statistical analysis allowed a comparison between groups adjusting for the variability in the width of alveolar bone. In other words, the study design allowed comparison of the sole effect of space provision on bone regeneration.

The results show a positive correlation between the width of the alveolar ridge at the base of the defect and the newly formed bone, with no difference in this correlation between sites receiving the different treatments. Sites providing a wide alveolar ridge showed enhanced bone formation, whereas sites exhibiting a narrow ridge showed limited bone formation for both treatments. One may speculate that in the presence of a wide alveolar ridge, the mucoperiosteal flap served the same mechanical function as the space-providing ePTFE device, whereas in the presence of a narrow ridge the flap and the device-supported flap collapsed onto the tooth surface providing limited space for alveolar bone regeneration. In other words, the characteristics of the mucoperiosteal flap alone or supported by the space-providing porous ePTFE device are not different from a wound mechanical point of view.

The results from this study also showed that sites receiving the space-providing porous ePTFE device exhibited enhanced bone formation compared with sites receiving mucoperiosteal flap surgery without the device after adjusting for the width of the alveolar ridge. In other words, a mechanical expansion of the wound site may enhance alveolar bone regeneration in periodontal sites even when cell occlusion is not provided. Based on present observations it may be concluded that even if gingival tissue interference may negatively influence bone formation, space provision appears a critical independent prognostic factor for alveolar bone formation in periodontal sites.

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