Comparison of Resorbable and Nonresorbable Guided Bone Regeneration Materials: A Preliminary Study

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The purpose of this study was to compare bone regeneration within a surgically created defect using three different resorbable membranes (polyglactin 910 knitted mesh/Vicryl, freeze-dried fascia lata, and crosslinked bovine type I collagen/BioMend) and two nonresorbable membranes (expanded polytetrafluoroethylene/Gore Tex, and polytetrafluoroethylene/Millipore). Each of three adult male dogs underwent surgical preparation of six bicortical defects of the calvarium, each 1.5 cm in diameter. The experimental barrier membranes were placed on both sides of the defects (inner and outer cranial tables). Five of the six defects were covered randomly by one of the five membrane materials, and one was left uncovered to serve as a negative control. The animals were sacrificed 10 weeks after membrane placement. Bone response was measured clinically, as well as radiographically, via densitometric examination. All surgical sites healed uneventfully. Variable degrees of new bone growth were present at all sites when evaluated by both clinical and radiographic examination. The general trend of observed osseous response indicates a greater, although not statistically significant, degree of bone growth using nonresorbable membranes. The animal model employed appears to be an efficient and reliable means of evaluating guided bone regeneration membranes.
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Key words: bone regeneration, canine calvarium, guided tissue regeneration, resorbable membranes

Guided tissue regeneration (GTR) is a predictable and desirable means of using the osteogenic potential of progenitor cells of bone, periosteum, or periodontal ligament to create new bone growth in a variety of osseous defects. Although the clinical application of GTR materials is comparatively new, historical developments that have led to current understanding originated in 1957, when Murray et al[1] demonstrated new bone growth in dog femur, ileum, and spinal column using a plastic fenestrated cage as a barrier to soft tissue invasion. Recognizing potential benefits of GTR in dentistry, Linghorne[2] presented the sequence of events of osteogenesis in 1960, which he described as "pathologic and physiologic phases," after bridging a 15-mm ostectomy site in dog fibula. Retrospectively, these early contributions were analogous to what is now recognized as guided *bone* regeneration (GBR).[3–7] These researchers made use of "tibial shavings" as a primitive type of *resorbable* barrier to soft tissue ingrowth during spinal fusion surgery.[1,2] As the concept of bone regeneration continued to develop, multiple techniques became available, using a variety of GTR materials to stimulate new bone growth in the treatment of bony defects. GoreTex (W. L. Gore Associates, Flagstaff, AZ) is currently the standard nonresorbable membrane for GBR.[8–12]

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Characteristics of the ideal barrier membrane are that it is: (*1*) bioinert, possessing enough rigidity to maintain space for protection of the blood clot, but flexible enough to be clinically manageable; (*2*) predictable in achieving the desired amount of bone growth; (*3*) cost effective; and (*4*) amenable to one-step surgical procedures. None of the materials currently available can satisfy all these requirements. The most recent evolution of these materials is the quality of being resorbable, thereby eliminating the need for removal at second-stage surgery. For more than a decade, resorbable GTR/GBR materials have been used experimentally for multiple procedures in animal and in vitro human studies, but primarily for periodontal reconstruction, with varying degrees of success.[13–18] Recently, there has been increased interest in these materials because of their many desirable qualities: they permit one-step surgical placement, they have host acceptance, and they have a reasonably manipulative consistency. The disadvantage of most of these materials is their unpredictable degree of resorption, which can significantly alter the amount of bone formation/regeneration.[19] Greenstein and Caton[20] have presented a thorough literature review from 1988 to 1992 on the use of various resorbable materials. These studies ranged from 10 days to 1 year in length, and generally regarded Vicryl mesh as the most reliable when retrospectively compared to other nonresorbable barriers. However, none of the articles compared resorbable barriers both to one another and to a nonresorbable control.

The use of barrier techniques has become standard for many surgical procedures requiring bone regeneration. The literature supports the use of nonresorbable materials for bone regeneration, which require a second surgical procedure for removal. Current studies have demonstrated bone regeneration using biodegradable barriers, but no studies have been performed comparing multiple resorbable barriers to one another using nonresorbable barriers as control. The purpose of this study was to compare bone regeneration between three different resorbable membranes and two nonresorbable membranes.

Materials and Methods

Approval for this study was obtained from the Institutional Lab Animal Care and Use Committee. Procedures were performed on three large, healthy, conditioned male dogs weighing 27 to 30 kg. Midline skin and subperiosteal incisions were made from an anterior to posterior direction overlying the calvarium. Full-thickness dissection was performed anteriorly to the frontal bones and orbit, posteriorly to the occipital bone, and laterally to the temporal bones. Six transosseous calvarial defects of at least 1.5 cm in diameter were created lateral to the midline with a neurosurgical Hudson brace. Because of anatomic limitations, the defect size was reduced to 1.5 cm for one of the three specimens. The underlying dura remained intact (Fig 1).

Each of five defects was covered by one of the membrane materials; one was left uncovered to serve as a negative control. The five membranes used were as follows: polyglactin 910 knitted mesh (Vicryl, Ethicon, Somerville, NJ), freeze-dried fascia lata (Dayton Tissue Bank, Dayton, OH), crosslinked bovine type 1 collagen (BioMend, Calcitek, Carlsbad, CA), expanded polytetrafluoroethylene (e-PTFE/GoreTex), and polytetrafluoroethylene (PTFE/Millipore, Marlborough, MA). Membranes were placed randomly in the three animals for a total of 18 sites in the frontal, parietal, and occipital bones (Fig 2). Barriers were placed on either side of the defect (both inner and outer tables) without the use of an interpositional material or spacer. Membranes were held in place against the inner table by pressure from the brain and dura, and secured with microscrew fixation to the outer cortex (Fig 3).

Following 10 weeks of healing, animals were euthanized and specimens harvested. Block resection was performed at each site. Standardized radiographs were made (one per site) with a collimated tube, parallel to the specimen, at a distance of 3 inches. The machine settings determined to provide the best combination for film definition were 70 kV and 15 mA for .2 seconds. Using a 35-mm slide scanner, these films were scanned at high resolution for image analysis on a Macintosh Centris 650 computer using NIH IMAGE 1.55 (NIH, Bethesda, MD) to determine densitometric evaluation for bone within the entire defect (Table 1). NIH software was originally used to evaluate wound healing for soft tissue. This method was adapted to accurately measure the area and density of a specimen by placing a computer-generated circular overlay of known diameter (1.5 or 2 cm for our purposes) over the outermost edge of the wound site on the radiograph. This initial measurement was maintained as a standard for the outside diameter of the remaining specimens. Internal measurements were determined by placement of points along areas of increased density within the circle. These parameters enabled the *quantitative* calculation of *area*. The *qualitative* measurement of *density* was determined by counting the number of pixels within this area, in a manner similar to the evaluation of radiographic densitometry. These computer-imaged results for area and internal density were analyzed nonparametrically using the Friedman statistic (Table 1).

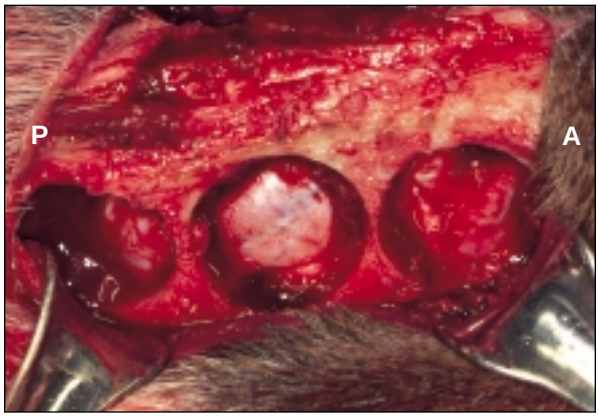

Fig 1 Clinical presentation of full-thickness calvarial defects with intact dura. (Top view of skull: A = anterior; P = posterior.)

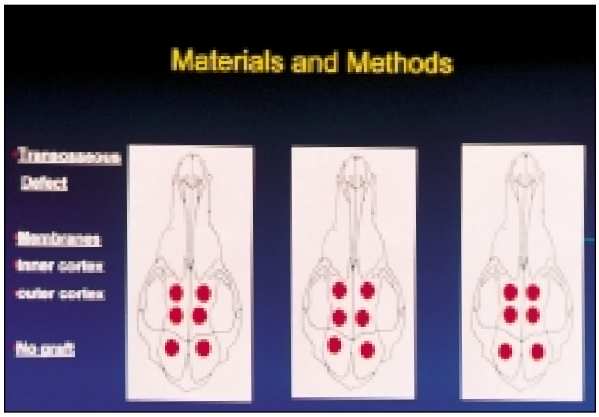

Fig 2 The various membranes and the control were randomly distributed. Membranes were placed on both outer and inner calvarium without the use of grafts or interpositional materials.

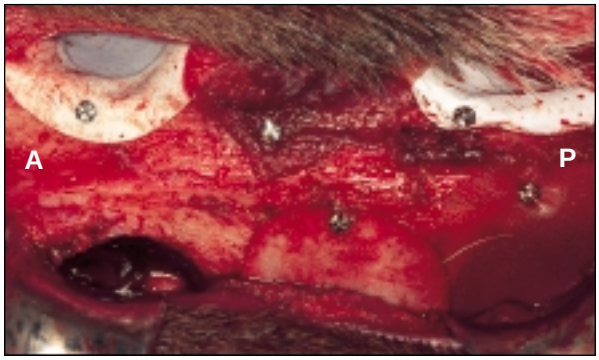

Fig 3 Clinical view of membranes in place with microscrew fixation. (Top view of skull: A = anterior; P = posterior.)

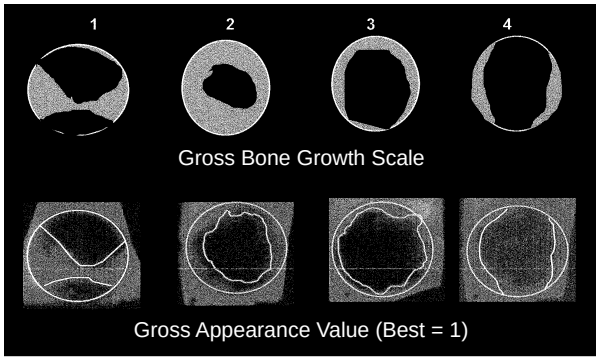

Fig 4 Total cross-sectional area of bridging bone representing Gross Bone Growth Scale (GBGS). Radiographs were scored on a scale of 1 to 4: 1 = bone bridging across the CSD; 2 = complete perimeter of bone surrounding CSD (bone "island"); 3 = incomplete perimeter on one side; 4 = incomplete perimeter on two sides.

Table 1 Computerized Densitometric Evaluation of Area and Density

	Membrane material (Mean ± SD)					
Variable	Vicryl	Biomend	Fascia	GoreTex	Millipore	Control (No membrane)
Area*	21.4 ± 9.46	25.7 ± 8.50	31.7 ± 2.82	32.5 ± 0.316	26.4 ± 9.18	21.9 ± 10.0
Density*	300.4 ± 346.3	243.2 ± 229.4	256.3 ± 260.5	392.0 ± 263.9	268.6 ± 95.2	295.6 ± 349.5

*No significant between-material differences ($P > .52$).

A second method of determining bone regeneration was by gross evaluation of radiographs of the specimens by three examiners who were blinded to the site examined, using a computer-generated scale for radiographic comparison of new bone growth (Fig 4). This gross bone growth scale (GBGS) was developed to identify bridging of bone over defects, assumed to represent bone regeneration that overcame the critical size defect. For this reason, more value was given for bone development that crossed (bridging) the defect. Using this criterion, each of the three examiners compared each occlusal radiograph to the GBGS, with lower scores representing best bone development. Following numeric assignments from the GBGS, these radiographic values were averaged for three dogs and analyzed nonparametrically using the Friedman statistic (Table 2).

Table 2 Scoring of Gross Bone Growth by Radiographic Type 1 to 4 as Evaluated By Three Examiners

	Membrane material* (Mean ± SD)					Control (No membrane)
	Vicryl	Biomend	Fascia	GoreTex	Millipore	
Gross appearance value†	2.67 ± 0.335	2.67 ± 0.335	2.67 ± 0.335	1.44 ± 0.510	1.33 ± 0.335	3.67 ± 0.335

*No significant between-material differences ($P > .13$)
†Best bone growth = 1.

Results

Primary closure was achieved for all wounds. All membranes were positioned to fully cover the defect site by 3 to 4 mm. Some difficulty was experienced in maintaining complete membrane coverage of the defect, with collapse of the space at the center following mild herniation of the brain. There were no complications during the intraoperative or postoperative course. Through gross evaluation, no signs of complication or migration of the membrane were found at autopsy. All membranes were completely resorbed and showed no evidence of granulation or untoward tissue response. Bone growth, as measured by densitometry, seemed to be arranged in three tiers, starting with GoreTex and fascia, followed by BioMend and Millipore, and then Vicryl and control; however, statistically there were no differences for any site in computer analysis, including the negative control ($P > .52$) (Table 1).

Similar findings were observed for gross bone growth analysis: the two nonresorbable membranes developed the best bone regeneration (Millipore = 1.44; GoreTex = 1.33); the resorbable membranes were grouped equally in the middle (Vicryl = 2.67; BioMend = 2.67; fascia = 2.67); and the control site was well behind (control = 3.67) (Table 2). However, these differences did not reach statistical significance ($P > .13$).

Discussion

The concept of GBR has become increasingly popular in reconstructive procedures for the oral and maxillofacial complex. GBR has been used in closure of oral-antral/oroparanasal communications,[21] in bone grafting in the maxillary sinus,[22,23] and, most extensively, for bone regeneration of perioperative and postoperative defects in dental implant surgery.[10,12,24,25] The opportunity to benefit from a one-step surgical procedure of resorbable materials is appealing to both surgeon and patient.

Currently, the most widely used resorbable membranes are fascia, lamellar bone, type I crosslinked bovine collagen (BioMend), and polyglactin 910 (Vicryl), with both Guidor (a polylactic acid/citric acid ester) and Resolut (a lactic/glycolide polymer) gaining popularity following recent FDA approval. While all of these materials share the advantage of single-entry surgery, studies indicate that they may differ significantly in their ability to provide other, more desirable, properties, such as predictable degradation, biocompatability, and a limited degree of inflammation.

GoreTex was used in this study as the nonresorbable control because of its history of success,[8,10,26] but the PTFE filter (Millipore) results tended to be similar to those of GoreTex (Tables 1 and 2). Millipore, however, is not FDA-approved for clinical usage.

An additional concern in membrane selection is whether or not a filler, for preservation of space, is necessary for bone regeneration.[2,27–30] In the past, variable results have been obtained using different filler materials between membranes, including hydroxyapatite (HA),[31,32] HA and demineralized bone,[26] collagen,[33] or autogenous bone.[34] Clearly, if no filler is used, space must be maintained for clot and bone formation. Because of their stiffness, Millipore and fascia were best suited for space maintenance in the absence of a filler material in this study. BioMend and fascia were more adaptable to soft tissue than to bone when reconstituted, but they did not maintain space well. This may explain why the defects managed with these membranes developed the least amount of new bone (Tables 1 and 2). Membrane stiffness may offer an advantage if no filler is used; however, the morphology of the defect being grafted, a factor that was controlled in this study, may also be relevant.

Since evaluation of bone regeneration materials in humans is an ethical problem, attempts have been made to develop an acceptable animal model. While many animal models have been used to evaluate bone regeneration using barrier techniques,[11,34–36] dog calvarium satisfies all the necessary criteria as proposed by Frame.[37] The most desirable of these are *(1)* adequate bulk to diminish risk of fracture;

(2) a large amount of available bone; and *(3)* allowance of accurate follow-up and radiologic assessment. Dog models have been used successfully for evaluation of GTR/GBR techniques for years,[16,26,31,38] and have a known reliable and reproducible critical size defect (CSD)[13,39] in calvarium.

Schmitz and Hollinger[40] define the CSD as the smallest size intraosseous wound in a particular bone and species of animal that will not heal spontaneously during the lifetime of the animal. The CSD necessary to accurately determine the amount of new bone growth in dog calvarium is 15 mm. Other benefits of calvarial bone include ease of graft coverage with primary soft tissue closure and, consequently, significantly decreased risk of membrane exposure or contamination. Considering all factors, this model appears adequate for evaluating several membranes efficiently, with the fewest potential complications.

Evaluation of the timing of membrane degradation, the type of bone available (new versus old), and the histologic evidence or absence of inflammation were beyond the scope of this study. Since previous studies comparing histologic and radiologic data have produced similar results,[6,37,39,41,42] radiologic/computer analyses were considered valid for this study. Friedenberg and Lawrence[39] documented a close correlation between radiographic and microscopic sections. Additional advantages of this type of analysis are cost-effectiveness, reliability, and ease of reproducibility.

A potential problem of densitometry, however, concerns the effects of averaging over a given area. Because of the variable thickness of bone in the calvarium as compared with the amount of available bone of equal thickness, density measuring may not accurately reflect bone growth into the defect. This may not be a factor in areas of constant bone thickness. As a result of these inherent limitations, the GBGS (Fig 4) gives more weight to "bridging" bone development that crossed the defect. In previous studies, bridging bone, as a predictable evaluator for new bone growth, has been consistently reliable.[4,6,18,34,41] The rationale is that most bony defects, including control defects greater than the CSD, will fill from the periphery. However, genuine bone regeneration can only be accomplished by crossing the defect when "guided" by the regeneration material. Consequently, in comparing radiographs to the GBGS, more value was given for bone development that crossed the defect (Table 2). Future studies employing this method of analysis on a greater number of subjects may provide enough power to differentiate these materials statistically.

Conclusions

Bone growth was seen with all GBR membranes and the control. There was a trend toward greater bone growth in nonresorbable membranes. However, a larger study is necessary to determine the relevance of these findings. This model appears to be useful for the reliable comparison of multiple membranes.

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