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Original

Non-bioabsorbable vs. bioabsorbable membrane: assessment of their clinical efficacy in guided tissue regeneration technique. A systematic review

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Abstract: In a 1998 review article, Laurell and colleagues performed a meta-analysis of relevant guided tissue regeneration (GTR) articles over the previous 20 years (1). The purpose of the present research was to expand on that work, particularly searching for trends discriminating between bioabsorbable and non-bioabsorbable barriers, as well as the use of enamel matrix derivative, with respect to interproximal bony defects. The most recent periodontal journals were reviewed and a search of PubMed (National Institutes of Health) was conducted via the internet covering 1990 to the present. Forty-nine articles were found to be relevant and within established parameters. The data were analyzed using (a) a variation of the methods described in Laurell et al. (1) and (b) statistics appropriate for inter-group comparisons. In most respects, all membranes and enamel matrix derivative (EMD) delivered better outcomes, in the range of 1 to 2 mm, than open flap debridement. The use of any barrier type or EMD configuration was found to yield more Clinical Attachment Level (CAL) gain than any open flap configuration. Other than collagen without grafts versus non-bioabsorbables without grafts, no other comparison between membranes or between membranes and EMD found any significant differences ($P > 0.05$). GTR was confirmed to be superior to open flap debridement. (J Oral Sci 51, 383-400, 2009)

Keywords: meta-analysis; regeneration; membranes; enamel matrix derivative.

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Introduction

Guided tissue regeneration (GTR) is defined as: "… procedures attempting to regenerate lost periodontal structures through differential tissue responses. Barrier techniques, using materials such as expanded polytetrafluoroethylene (ePTFE), polyglactin, polylactic acid, calcium sulfate, and collagen, are employed in the hope of excluding epithelium and the gingival corium from the root in the belief that they interfere with regeneration." (2). During the 1980's and 1990's, a large volume of investigation into guided tissue regeneration (GTR) using membranes established its effectiveness in treating the specific periodontitis-induced resorptive defects, particularly vis-à-vis other surgical and non-surgical modalities. In a 1998 review article, Laurell and colleagues performed a meta-analysis of articles over the previous 20 years, comparing the outcomes from (a) open flap, versus (b) open flap plus bone grafts, versus (c) GTR in "intrabony" defects (1). In their final analysis, Laurell and colleagues combined the results from all GTR articles,

and found that the average CAL gain was 4.2 mm, and that there were no significant differences in the outcomes between bioabsorbable and non-bioabsorbable membranes. Greenstein and Lamster included Laurell and colleagues' results, and compared them to representative results of other therapies, including scaling and root planing, controlled release antibiotic fibers, and enamel matrix protein, with the conclusion that GTR produced the overall best result, according to their criteria (3).

The next generation of strategies for regeneration was enamel matrix derivative (EMD). EMD has been found to exhibit periodontal regeneration properties, specifically associated with amelogenin (4). EMD is viewed as the third generation of periodontal regeneration methods, having been preceded by bone replacement grafts and GTR. In a 2002 review article, Kalpidis and Ruben performed a meta-analysis of articles of clinical trials over the previous 5 years, comparing the outcomes from (a) open flap debridement (OFD) (Clinical Attachment Gain [CAL gain] of 2.1 ± 0.7 mm), versus (b) GTR (CAL gain of 3.8 ± 0.8 mm), versus (c) EMD guided bone regeneration (EGR) (CAL gain of 3.2 ± 0.9 mm) in "intrabony" defects (5). A number of years have elapsed since the Laurell et al. (1) and Kalpidis and Ruben (5) articles, and more research has been accomplished regarding the outcomes of regeneration.

The purpose of this investigation was to expand on the work of Laurell et al. (1) and Kalpidis and Ruben, (5) particularly searching for trends discriminating between bioabsorbable and non-bioabsorbable barriers, and different types of bioabasorbable barriers, as well as EMD, with respect to interproximal intrabony defects resulting from periodontitis.

Materials and Methods

In order to confirm that GTR leads to more CAL gain than open flap debridement (OFD) in interproximal, infrabony periodontal defects, Laurell et al. was used to identify 11 usable articles which had investigated OFD alone, without citric acid, and 11 usable articles which had investigated OFD with bone grafting, and without citric acid (1). Five new articles available since 1998 were added to that set of "OFD alone", while one new article on OFD with bone grafting was added to that set of "OFD with bone grafting".

For articles covering GTR during the 1990's and the first five years of this decade, a search of PubMed (National Institutes of Health) was conducted via the internet. The following parameters were used: (a) All fields; (b) Clinical trials; (c) All adult 19+ years; (d) Publication date from 1990 to 2005; (e) Only items with abstracts; (f) Human; (g) Dental journals; and (h) Gender – both male and female. Furthermore, a manual search of 2000 to 2005 was accomplished of each issue of the Journal of Periodontology, the Journal of Periodontal Research, the International Journal of Periodontics and Restorative Dentistry, and the Journal of Clinical Periodontology. Only those articles investigating regeneration of periodontal bone in infrabony / intrabony defects were processed. In analyzing the success of GTR and EMD, only those articles which featured the following data were used: (a) Number of Defects; (b) Initial Probing Depth; (c) Residual Probing Depth; and (d) Clinical Attachment Level Gain. Defect Depth and Bone Gain were recorded where published in the respective articles. In considering synthetic barriers, we selected for analysis only those commercial barriers which are currently available in the United States, and have been accepted for use in guided tissue regeneration by the United States Federal Drug Administration. Given these constraints, 49 articles on guided tissue regeneration and enamel matrix derivative were found to be relevant.

Following the method of Laurell and colleagues, we weighted the power of each study "… according to the number of defects treated." (1) .That is, the number of defects treated (n) was multiplied by the mean that was derived for each category of data from the respective articles, such as CAL gain. The resulting values from this multiplication were summed for the specific category from all relevant articles, and that sum then divided by the total number of defects ($N = n_1 + n_2 + \ldots$) in the respective category across all the relevant articles that were used in each analysis. The data were then analyzed using two levels of analysis. The first sought statistically significant comparisons of the data, and that will be discussed in the Results and in the Discussion. The second level of analysis was a simplistic meta-analysis method which compared the effectiveness of each barrier and which followed the method described in Laurell et al. (1) with a modification. Instead of deriving standard deviation values assessed from the mean values of each study, as Laurell and colleagues did, we simply reported the averages of the mean values, with the range of those mean values.

Results

The data is categorized according to groupings, each group corresponding to the research articles listed in a table. Two approaches were used in analyzing the data. Section I consists of three parts, each answering a question using statistical analyses. The three questions are: (a) Is there a significant correlation between Initial Probing Depth (IPD) and CAL gain for each grouping? (b) Is there a significant CAL gain for each grouping? And, (c) is there any

Table 1 Open flap debridement alone without grafts

Author, Year	Type of Surgery	N Defect	Probing Depth Initial	Probing Depth Residual	Defect Depth	CAL Gain	Bone Gain
Aimetti et al. (6) 2005	OFD	18	6.22±0.88	3.83±0.86	NR	1.50±0.99	1.05±0.94
Borghetti et al. (7) 1993	OFD	9	5.2±1.5	3.8±1.1	2.6±0.7	0.9±1.3	0.8±1.2
Cortellini et al. (8) 1995	OFD	15	8.3±2.0	3.7±1.3	5.3±1.8	2.5±0.8	NR
Cortellini et al. (9) 1996	OFD	12	8.5±2.0	4.2±0.9	6.7±1.1	2.3±0.8	NR
Francetti et al. (10) 2004	OFD	12 24 - months	6.71±1.25	3.71±1.60	4.81±0.58	2.71±0.76	NR
Froum et al. (11) 1982	OFD	31	7.4±1.9	4.1±1.7	3.7±1.6	1.4±1.0	1.2±1.0
Kim et al. (12) 1996	OFD	18	7.2±1.2	3.9±0.9	5.8±1.8	2.0±1.7	0.5±2.0
Masters et al. (13) 1996	OFD	15	7.0±1.3	3.5±1.0	3.9±0.9	2.4±1.8	1.3±1.8
Mattson et al. (14) 1995	OFD	9	6.4±1.4	4.5±1.7	4.1±1.3	0.4±2.0	1.1±1.0
Mellonig et al. (15) 1984	OFD	15	6.5±1.3	3.7±1.2	3.3±1.2	1.5±1.9	1.3±1.2
Renvert and Egel-berg (16) 1981	OFD	19	7.5±1.5	4.7±1.4	4.2±1.5	1.2±0.9	0.9±1.2
Renvert et al. (17) 1985	OFD	25	6.8±1.1	4.1±0.6	4.1±1.6	1.3±0.8	0.7±0.9
Sculean et al. (18) 2005	OFD	16	8.0±1.2	4.4±1.7	3.7±1.3	1.9±1.1	NR
Tonetti et al. (19) 2004	OFD	62	7.9±1.5	NR	5.9±2.2	2.5±1.5	NR
Vouros et al. (20) 2004	OFD	12	7.72±0.68	5.22±0.84	NR	Initial 8.52±0.97 Final 6.09±0.94 = 2.43	NR
Yukna et al. (21) 1985	OFD	42	6.3±0.2	3.5±0.3	3.4±0.2	1.3±0.2	0.8±0.2

NR = not reported
Measurements made in mm; means are ± standard deviation (SD)
OFD = Open Flap Debridement

significant difference between the groups, and is there any significant difference when combining Groups 1 and 2 (OFD), versus Groups 3 and 4 (ePTFE), versus Groups 5 through 7 (all bioabsorbable barriers), versus Group 8 (EMD by itself), versus Group 9 (EMD with graft and/or barrier), and versus Groups 3 through 9 (combination of all GTR and EMD).

Section II reflects a "simplistic data analysis" of each group, in that simple comparisons of averages for initial probing depth (IPD) and CAL gain were derived, with normalization to the IPD of open flap debridement (OFD) without graft material. Normalization was accomplished in order to eliminate the influence of varying IPDs, since we found that there is a correlation between IPD and CAL gain.

Section I. Statistical Data Analyses

The data analysis of this section of the study consists of three parts:

Correlation between *Initial probing Depth* and *Cal Gain* in each category.

The significance of the *Cal Gain* in each category.

Analysis of variance of *Cal Gain* between categories.

Since there were only two articles listed in Table 10, there is no comparison of Plasma Rich Protein in the following analyses. Only the groupings from Tables 1 through 9 are

Table 2 Open flap debridement with grafts

Author, Year	Type of Surgery	N Defects	Probing Depth Initial	Probing Depth Residual	Defect Depth	CAL Gain	Bone Gain
Barnett et al. (22) 1989	OFD + FDBA	19	6.7±2.0	3.7±1.5	3.2±1.5	2.2±1.7	2.1±1.4
Borghetti et al. (7) 1993	OFD + AB	9	6.0±1.5	3.9±1.1	3.4±1.8	1.3±1.6	1.8±0.7
Bender et al. (23) 2005	OFD + DFDBA	17	7.6±2.1	4.8±1.3	NR	1.6±1.1	2.2±1.8
Bowen et al. (24) 1989	OFD + DFDBA	17	6.4±1.7	3.5±1.2	3.6±1.1	2.1±1.8	2.2±1.1
Francis et al. (25) 1995	OFD + DFDBA	11	7.1±2.7	3.5±2.3	4.5±1.6	2.4±2.3	3.6±1.9
Guillemin et al. (26) 1993	OFD + DFDBA	15	7.1±2.1	4.7±1.9	3.3±2.5	2.8±0.9	1.9±1.7
Masters et al. (13) 1996	OFD + DFDBA	15	6.7±1.4	4.0±1.1	4.2±0.7	1.5±1.8	2.2±1.8
Mellonig et al. (15) 1984	OFD + DFDBA	32	7.9±1.9	4.8±1.4	4.0±1.6	2.9±1.3	2.6±1.4
Quintero et al. (27) 1982	OFD + DFDBA	27	NR	NR	3.8	1.9	2.4
Renvert et al. (17) 1985	OFD + AB	25	6.3±0.7	4.4±1.2	3.9±1.1	1.2±1.0	2.6±1.4
Rumelhart et al. (28) 1989	OFD + FDBA	11	6.3±2.4	4.1±1.2	3.7±2.1	1.8±1.8	2.5±1.5
Rumelhart et al. (28) 1989	OFD + DFDBA	11	6.3±4.2	4.2±1.3	3.4±1.5	2.0±1.8	1.7±1.0

NR = Not Reported
OFD = Open Flap Debridement
DFDBA = Demineralized Freeze-Dried Bone Allograft
FDBA = Freeze-Dried Bone Allograft
AB = Autologous Bone
Measurements made in mm; means ± SD

analyzed and compared.

Part A Correlation

The correlations between Initial Probing Depth (IPD) and CAL Gain in each of the nine (9) categories of reviewed studies were first calculated with simple linear correlation (Pearson's correlation coefficient r). The results are summarized in the following table [(**) indicates significance at the 0.01 level ($P < 0.01$) and (*) indicates significance at the 0.05 level ($P < 0.05$)]:

Grouping / Table	Number of Studies	r	*P*value
1	16	.62	.01**
2	11	.61	.047*
3	17	.73	.011**
4	6	.66	.158
5	4	.40	.596
6	6	.76	.08
7	12	.71	.01**
8	22	.44	.042
9	10	.73	.016**

The correlations between IPD and CAL Gain are significant at the .01 or .05 level in six of the nine categories in which the number of studies are ten or more. In case one may question the validity of using this parametric procedure, a non-parametric method, the Spearman's Rho, was also conducted and the results summarized in the following table:

Grouping / Table	Number of Studies	Rank Correlation	*P*value
1	16	.55	.027*
2	11	.66	.027*
3	17	.79	.0002**
4	6	.53	.281
5	4	.40	.600
6	6	.94	.005**
7	12	.84	.0007**
8	22	.43	.044*
9	10	.70	.034*

The results of the rank-correlation are similar to the Pearson's r correlation with one more category (#6) showing a significant relationship.

Table 3 Guided tissue regeneration using non-bioabsorbable barriers without graft material

Author, Year	Barriers	N Defects	Probing Depth Initial	Probing Depth Residual	Defect Depth	CAL Gain	Bone Gain
Caffesee et al. (29) 1997	e-PTFE	6	7.4±1.5	3.7	NR	3.0±1.2	NR
Cortellini et al. (8) 1995	e-PTFE titanium	15	8.4±2.5	2.1±0.5	5.5±2.9	Begin 9.9±3.2 Final 4.7±1.8 = 5.2	NR
Cortellini et al. (8) 1995	e-PTFE	15	8.2±2.3	2.7±1.0	5.8±2.7	Begin 10.3±2.4 Final 6.3±1.9 = 4.0	NR
Cortellini et al. (9) 1996	e-PTFE	12	8.8±1.3	2.9±0.9	7.0±1.5	Begin 10.8±1.8 Final 5.6±1.6 = 5.2	NR
Gouldin et al. (30) 1996	e-PTFE	25	7.2±1.3	3.5±1.3	8.5±2.5	2.2±1.4	2.2±1.5
Guillemin et al. (26) 1993	e-PTFE	15	7.1±2.1	4.7±1.9	7.0±2.7	2.8±0.9	1.9±1.7
Kilic et al. (31) 1997	e-PTFE	10	8.90±2.44	3.07±1.37	NR	3.72±1.96	1.60±1.66
Kim et al. (12) 1998	e-PTFE	8	7.9±1.6	3.7±1.0	3.7±1.3	2.6±1.4	NR
Paolantonio et al. (32) 1998	e-PTFE	22	7.9±1.5	2.8±0.5	5.5±1.4	4.0±1.5	4.2±0.6
Silvestri et al. (33) 2003	e-PTFE	49 3 wall	8.1±1.9	NR	6.1±1.7	4.3±1.9	
Tonetti et al. (34) 1996	e-PTFE Titanium with papillary preservation	Assume 15	8.4±2.5	PD reduction 6.3±2.5	NR	5.3±2.2	“available space” 9.4±3
Tonetti et al. (34) 1996	e-PTFE coronal to alveolar crest	Assume 15	8.2±2.3	PD reduction 5.5±2.6	NR	4.1±1.9	“available space” 7.9±2.5
Tonetti et al. (35) 2002	e-PTFE	83 EDTA 1,2,3 wall	7.7±1.5	NR	5.4±2.0	2.5±1.5	NR
Yoshinari et al. (36) 2001	e-PTFE	20	6.0±0.5	PD reduction 3.8±0.5	NR	2.0±0.5	NR
Yoshinari et al. (36) 2001	e-PTFE + 2% minocycline ointment	20	5.3±0.5	PD reduction 3.5±0.4	NR	3.0±0.3	NR
Zucchelli et al. (37) 1999	e-PTFE titanium + topical Metronidazole	26	9.1±1.4	PD reduction 6.7±1.2	NR	4.8±1.2	NR
Zucchelli et al. (37) 1999	e-PTFE titanium + systemic Amoxicillin	30	8.9±1.8	PD reduction 6.5±1.6	NR	5.3±1.7	NR

e-PTFE = expanded polytetrafluoroethylene
Tonetti et al. (34) does not specifically state the numbers of defects in each subpopulation, only that there were 45 patients, each with one defect, and that the population was divided into three groups.
NR = not reported
Measurements made in mm; means ± SD

Part B CAL-Gain Statistics

The results presented in the following table clearly show that the CAL-Gain levels in all of the nine categories are highly significant. The reported sample sizes in the studies included in each grouping varied greatly. However, due to the different criteria used in choosing subjects

Table 4 Guided tissue regeneration using non-bioabsorbable barriers with graft material

Author, Year	Barriers	N Defects	Probing Depth Initial	Probing Depth Residual	Defect Depth	CAL Gain	Bone Gain
Aichelmann-Reidy et al. (38) 2004	e-PTFE + DFDBA	19	6.2±1.1	2.9±1.4	3.8±1.0	1.7±1.4	2.5±0.9
Gouldin et al. (30) 1996	e-PTFE + DFDBA	25	8.0±1.7	4.3±1.9	9.4±2.1	2.4±1.6	2.5±1.7
Guillemin et al. (26) 1993	e-PTFE + DFDBA	15	7.4±1.6	5.1±1.7	7.4±2.4	3.2±1.5	2.2±1.5
Kilic et al. (31) 1997	e-PTFE + HAC	10	8.52±1.64	2.67±0.74	NR	3.80±1.98	1.90±1.66
Walters et al. (39) 2003	Porous ePTFE (Gore-Tex) + PepGen (Bovine HA)	12	8.1±1.6	3.8±0.9 (9 months)	NR	2.4±1.9	NR
Walters et al. (39) 2003	Non-Porous ePTFE (Tef-Gen) + PepGen (Bovine HA)	12	8.8±1.8	4.0±1.5 (9 months)	NR	2.9±1.7	NR

e-PTFE = expanded polytetrafluoroethylene
HA = Hydroxyapatitie
DFDBA = Demineralized Freeze-Dried Bone Allograft
HAC = Hydroxyapatite-Collagen alloplastic graft
NR = not reported
Measurements made in mm; means ± SD

Table 5 Guided tissue regeneration using collagen bioabsorbable barriers without graft material

Author, Year	Types of Barriers	N Defects	Probing Depth Initial	Probing Depth Residual	Defect Depth	CAL Gain	Bone Gain
Chen et al. (40) 1995	Collagen only	8	7.4±0.4	4.2±0.4	NR	2.0±0.4	NR
Mattson et al. (14) 1995	Collagen Part I	13	7.79±1.59	3.56±0.64	NR	2.50±1.44	NR
	Collagen Part II	9	7.16±0.93	4.04±1.11	NR	2.37±2.10	3.21±1.15
Mattson et al. (41) 1999	Collagen	23	6.18±0.89	2.97±1.72	NR	2.58±1.90	2.15±1.99

Mattson et al. (41) reported data for "average" depths, and "deepest" depths. We include only the "deepest" depths here.
NR = not reported
Measurements made in mm; means ± SD

among studies, for our statistical analysis we have decided not to "weight" each study by its sample size but rather treat each study as "equal".

Grouping / Table	Number of Studies	CAL-Gain Mean (mm)	Standard Deviation	*P*value	Est. Effects
1	16	1.77	0.67	.0000	-1.27
2	11	1.98	0.59	.0000	-1.05
3	17	3.77	1.15	.0000	0.731
4	6	2.73	0.73	.0003	-0.301
5	4	2.36	0.26	.0003	-0.672
6	6	3.50	0.73	.0001	0.461
7	12	3.20	0.71	.0000	0.163
8	22	3.52	1.15	.0000	0.488
9	10	3.88	0.99	.0000	0.850

Grand Mean = 3.034

Part C ANOVA

An attempt was made to compare the CAL-Gain in the nine categories, using the guideline of meta-analysis recommended by Hedges and Olkin (1985) (73). The initial analysis of variance shows that the difference among the nine categories on CAL-Gain is highly significant as shown in the following ANOVA table.

Table 6 Guided tissue regeneration using collagen bioabsorbable barriers with graft material

Author, Year	Types of Barriers	N Defects	Probing Depth Initial	Probing Depth Residual	Defect Depth	CAL Gain	Bone Gain
Camargo et al. (42) 2000	Collagen + cancellous bovine bone mineral granules	22 Buccal	7.14±0.87	3.11±0.82	NR	3.29±1.12	3.81±0.82
Chen et al. (40) 1995	Collagen + DFDBA	7	7.6±0.4	4.2±0.5	NR	2.3±0.5	NR
Orsini et al. (43) 2001	Collagen + AB	12	8.0±1.28	3.58±0.51	NR	Initial 8.83±1.34 Final 5.25±0.75 = 3.58	NR
Sculean et al. (18) 2005	BioGide (collagen) + BioOss Collagen	16	8.3±1.5	2.9±1.3	3.8±1.2	4.1±0.9	NR
Tonetti et al. (19) 2004	BioGide + BioOss	62 primarily 2 walls	7.8±1.6	NR	5.6±1.9	3.3±1.7	NR
Vouros et al. (20) 2004	BioGide + BioOss	14	8.82±1.03	3.73±1.14	NR	Initial 10.38±1.77 Final 5.98±1.71 = 4.4	NR

Although Sculean et al. (18) provides some data from 4 years after surgery, only the 1-year data was used in the analysis in this article. Camargo et al. (42) reported data for both buccal and lingual defects. Only the data for the buccal defects are listed in the table.
AB = Autogenous Bone
DFDBA = Demineralized Freeze-Dried Bone Allograft
NR = not reported
Measurements made in mm; means ± SD

Source	Sum of Square	df	MSS	F-ratio	*P*-value
Between	63.46	8	7.93	9.58	.000
Within	78.68	95	.83		
Total	142.16				

A Tukey post-hoc comparisons showed the following pair-wise results:

Y indicates significant difference on CAL-Gain between categories with *P*-value less than or equal to 0.05.

N indicates non-significant difference on CAL-Gain between categories with *P*-value greater than 0.05.

Grouping / Table	1	2	3	4	5	6	7	8	9
1		N	Y	N	N	Y	Y	Y	Y
2			Y	N	N	Y	N	Y	Y
3				N	Y	N	N	N	N
4					N	N	N	N	N
5						N	N	N	N
6							N	N	N
7								N	N
8									N

A selected numbers of contrasts were analyzed by using Scheffe's comparisons. The selection was based on the similar characteristics of the categories which were divided into six groups: (Categories 1 and 2), (Categories 3 and 4), (Categories 5 to 7), (Category 8), (Category 9), and (Categories 3 to 9). The results of comparisons among these groups are summarized in the following table:

Y indicates significant difference on CAL-Gain between groups with of *P*-value less than or equal to 0.05.

N indicates non-significant difference on CAL-Gain between groups with *P*-value greater than 0.05.

Groupings	(1,2)	(3,4)	(5-7)	(8)	(9)	(3-9)
(1,2)		Y	Y	Y	Y	Y
(3,4)	Y		N	N	N	
(5-7)	Y	N		N	N	
(8)	Y	N	N		N	
(9)	Y	N	N	N		
(3-9)	Y					

Section II. Simplistic Data Analysis

Open Flap Debridement

Analysis was accomplished in order to reconfirm Laurell et al. (1) and to establish a reference relationship between IPD and CAL gain. Tables 1 and 2 list the articles and data used in analyzing OFD outcomes for interproximal infrabony defects.

Table 7 Polylactic acid derivatives without graft material

Author, Year	Types of Barriers	N Defects	Probing Depth Initial	Probing Depth Residual	Defect Depth	CAL Gain	Bone Gain
Aimetti et al. (6) 2005	Resolut XT (poly-glycolic – poly-lactic acid)	18 Wide, shallow 1 wall defects	6.61±0.85	3.17±0.86	NR	2.89±0.90	2.13±1.21
Becker et al. (44) 1996	Resolut	30	7.6±1.6	3.6±1.3	NR	2.9±2.0	NR
Bratthall et al. (45) 1998	Resolut	11	6.9±0.4	3.3±0.2	NR	2.0	NR
Caffesee et al. (29) 1997	Resolut	6	7.5±1.9	3.7	NR	2.3±2.0	NR
Cortellini et al. (9) 1996	Resolut	12	9.8±2.4	3.3±0.9	7.2±1.4	4.6±1.2	NR
Mattson et al. (41) 1999	Resolut	23	6.14±2.02	2.59±1.52	NR	2.77±2.13	1.90±1.92
Sanz et al. (46) 1997	Resolut	12	8.1±1.4	3.1±1.0	3.8±1.5	3.8±1.5	NR
Sculean et al. (47) 1999	Resolut	52	8.4±1.3	3.6±1.3	NR	3.4±1.4	NR
Sculean et al. (48) 1999	Resolut	7	11.4±2.2	5.6±1.3	NR	3.6±1.7	2.1±1.0
Sculean et al. (49) 2001	Resolut	12	8.1±1.8	(1 year) 3.6±0.8	4.2±1.7	Begin 9.8±2.3 Final (1 year) 6.6±1.7= 3.2	NR
Tonetti et al. (50) 1998	Resolut	72	8.3±1.9	4.27±1.32	NR	3.04±1.64	NR
Windisch et al. (51) 2002	Resolut	8	10.27±2.77	4.63±1.51	NR	3.87±1.64	1.93±1.04

Although Sculean et al. (47) provides some data from 4 years after surgery, only the 1-year data was used in the analysis in this article. Tonetti et al. (50) does not specifically state the numbers of defects in each subpopulation, only that there were 45 patients, each with one defect, and that the population was divided into three groups.
NR = not reported
Measurements made in mm; means ± SD

Group 1: Open Flap Debridement, Without Graft Material

From Table 1, the average mean CAL gain for interproximal defects using OFD alone was 1.81 mm, with a range of 0.4 mm to 2.5 mm. The corresponding average IPD was 7.19 mm.

Group 2: Open Flap Debridement, With Graft Material

From Table 2, the average mean CAL gain for interproximal defects using OFD with graft material was 2.02 mm, with a range of 1.2 mm to 2.9 mm. The corresponding average IPD was 6.89 mm. When normalized to the average IPD of OFD (7.19 mm), the CAL gain of OFD with graft material would be 2.10 mm.

Guided Tissue Regeneration

Group 3: Non-Bioabsorbable Barriers without Graft Material

From Table 3, analysis of research using non-bioabsorbable barriers, without graft material, and with or without titanium, resulted in an average mean CAL gain for interproximal defects of 3.64 mm, with a range of 2.0 mm to 5.3 mm. The corresponding average IPD was 7.84 mm. When normalized to the average IPD of OFD (7.19 mm), the CAL gain of ePTFE without graft material would be 3.34 mm

Group 4: Non-Bioabsorbable Barriers with Graft Material

Using Table 4, analysis of research using non-bioabsorbable barriers with graft material for interproximal defects resulted in the average mean CAL gain of 2.60 mm, with a range of 1.7 mm to 3.8 mm. The corresponding average IPD was 7.71 mm. When normalized to the average IPD of OFD (7.19 mm), the CAL gain of ePTFE with graft material would be 2.60 mm.

Table 8 Regeneration using enamel matrix derivative (EMD); no grafts, no barriers

Author, Year	EMD only, or with Barriers or Grafts	N Defects	Probing Depth Initial	Probing Depth Residual	Defect Depth	CAL Gain	Bone Gain
Cardaropoli and Leonhardt (52) 2002	EMD	10	10.30±1.05	3.15±0.47	6.10±1.61	6.45±0.50	
Francetti et al. (10) 2004	EMD	12	7.86±1.46	3.00±0.82	5.93±1.25	4.29±1.38	
Froum et al. (53) 2001	EMD	53	7.99±1.46	("PD reduction") 4.94±NR	5.63±1.24	4.26±NR	
Gurinsky et al. (54) 2004	EMD	34	7.5±0.3	3.6±0.2	4.9±6.3	3.2±0.3	2.6±0.4
Heden et al. (55) 1999	EMD	145	8.6±2.14	3.4±1.21	NR	4.6±2.13	
Heijl et al. (56) 1997	EMD	34	7.8±1.1	16 months 4.5±1.0	NR	16 months 2.3±1.6	
Lekovic et al. (57) 2000	"EMP"	21 buccal	7.33±1.22	5.42±1.26	NR	1.72±1.33	
Okuda et al. (58) 2000	EMD	18	6.33±0.91	3.39±0.85	4.50±1.20	1.72±1.07	
Rosling et al. (59) 2005	EMD	14	7.57±1.02	3.40±1.82		Begin 12.93±2.00 Final 11.35±1.58 = 1.58	
Sanz et al. (60) 2004	EMD	35	7.9±1.8	NR	6.2±2.3	3.1±1.8	
Sculean et al. (48) 1999	EMD	7	11.3±1.8	5.6±1.3	NR	3.2±1.2	
Sculean et al. (61) 1999	EMD	16	8.1±1.7	8 months 4.3±1.3	NR	3.4±1.1	
Sculean et al. (49) 2001	Emdogain	12	8.1±1.8	(1 year) 3.8±1.2	4.2±1.7	Begin 9.8±2.0 Final (1 year) 6.4±1.6 = 3.4	
Sculean et al. (62) 2001	EMD	14	8.4±1.9	4.3±1.2	NR	3.4±1.5	
Sculean et al. (63) 2005	EMD	15	8.5±1.5	4.0±1.6	4.1±1.1	3.9±1.8	
Silvestri et al. (64) 2000	EMD	10	7.7±2.2	"PD reduction" 4.8±1.6	5.9±1.8	"PAL gain" 4.5±1.6	
Silvestri et al. (33) 2003	EMD	49	8.5±1.6	"PD reduction" 5.3±1.9	NR	4.1±1.8	
Tonetti et al. (35) 2002	EMD	83 EDTA 1,2,3 wall	8±1.5	NR	5.8±2.1	3.1±1.5	
Wachtel et al. (65) 2003	EMD (micro-flaps)	13	7.0±1.3	3.1±0.6	NR	3.6±1.6	
Windisch et al. (51) 2002	EMD	8	10.33±1.51	5.33±1.37	NR	2.67±1.03	
Zucchelli et al. (66) 2002	EMD	30	9.2±1.0	4.0±0.7	6.1±1.3	Begin 9.9±1.4 Final 5.8±1.1 = 4.1	
Zucchelli et al. (67) 2003	EMD	30	9.2±1.1	PD reduction 5.8±0.8	6.1±1.3	4.9±1.0	4.3±1.5

Used 1-year data from Sculean et al. (49) in the analysis for CAL. Although 4-year data was available, 1-year data was used for standardization with other articles. Windisch et al. (51) data is at 6 months.
Froum et al. (52): no standard deviation for probing depth (PD) reduction, CAL gain, or Bone Gain. No Final PD.
NR = not reported
Measurements made in mm; means ± SD

Table 9 Regeneration using enamel matrix derivative (EMD) plus barrier and/or graft

Author, Year	EMD with Barriers or Grafts	N Defects	Probing Depth Initial	Probing Depth Residual	Defect Depth	CAL Gain	Bone Gain
Gurinsky et al. (54) 2004	EMD + DFDBA	33	7.5±0.3	4.0±0.2	5.2±0.3	3.0±0.3	3.7±0.2
Lekovic et al. (57) 2000	"EMP" + BPBM	21 buccal	7.74±1.41	6 months 3.71±1.13	NR	6 months 3.13±1.41	
Lekovic et al. (68) 2001	Compos-ite "EMP" + BPBM + collagen +Polylactic Acid	18 buccal	8.46±1.86	3.51±0.77	NR	3.89±1.16	
Rosen and Reynolds (69) 2002	EMD / DFDBA + Atrisorb	10	8.4±1.6	3.0±0.8	NR	4.5±1.1	
Rosen and Reynolds (69) 2002	EMD / FDBA + Atrisorb	12	8.9±2.0	3.2±1.0	NR	5.3±1.7	
Sculean et al. (62) 2001	EMD + Resolut	14	8.6±1.5	4.3±1.3	NR	3.4±1.1	
Sculean et al. (70) 2002	EMD + Bioactive Glass	14	8.07±1.14	3.92±0.73	3.9±1.6	Begin 9.64±1.5 Final 6.42±1.08 = 3.22	
Sculean et al. (63) 2005	EMD + bioactive glass	15	8.5±1.1	4.4±1.2	4.3±1.0	3.2±1.7	
Velasquez-Plata et al. (71) 2002	EMD + BDX	16	6.9±0.9	2.9±0.6	5.3±0.9	3.4±0.9	
Zucchelli et al. (67) 2003	EMD + BPBM (BioOss) Bovine Porous Bone Mineral	30	9.4±1.1	PD reduction 6.2±0.4	6.1±1.2	5.8±1.1	5.3±1.1

BPBM = "Bovine Porous Bone Mineral" (Bio-Oss)
BDX = "Bovine-Derived Xenograft" (Bio-Oss)
NR = not reported
Measurements made in mm; means ± SD

Bioabsorbable Barriers

Group 5: Collagen without Grafts

Using Table 5, analysis of research using collagen barriers without graft material for interproximal defects resulted in the average mean CAL gain of 2.44 mm, with a range of 2.0 mm to 2.58 mm. The corresponding average IPD was 6.93 mm. When normalized to the average IPD of OFD (7.19 mm), the CAL gain of collagen without graft material would be 2.53 mm.

Group 6: Collagen with Grafts

Using Table 6, analysis of research using collagen barriers with graft material for interproximal defects resulted in the average mean CAL gain of 3.48 mm, with a range of 2.3 mm to 4.1 mm. The corresponding average IPD was 7.87 mm. When normalized to the average IPD of OFD (7.19 mm), the CAL gain of collagen with graft material would be 3.18 mm.

Group 7: Polylactic Acid Derivatives without Grafts

Using Table 7, analysis of research using polylactic acid (PLA) barriers without graft material for interproximal defects resulted in an average mean CAL gain of 3.15 mm, with a range of 2.0 mm to 4.6 mm. The corresponding average IPD was 7.70 mm. When normalized to the average IPD of OFD (7.19 mm), the CAL gain of PLA without graft material would be 2.94 mm.

Biologically Active Materials

Group 8: Enamel Matrix Derivative Guided Bone Regeneration

Using Table 8, analysis of research using enamel matrix derivative (EMD) without graft material or membranes, resulted in an average mean CAL gain of 3.71 mm, with a range of 1.58 mm to 6.45 mm. The corresponding average IPD was 8.38 mm. When normalized to the average IPD of OFD (7.19 mm), the CAL gain of EMD by itself would be 3.18 mm.

Table 10 Regeneration using platelet rich plasma (PRP)

Author, Year	Barriers	N Defects	Probing Depth Initial	Probing Depth Residual	Defect Depth	CAL Gain	Bone Gain
Okuda et al. (72) 2005	PRP with Porous Hydroxy apatite	35	7.7±1.5	3.0±0.8	NR	Initial 8.4±1.8 Final 5.0±1.8 = 3.4	NR
Lekovic et al. (73) 2002	OFD + Platelet Rich Plasma + BPBM	21	7.81±1.32 Buccal	3.62±1.12 6 months buccal	NR	4.12±0.78 6 months buccal	4.96±1.28 buccal

Due to the low number of articles, no sophisticated data analysis was accomplished on PRP data.
NR = not reported
Measurements made in mm; means ± SD

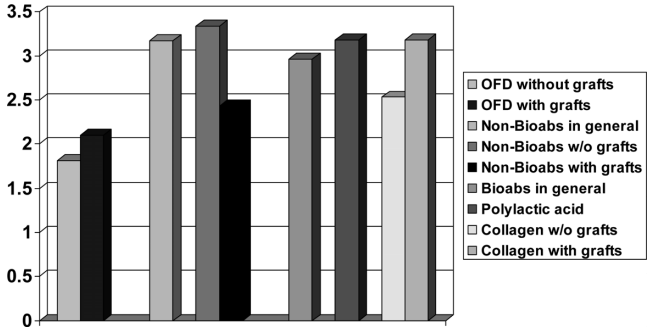

Fig. 1 In order to eliminate differences due solely to a variation in initial probing depth, all other CAL gains were normalized to the IPD of OFD without grafts (7.19 mm). The bar graphs indicate a trend towards more CAL gain when using barriers in GTR, versus OFD.

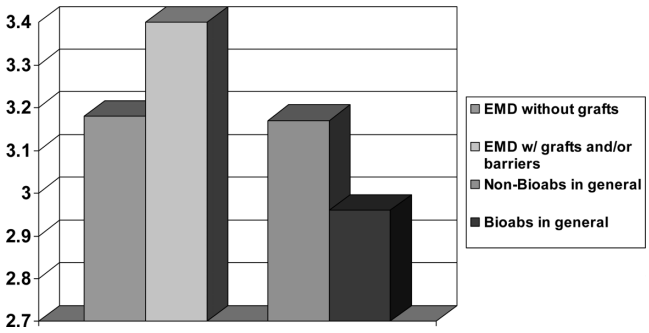

Fig. 2 Using biologically active molecules appears to give results comparable to those when using GTR. EMD with grafts and/or barriers tended to yield the greatest amount of CAL gain, at 3.4 mm.

Group 9: Enamel Matrix Derivative with Graft Material and/or Barriers

Using Table 9, analysis of research using EMD with graft material and/or membranes, resulted in an average mean CAL gain of 3.89 mm, with a range of 3.0 mm to 5.8 mm. The corresponding average IPD was 8.23 mm. When normalized to the average IPD of OFD (7.19 mm), the CAL gain of EMD with graft material and/or membranes would be 3.40 mm.

The comparisons of these average CAL gains are shown in Fig. 1 and 2.

Platelet Rich Plasma

Using Table 10, analysis of research using Platelet Rich Plasma (PRP) and graft material (two articles), resulted in an average mean CAL gain of 3.67 mm, with a range of 3.4 mm to 4.12 mm. The corresponding average IPD was 7.74 mm. When normalized to the average IPD of OFD (7.19 mm), the CAL gain of PRP with graft material would be 3.58 mm.

Discussion

In-Depth Statistical Data Analysis

Consistently, a correlation between the IPD and CAL gain was found for each surgical approach. In most cases, the correlation was statistically significant ($P < 0.05$), both by using the Pearson's r correlation and the Spearman's Rho. The only correlations which were not found to be significant were those where a low number of articles existed, and therefore weakened the statistical analysis. We attempted to fit the data into non-linear equations, but found that linear correlations between IPD and CAL gain gave the best "fit" in comparing the groupings.

The CAL gains from each grouping (ranging from 1.77 mm to 3.88 mm) are highly significant, implying that one could reliably anticipate the corresponding amount of CAL gain from whatever surgical method and barrier or biologically active molecule is utilized.

In comparing the CAL gains from each grouping, the ANOVA reveals significant differences in outcomes between (a) non-bioabsorbable membranes without grafts

[3.77 mm] versus OFD with and without grafts [1.98 mm and 1.77 mm]; (b) non-bioabsorbable membranes without grafts [3.77 mm] versus collagen without grafts [2.36 mm]; (c) collagen with grafts [3.50 mm] versus OFD with and without grafts [1.98 mm and 1.77 mm]; (d) polylactic acid derivatives without grafts [3.20 mm] versus OFD without grafts [1.77 mm]; and (e) EMD with and without grafts/barriers [3.88 mm and 3.52 mm] versus OFD with and without grafts [1.98 mm and 1.77 mm]. All other comparisons found no significant differences ($P > 0.05$). It is possible that the lack of statistical significance when comparing non-bioabsorbable barriers with graft material to OFD with or without graft material, may be due to the low number of studies (six) using non-bioabsorbable barriers with graft material. Similarly, the same may be true of collagen without graft material compared to OFD with or without graft material, in that only four sets of data were found which used collagen without graft material. However, the mean CAL gains for all groups were found to be highly significant. Therefore it is possible that even with more research, the same ANOVA outcome will prevail. Considering another unexpected outcome, it is also possible that polylactic acid derivatives without grafts may be statistically superior to OFD with grafts if the newer generation of polylactic acid barriers is used. Clearly, by this analysis, (a) non-bioabsorbable membranes without grafts, (b) collagen with grafts, and (c) any combination of EMD with or without barriers are all superior to OFD with or without grafts, and (d) polylactic acid without grafts is superior to OFD without grafts.

Statistical versus Clinical Significance

Often there is a question whether a comparison that is found to be statistically significant is actually clinically significant (75). As a guide, we would like to suggest that if a comparison is found to be statistically significant and the difference between the two numbers being compared is greater than the standard error of measurement for whatever device is being used, then the difference may be considered clinically significant too. For example, if the standard error of measurement for probing with an automated probe used in a study is found to be 1.0 mm, then any difference less than 1 mm, however statistically significant, would not be considered clinically significant.

Simplistic Data Analysis

Relationships of the Initial Probing Depths to the CAL gains

Several researchers have reported a correlation between IPD and CAL gain (1,41,76). Laurell et al performed a correlation analysis on articles which presented individual data for each subject within the research population (1). They found that both CAL gain and bone fill correlated significantly with defect depth, R = 0.52 and 0.53. Some of the studies which we investigated did not include "defect depth," but all did include initial probing depth (IPD), and that was used in our analyses. Since there appears to be a direct relationship between IPD and OFD, one would expect that if a study used IPDs of greater depth, then the outcomes would yield greater CAL gains. That is what we found when we did a separate analysis on data from GTR studies using titanium-backed ePTFE membranes. Initially it appeared that titanium-backed membranes yielded significantly more CAL gain. However, the researchers involved in those articles were using the titanium backed ePTFE for IPDs that were deeper than other groups, so if the data were normalized to a standard IPD, that CAL gain was more in line with CAL gains derived from other barrier membranes at a standard IPD. Therefore, in our trend comparison below, we normalized all average CAL gains to the IPD of OFD without grafts in order to compare the effectiveness of the different membranes and biologically active molecules.

Trend Comparison of the Different Membranes and Biologically Active Products, with and without Graft Material

Using our data, Fig. 1 of CAL gains from the different surgical approaches illustrates that OFD resulted in far less CAL gain when compared to (a) non-bioabsorbable membranes in general and to (b) bioabsorbable membranes in general. Therefore, regarding OFD versus GTR, our findings support what others have found. Figure 1 also indicates that the outcomes from using non-bioabsorbable and bioabsorbable membranes are similar, except for a slight decrease in CAL gain when using non-bioabsorbables with grafts and when using collagen without graft material. Figure 2 illustrates that EMD without grafts has an average outcome similar to that of non-bioabsorbable membranes in general, and to a lesser degree, bioabsorbable membranes in general. On the other hand, EMD with grafts and / or membranes produced an average CAL gain about 7% higher than EMD without grafts and / or membranes, and non-bioabsorbable membranes.

Bone Grafting. When considering GTR with membranes, the use of bone graft as an adjunct to e-PTFE does not appear to enhance the CAL gain (2.60 mm, normalized versus 3.34 mm, normalized). On the other hand, adding bone grafting to collagen membranes does appear to enhance the CAL gain vis-à-vis OFD.

Collagen versus Polylactic Acid. The analysis of pertinent articles revealed that the use of polylactic acid

barriers tended to result in about the same CAL gain. The data for the two groups was not significantly different by the ANOVA process.

Use of Antibiotics. Two of the articles include the use of antibiotics with non-bioabsorbables.(36,37) However, the variables between the investigations are so extreme that no overall trend or conclusion about the use of antibiotics can be made authoritatively. Zucchelli and colleagues compared topical metronidazole with systemic amoxicillin, finding a CAL gain or 4.8 mm in the former, and 5.3 mm in the latter (37). Yoshinari et al. compared 2% minocycline ointment using e-PTFE versus no ointment, and found that the antibiotic usage was associated with about 1.0 mm more CAL (36). When combining data from the two articles, we found an average CAL gain of 4.52 mm.

Unusual Barriers. Our literature search found only one article which investigated bioactive glass, which appears to have wound healing which is significantly different from barrier membranes (78). In that article, for those initial probing depths equal to or less than 7 mm, the CAL gain was 2.2 ± 0.77 mm, which is less than the averages that we found for non-bioabsorbable membranes in general (3.17 mm) and bioabsorbable membranes (2.83 mm). However, Park and colleagues did report much greater CAL gain (4.0 ± 1.3 mm) with deeper probing depths (> 7 mm) (78).

Comparison with other Meta-Analyses of Regeneration Research. When comparing OFD with GTR, the outcomes for OFD (increases in CAL of 1.81 mm without graft material, and 2.10 mm with graft material) were less than those for GTR, whether using non-bioabsorbable or bioabsorbable barriers, with or without graft material (Fig. 1). These relative outcomes are consistent with Laurell et al. (1). When analyzing the set of data for all membranes in their respective categories, the average CAL gain when treating interproximal / infrabony defects was approximately 3.17 mm when considering non-bioabsorbable barriers with and without graft material (combining Tables 3 and 4), and 2.96 mm when considering all bioabsorbable barriers with and without graft material (combining Tables 5, 6, and 7). These results fall somewhat short of the 4.2 mm found by Laurell and colleagues when considering all membranes, both non-bioabsorbable and bioabsorbable, and not distinguishing whether or not graft material was used (1). Laurel and colleagues included research from 3 articles which utilized a specific bioabsorbable, polylactic acid membrane (Guidor AB, Huddinge, Sweden) which was available, but is not currently marketed in the United States. These 3 articles all reported CAL gains well above 4.0 mm, which therefore shifted their mean CAL gain higher. Otherwise, Laurell and colleagues would have reported a mean CAL gain relatively similar to our data.

In an elaborate statistical meta-analysis, Needleman et al. found that "… for GTR the weighted mean difference between test and control was 1.11 mm, …" and for "GTR + bone substitutes 1.25 mm," which is also consistent with our findings (77). However, Needleman and colleagues grouped all non-bioabsorbable and bioabsorbable membranes together in their analysis. Their article does point out the major limitation of meta-analysis studies of GTR; that is, a "marked variability between studies." (77). In reviewing the source articles, there appears to be a chronological trend towards standardizing the studies to the extent, for instance, that in more recent articles the number of walls of the bony defects are specified, and subjects who smoke are now being excluded from the studies.

In a 2003 systematic review, Murphy and Gunsolley found that "… GTR was favored over open flap debridement (OFD) therapies ($P < 0.0001$)." (79). Unlike our results, Murphy and Gunsolley found no differences "… among barrier types, but barrier types could explain some heterogeneity in the results." The authors analyzed articles in two main categories: Intrabony defects and Furcation defects. We only analyzed articles which dealt with Intrabony defects. For Murphy and Gunsolley, the total number of studies for the Intrabony defects category was 44. Their exclusion criteria are valid and their further evaluation of the methodologies revealed what we found regarding lack of standardization, ranging from the patients smoking to the length of the studies. Their study reflects a higher degree of evidence-based processing of the different articles compared to our inclusion/exclusion criteria. Thus, we identified and used 49 articles. On the other hand, Murphy and Gunsolley did not take into account the effect of the IPD on the final outcome; that is, they did not accomplish a normalization of the CAL gain, so that those studies with inherently deeper IPDs are not adjusted for the fact that a deeper IPD will provide a greater amount of CAL gain. We accomplished that normalization under the Simplistic Data Analysis above, and have those outcomes in Figs. 1 and 2. Muphey and Gunsolley did not find differences between barrier types. We did find differences between barrier types and whether grafts were or were not used.

Limitations. The meta-analysis procedures used in this work have inherent limitations. (a) Raw data was not available, therefore an overall standard deviation derived from the raw data was impossible to calculate. (b) Since each article involved a unique research protocol, there are bound to be at least subtle differences in population

inclusion criteria. For instance, some articles allowed smokers, others did not. (c) Finally, with the CAL gains dependent on the IPD, statistics involving correlations derived from raw data, and leading to the ability to compare to a specific reference IPD, are required for meaningful comparisons between barriers.

Conclusion. Non-bioabsorbable membranes without graft material, collagen membranes with graft material, and EMD with or without graft material were all found to be superior to OFD with or without graft material. In addition, polylactic acid derivatives without grafts were found to be superior to OFD without grafts, and non-bioabsorbables without graft material were found to be superior to collagen without graft material. Based on the lack of significant differences mentioned above, it would be rational to conduct 3 split-mouth prospective research studies in order to confirm: (a) whether the CAL gain using non-bioabsorbable barriers with graft material is or is not statistically different from OFD with or without graft material; (b) whether the CAL gain using collagen without graft material is or is not statistically different from OFD with or without graft material; and (c) whether the CAL gain using the newer generation of polylactic acid is or is not statistically different from OFD with graft material. The following constraints are suggested: (a) Intrabony defects which are as identical as possible; (b) Patients who are healthy and do not smoke; and (c) Standardization of the use of antibiotics and root preparation. Also, in accordance with Greenstein and Lamster, a power analysis, a sample size determination, and a definition of a clinically relevant threshold for CAL gain should be established prior to commencement of the study (75).

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