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Ten-year results following treatment of intra-bony defects with enamel matrix proteins and guided tissue regeneration

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Abstract

Background: Surgery utilizing an enamel matrix protein derivative (EMD) or guided tissue regeneration (GTR) has been shown to promote periodontal regeneration.

Aim: To evaluate the 10-year results following treatment with EMD, GTR, EMD+GTR, and open flap debridement (OFD).

Material and Methods: Thirty-eight patients out of an initial group of 56 participants were treated with one of the four modalities. Results were evaluated before surgery, at 1 year, and at 10 years. Primary outcome variable was CAL change.

Results: Treatment with EMD yielded a mean CAL gain of 3.4 ± 1.0 mm ($p<0.001$) and 2.9 ± 1.4 mm ($p<0.001$) at 1 and 10 years, respectively. GTR resulted in a mean CAL gain of 3.2 ± 1.4 ($p<0.001$) at 1 year and 2.8 ± 1.2 mm ($p<0.001$) at 10 years. Mean CAL gain in the EMD+GTR group was of 3.3 ± 1.1 mm ($p<0.001$) and 2.9 ± 1.2 mm ($p<0.001$) at 1 and 10 years, respectively. Treatment with OFD demonstrated a mean CAL gain of 2.0 ± 1.2 mm ($p<0.01$) at 1 year and 1.8 ± 1.1 mm ($p<0.01$) at 10 years. Compared with OFD, the three regenerative treatments resulted in statistically significant ($p<0.05$) higher CAL gain, at both 1 and 10 years. The CAL change between 1 and 10 years did not present statistically significant differences in any of the four groups.

Conclusion: The present results indicate that the clinical outcomes obtained with all four approaches can be maintained over a period of 10 years.

Key words: bioresorbable membranes; enamel matrix protein derivative; guided tissue regeneration; long-term results; regenerative periodontal therapy

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The goal of regenerative periodontal therapy is to completely restore the tooth's supporting apparatus, which has been lost due to inflammatory periodontal disease or injury and is characterized by the formation of new cementum with inserting collagen fibers, new periodontal ligament (PDL), and new alveolar bone (Karring et al. 2003).

Several treatment modalities such as the use of different types of bone grafts, root surface demineralization, guided tissue regeneration (GTR), growth factors, or the application of an enamel matrix protein derivative (EMD) have been used with varying degrees of success in order to accomplish this goal (Bowers et al. 1989, Lynch et al. 1991, Brunsvold & Mellonig 1993, Lowenguth & Blieden 1993, Hammarström 1997, Karring et al. 2003). Treatment with GTR involves the placement of a bioresorbable or non-bioresorbable barrier membrane over the periodontal defects and the denuded root surfaces, thus allowing PDL and bone cells to selectively repopulate the isolated spaces (Karring et al. 2003). The rationale for the clinical use of EMD is the observation that enamel matrix proteins (EMPs) are deposited along the surface of developing tooth roots before cementum formation (Hammarström 1997). Findings from in vitro studies indicate that EMD may modulate the behaviour of a variety of dental and non-dental cell types by upregulating cAMP levels,

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inducing the synthesis and secretion of TGF-β and IL-6 in PDL cells and gingival fibroblasts, and stimulating the proliferation of pre-osteoblasts and the differentiation of immature osteoblasts (Schwartz et al. 2000, Van der Pauw et al. 2000, Lyngstadaas et al. 2001, Okubo et al. 2003). It has also been suggested that EMD may act as a cytostatic agent on cultured epithelial cells and may even inhibit dental plaque vitality (Kawase et al. 2000, Sculean et al. 2001a, Arweiler et al. 2002). Thus, the available data seem to indicate that EMD may influence periodontal wound healing by an indirect stimulatory effect on the release of growth factors during periodontal wound healing and by inhibiting or at least retarding epithelial downgrowth (Kawase et al. 2000, Schwartz et al. 2000, Van der Pauw et al. 2000, Lyngstadaas et al. 2001, Okubo et al. 2003).

Observations from human histological case reports have provided evidence that periodontal regeneration may be accomplished following treatment with GTR or EMD (Nyman et al. 1982, Gottlow et al. 1986, Heijl 1997, Mellonig 1999, Sculean et al. 1999a, b, 2000a, Yukna & Mellonig 2000, Bosshardt et al. 2005, Majzoub et al. 2005). Data from controlled clinical studies have shown that both therapies may lead to an additional gain of clinical attachment level (CAL) when compared with open flap debridement alone (OFD) (Cortellini et al. 1996a, Tonetti et al. 2002, Esposito et al. 2005, Needleman et al. 2006). On the other hand, in intra-bony defects, no significant differences were found between treatment with EMD or GTR (Pontoriero et al. 1999, Sculean et al. 1999b, 2001b, Silvestri et al. 2000, Zucchelli et al. 2002).

Clinical studies on GTR have indicated that the short-term results can be maintained on a long-term basis in the great majority of cases (Gottlow et al. 1992, Cortellini et al. 1996b, De Sanctis & Zucchelli 2000, Sculean et al. 2001c, 2004, 2006, Eickholz & Hausmann 2002, Cortellini & Tonetti 2004, Eickholz et al. 2004, Stavropoulos & Karring 2004). On the other hand, the data presenting the long-term outcome following treatment of intra-bony defects with EMD are still more limited (Heijl et al. 1997, Sculean et al. 2001c, 2003, 2006, 2007a, b, Francetti et al. 2004, Rasperini et al. 2005, Heden & Wennström 2006). Moreover, up to now, there are virtually no data from prospective controlled clinical studies evaluating the clinical results obtained in intra-bony defects following treatment with EMD or a combination of EMD+GTR over a period of up to 10 years.

Therefore, the aim of this follow-up study was to present the 10-year clinical results following treatment of intra-bony defects with EMD, GTR, a combination of EMD+GTR, and OFD.

Material and Methods

Study population

The study population consisted, at baseline, of a total of 56 patients, which were included in the study based on signed informed consent (Sculean et al. 2001b). The study was in accordance with the Helsinki Declaration of 1975, as revised in 1983. The 5-year results of the study have been reported previously (Sculean et al. 2004). Each patient received verbal and written explanations about the possible risks of the study and the possibility to withdraw at any time. All patients had signed the informed consent form.

Criteria for patient selection were (1) presence of one intra-bony defect with a probing depth of at least 6 mm and an intra-bony component of at least 3 mm as detected on the radiographs, (2) no systemic diseases that could interfere with periodontal healing, (3) no use of antibiotics in the 6 months before treatment, and (4) good level of oral hygiene (i.e. a plaque index score PlI $\leqslant$ 1). Three months before surgery, all the patients received oral hygiene instructions and full mouth supra- and subgingival scaling and root planing under local anaesthesia.

The following clinical measurements were made 1 week before, at 1 year, and at 10 years after surgery by the same blinded and previously calibrated examiner (F. S.): plaque index (PlI) (Silness & Löe 1964), gingival index (GI) (Löe 1967), bleeding on probing (BOP), probing pocket depth (PPD), gingival recession (GR), and clinical attachment level (CAL). The measurements were made at six sites per tooth, mesiovestibular (mv), midvestibular (v), distovestibular (dv), mesiolingual (ml), midlingual (ml), and distolingual (dl), with the same type of manual periodontal probe (PCP 12, Hu-Friedy, Chicago, IL, USA). The cemento–enamel junction (CEJ) was used as a fixed reference for the CAL measurements. In cases where the CEJ was not clearly visible, a restoration margin was used for these measurements. Intra-oral photographs with the probe in place were made at all time points, in order to document and ensure the exact position of the probe.

Examiner calibration was performed at baseline, at 1, 5, and 10 years as follows: five patients, not enrolled in the study, and showing at least four teeth with probing depths of $\geqslant$6 mm on at least one aspect of each tooth, were evaluated by the examiner on two separate occasions, 48 h apart. Calibration was accepted if measurements at baseline and at 48 h were similar to the millimeter at $\geqslant$90%.

Surgical procedure

All surgical procedures were performed by the same surgeon (A. S.) at the Department of Periodontology and Conservative Dentistry, University of Saarland, Homburg, Germany. The surgeries were performed in the period between October 1996 and September 1997. After intra-crevicular incisions, full-thickness mucoperiosteal flaps were raised vestibularly and lingually. Vertical releasing incisions mesially or distally to the treated defects were performed only in cases where it was necessary for better access, or to achieve a better closure of the surgical site. All granulation tissue was removed from the defects, and the roots were thoroughly scaled and planed using hand and ultrasonic instruments. During surgery, the following measurements were made by the same examiner who performed all clinical measurements (F. S.): distance from the CEJ to the bottom of the defect (CEJ-BD), distance from the CEJ to the most coronal extension of the alveolar bone crest (CEJ-BC). The intra-bony component (INTRA) of the defects was defined as (CEJ-BD) – (CEJ-BC).

Randomization, for the generation of a true random sequence, was achieved using a random number table. After preparation of the surgical site, the randomization envelope was opened and the defects were assigned to one of the following treatments:

1. EMD: (Emdogain®, BIORA, AB, Malmö Sweden, now Straumann, Basel, Switzerland) (10 patients).
2. GTR: (Resolut®, first generation of the barrier, Gore-Tex, Flagstaff, AZ, USA) (10 patients).

3. Combination: EMD+GTR (nine patients).
4. OFD: nine patients).

When EMD or the combination of EMD+GTR were used, the root surfaces adjacent to the defects were conditioned for 2 min. with 24% EDTA gel (pH 6.7) (PrefGel®, BIORA AB, Malmö, Sweden, now Straumann, Basel, Switzerland) in order to remove the smear layer and thus allow EMD to precipitate onto a root surface free of organic remnants (Blomlöf et al. 1996). Subsequently, the defects and the adjacent mucoperiosteal flaps were thoroughly rinsed with sterile saline to remove residual EDTA remnants. After root conditioning, EMD was applied on the root surfaces according to the instructions given by the manufacturer.

After application of EMD, the flaps were repositioned coronally and closed with vertical or horizontal mattress sutures.

At the sites receiving GTR treatment, a bioresorbable membrane of an appropriate configuration was selected, trimmed, and adapted over the defect in such a manner that the entire defect and 2–3 mm of the surrounding alveolar bone were completely covered. The membrane was fixed to the same or to the neighbouring teeth with bioresorbable sutures (Dexon® II, Davis & Geck Inc., Manati, Puerto Rico).

At the sites receiving combined EMD+GTR treatment, the bioabsorbable membranes were first loosely adapted over the defects and, only after the application of EMD, tightly sutured to the same or to the neighbouring teeth.

The same surgical protocol was used for the control sites, however, without any additional procedure.

In all cases, the flaps were repositioned coronally and sutured with vertical or horizontal mattress sutures (5-0, Gore-Tex®, Flagstaff, AZ, USA) (Laurell et al. 1994).

Postoperative management and supportive periodontal therapy

All patients received antibiotics for 10 days (3×500 mg amoxicillin) to prevent postoperative complications. The postoperative care consisted of 0.2% chlorhexidine digluconate solution rinses twice a day for 6 weeks. Only after this period was tooth brushing resumed in the operated areas. The sutures were removed 14 days after the surgery. Recall appointments were scheduled every second week during the first 2 months following surgery, and then once per month for the first year, postoperatively. After the first year and during the remaining observation period of 10 years, patients were recalled every 3 months. During the 10-year observation period, the recall appointments, consisting mainly of reinforcement of oral hygiene measures and professional supragingival tooth cleaning, were performed by one of the two dentists (A. K. or A. M.), who were involved in neither the surgical part of the study nor the data recording.

Statistical analysis

The statistical analysis was performed using a software programme (SPSS® for Windows version 12.0, SPSS Inc., Chicago, IL, USA).

The primary outcome variable was CAL change. In the calculations, only the deepest measure per tooth was included. The same site was measured at 1 and 10 years. First, ANOVA was conducted to determine whether differences existed among the groups. Then, a post hoc range test and pairwise multiple comparisons of all possible combinations were performed using the Scheffé's *F*-test. The *a* error was set at 0.05. The paired *t*-test was used to compare the data from baseline to those at one, and at 10 years, for each treatment group. The power of the study, given 1 mm as a significant difference between groups, was calculated to be 0.60.

Owing to the fact that the number of smokers was very limited (i.e. one in the EMD group, none in the GTR group, one in the EMD+GTR group, and none in the OFD group), no analysis was performed in order to evaluate the effect of smoking on the clinical outcome.

Results

Thirty-eight patients with a mean age of (52 ± 12.6 years) completed the 10-year evaluation. Reasons for drop out were death (one patient in the EMD group), moving in another area (one patient in the EMD group, two in the GTR group, two in the EMD+GTR group, and one in the control group), non-compliance (the remaining 11 patients). Non-compliant patients were those who refused to attend the offered regular maintenance programme (four visits per year, including oral hygiene reinforcement and professional tooth cleaning). These patients were no longer interested in visiting the department for evaluation of their periodontal status. Thus, in the present analysis, only the data of the 38 available patients have been included.

The postoperative healing was generally uneventful and consisted mainly of postoperative swelling and/or diarrhoea due to the antibiotic regimen. The diarrhoea disappeared following completion of the antibiotic regimen. Neither allergic reactions nor suppuration or abscesses were observed after any of the treatments. Membrane exposure occurred at three out of the 10 sites treated with GTR and at two out of the nine sites treated with EMD+GTR. The exposed parts of the membranes disintegrated within a few days after exposure, without any side effects.

The means for PlI, GI, and BOP of the full mouth for all four treatment groups at baseline and after 1 and 10 years are summarized in Table 1. Frequency distributions for PlI, GI, and BOP at the treated sites for all four treatment groups at baseline and after 1 and 10 years are summarized in Tables 2–4. The mean PlI did not reveal a statistically significant difference between the groups at baseline and after 1 and 10 years. Although at 10 years the PlI increased slightly in all four treatment groups, this difference was not found to be statistically significant when compared with the baseline or 1-year results. A statistically significant difference was observed in all four treatment groups when comparing the 1- and 10-year GI and BOP values to the baseline values ($p < 0.001$). However, no statistically significant differences were observed between 1- and 10-year results (Tables 1–4).

The distribution of the defects according to their configuration is presented in Table 5.

The baseline defect characteristics are presented in Table 6. No statistically significant difference in the initial depth of the intra-bony component was found between the four groups.

The sites treated with EMD demonstrated a mean CAL change from 10.4 ± 1.6 to 7.0 ± 1.3 mm ($p < 0.001$) and 7.5 ± 1.4 mm ($p < 0.001$) at 1 and 10 years, respectively (Table 7). Mean CAL gain at 10 years was 2.9 mm (CI 95% 1.7–4.0). Treatment with GTR resulted in a mean CAL change from 10.3 ± 1.6 to 7.1 ± 1.2 mm ($p < 0.001$)

at 1 year and 7.5 ± 1.2 mm ($p < 0.001$) at 10 years (Table 7). Mean CAL gain at 10 years was 2.8 mm (CI 95% 1.9–3.8). At the sites treated with EMD+GTR, mean CAL changed from 10.2 ± 1.4 to 6.9 ± 1.1 ($p < 0.001$) and 7.3 ± 1.2 mm ($p < 0.001$) at 1 and 10 years, respectively (Table 7). At 10 years, mean CAL gain was 2.9 mm (CI 95% 1.8–3.7). Treatment with OFD yielded a mean CAL change from 10.4 ± 1.3 to 8.4 ± 1.2 mm ($p < 0.001$) at 1 year and to 8.6 ± 1.0 mm ($p < 0.001$) at 10 years (Table 7). At 10 years, mean CAL gain was 1.8 mm (CI 95% 0.8–2.4).

At both 1 and 10 years, all four treatments led to statistically significant CAL gain compared with baseline ($p < 0.001$). Compared with OFD, the three regenerative treatments resulted in statistically significant ($p < 0.05$) higher CAL gain, at both 1 and 10 years. The CAL change between 1 and 10 years did not present statistically significant differences in any of the four groups.

The frequency distribution of CAL gain compared with baseline is shown in Table 8. At 10 years, a CAL gain of ⩾3 mm was found in six defects of the EMD and GTR groups, respectively, and in five defects of the EMD+GTR group. A CAL gain of ⩾3 mm was measured in one defect of the OFD group.

Table 1. Plaque index (PlI), gingival index (GI), and bleeding on probing (BOP) of the full mouth at baseline, and at 1 and 10 years following treatment

Parameter	Treatment	Baseline	1 year	*p* value (baseline–1 year)	10 years	*p* value (1 year–10 years)
PlI						
	EMD mean (± SD)	0.8 ± 0.4	0.9 ± 0.4	NS	1.2 ± 0.8	NS
	GTR mean (± SD)	0.7 ± 0.5	0.7 ± 0.5	NS	1.3 ± 0.7	NS
	EMD+GTR mean (± SD)	0.9 ± 0.3	0.7 ± 0.4	NS	1.1 ± 0.8	NS
	OFD mean (± SD)	0.6 ± 0.5	0.7 ± 0.4	NS	1.0 ± 0.4	NS
GI						
	EMD mean (± SD)	1.7 ± 0.5	0.6 ± 0.4	<0.001	1.0 ± 1.0	NS
	GTR mean (± SD)	1.8 ± 0.8	0.8 ± 0.6	<0.001	1.1 ± 0.9	NS
	EMD+GTR mean (± SD)	1.6 ± 0.5	0.6 ± 0.5	<0.001	1.0 ± 0.8	NS
	OFD mean (± SD)	1.7 ± 0.8	0.7 ± 0.7	<0.001	1.0 ± 0.7	NS
BOP (%)						
	EMD mean (± SD)	50 ± 5.7	30 ± 3.2	<0.001	40 ± 4.4	NS
	GTR mean (± SD)	50 ± 6.1	30 ± 3.9	<0.001	40 ± 3.7	NS
	EMD+GTR mean (± SD)	56 ± 4.0	33 ± 4.1	<0.001	44 ± 3.9	NS
	OFD mean (± SD)	56 ± 5.9	33 ± 3.5	<0.001	44 ± 4.3	NS

Discussion

The results of the present study indicate that treatment of intra-bony defects with EMD, GTR, EMD+GTR, and OFD

Table 2. Frequency distribution of PlI at the treated sites, at baseline and at 1 and 10 years

PlI	EMD, no. (%)			GTR, no. (%)			EMD+GTR, no. (%)			OFD, no. (%)		
	baseline	1 year	10 years	baseline	1 year	10 years	baseline	1 year	10 years	baseline	1 year	10 years
0	8 (73%)	9 (80%)	6 (60%)	7 (70%)	8 (70%)	6 (60%)	7 (78%)	7 (78%)	6 (67%)	7 (78%)	8 (89%)	6 (67%)
1	2 (27%)	1 (20%)	4 (40%)	3 (30%)	2 (20%)	4 (40%)	2 (22%)	2 (22%)	3 (33%)	2 (22%)	1 (11%)	3 (33%)
2												
3												
Total no.		10			10			9			9	

PlI, plaque index; EMD, enamel matrix protein derivative; GTR, guided tissue regeneration; OFD, open flap debridement.

Table 3. Frequency distribution of GI at the treated sites, at baseline and at 1 and 10 years

GI	EMD, no. (%)			GTR, no. (%)			EMD+GTR, no. (%)			OFD, no. (%)		
	baseline	1 year	10 years	baseline	1 year	10 years	baseline	1 year	10 years	baseline	1 year	10 years
0	4 (40%)	8 (80%)	5 (50%)	5 (50%)	8 (80%)	7 (70%)	4 (45%)	7 (78%)	6 (67%)	5 (56%)	6 (67%)	6 (67%)
1	4 (40%)	2 (20%)	4 (40%)	4 (40%)	2 (20%)	3 (30%)	4 (45%)	2 (22%)	3 (33%)	4 (44%)	3 (33%)	3 (33%)
2	1 (20%)		1 (10%)	1 (10%)			1 (12%)					
3												
Total no.		10			10			9			9	

GI, gingival index; EMD, enamel matrix protein derivative; GTR, guided tissue regeneration; OFD, open flap debridement.

Table 4. Frequency distribution of BOP at the treated sites, at baseline and at 1 and 10 years

BOP	EMD, no. (%)			GTR, no. (%)			EMD+GTR, no. (%)			OFD, no. (%)		
	baseline	1 year	10 years	baseline	1 year	10 years	1 year	10 years	5 years	baseline	1 year	10 years
+	8 (80%)	1 (10%)	4 (40%)	7 (70%)	2 (20%)	4 (40%)	6 (67%)	3 (33%)	5 (56%)	7 (78%)	2 (22%)	4 (44%)
−	2 (20%)	9 (90%)	6 (60%)	3 (30%)	8 (80%)	6 (60%)	3 (33%)	6 (67%)	4 (44%)	2 (22%)	7 (78%)	5 (56%)
Total no.		10			10			9			9	

BOP, bleeding on probing; EMD, enamel matrix protein derivative; GTR, guided tissue regeneration; OFD, open flap debridement.

may result in statistically significant reductions in PPD and gains of CAL, which can be maintained over a period of 10 years. No statistically significant differences between the three regenerative procedures were found in any of the investigated clinical parameters at both 1 and 10 years after therapy. However, all three regenerative treatments revealed statistically significantly higher gains of clinical attachment when compared with OFD alone.

Table 5. Distribution and configuration of treated defects

	EMD	GTR	EMD+GTR	OFD
1–2 wall	3	3	1	2
2wall	6	6	7	5
3 wall	1	1	1	2

EMD, enamel matrix protein derivative; GTR, guided tissue regeneration; OFD, open flap debridement.

The finding that treatment of intra-bony defects with EMD may result on a short-term basis (up to 1 year) in statistically significantly improvements in PPD and CAL compared with baseline is generally in accordance with previous results (Heijl et al. 1997, Pontoriero et al. 1999, Okuda et al. 2000, Silvestri et al. 2000, Froum et al. 2001, Sculean et al. 2001b, Tonetti et al. 2002, Zucchelli et al. 2002, Cortellini & Tonetti 2007a, b, Cortellini et al. 2008, Jepsen et al. 2008, Ozcelic et al. 2008). Recent data, however, indicate that the clinical outcomes of CAL gain and defect resolution following regenerative treatment with EMD may be further improved by using a minimal invasive surgical technique under an operation microscope (Cortellini & Tonetti 2007a, b, Cortellini et al. 2008). In these studies, mean CAL gain measured 4.8 ± 1.9 and 4.9 ± 1.7 mm, respectively, thus pointing to the significant influence of the surgical technique upon the obtained results (Cortellini & Tonetti 2007a, b, Cortellini et al. 2008).

Table 8. Frequency distribution of CAL gain at 10 years

	CAL gain 0–2 mm	CAL gain ⩾3 mm
EMD	4	6
GTR	4	6
EMD+GTR	4	5
OFD	8	1

EMD, enamel matrix protein derivative; GTR, guided tissue regeneration; OFD, open flap debridement.

The present results are also in line with the conclusions of a recent systematic review, which has analyzed the potential benefit of EMD when used in addition to OFD (Esposito et al. 2005). The results have shown that EMD-treated sites displayed statistically significant CAL improvements (i.e. mean difference 1.2 mm, 95% CI 0.7–1.7) when compared with OFD (Esposito et al. 2005). However, it is important to realize that until now there are no published 10-year data on the clinical outcome following treatment with EMD or EMD+GTR up to a period of 10 years, and therefore, a comparison with other long-term studies is difficult. On the other hand, the present 10-year results obtained with EMD are in agreement with previous results that have evaluated this treatment modality up to a period of 9 years (Heijl et al. 1997, Sculean et al. 2001c, 2003, 2006, 2007a, b, Francetti et al. 2004, Rasperini et al. 2005, Heden & Wennström 2006). In a controlled clinical trial comparing treatment of intra-bony defects with EMD with that with flap surgery, Heijl et al. (1997) reported, at 8 months, a mean CAL gain of 2.1 mm after treatment with EMD and 1.5 mm after flap surgery alone (control). In a 4-year follow-up study, a total of 46 intra-bony defects in 33 patients were consecutively treated with EMD (Sculean et al. 2003), and the results have indicated stable results at 1 year, postoperatively. Moreover, a re-entry surgery performed after 4 years in one case has demonstrated an almost complete fill of the intra-bony component. Recent data from a case series report have shown that the results can be maintained up to a period of 9 years (Sculean et al. 2007b). Similar findings were made in three cases that were re-entered after 7 years following treatment with EMD (Rasperini et al. 2005).

Table 6. Baseline defect characteristics expressed in mm (mean ± SD)

Treatment	PPD	GR	CAL	CEJ-BBD	CEJ-crest	Intra-bony depth
EMD	8.4 ± 1.9	2.0 ± 1.3	10.4 ± 1.6	11.3 ± 1.5	7.1 ± 1.3	4.2 ± 1.2
GTR	8.4 ± 1.7	1.9 ± 1.5	10.3 ± 1.6	11.1 ± 1.3	7.0 ± 1.2	4.1 ± 1.3
EMD+GTR	8.6 ± 1.5	1.6 ± 1.0	10.2 ± 1.4	11.0 ± 1.4	7.0 ± 1.3	4.0 ± 1.4
OFD	8.6 ± 1.5	1.8 ± 1.1	10.4 ± 1.3	11.4 ± 1.3	7.0 ± 1.4	3.9 ± 1.3

EMD, enamel matrix protein derivative; GTR, guided tissue regeneration; OFD, open flap debridement; PPD, probing pocket depth; GR, gingival recession; CAL, clinical attachment level; CEJ, cemento–enamel junction.

Table 7. Clinical parameters (in mm) at baseline and at 1 and 10 years

Parameter	Treatment	Baseline	1 year	*p* value (baseline – 1 year)	10 years	*p* value (1 year–10 years)
PPD						
	EMD mean (± SD)	8.4 ± 1.9	4.3 ± 1.2	<0.001	4.8 ± 1.1	NS
	GTR mean (± SD)	8.4 ± 1.7	4.2 ± 1.3	<0.001	5.0 ± 1.0	NS
	EMD+GTR mean (± SD)	8.6 ± 1.5	4.3 ± 1.3	<0.001	5.1 ± 1.2	NS
	OFD mean (± SD)	8.6 ± 1.5	4.9 ± 1.8	<0.001	5.1 ± 1.3	NS
GR						
	EMD mean (± SD)	2.0 ± 1.3	2.7 ± 1.2	<0.001	2.7 ± 1.1	NS
	GTR mean (± SD)	1.9 ± 1.5	2.9 ± 1.3	<0.001	2.5 ± 1.2	NS
	EMD+GTR mean (± SD)	1.6 ± 1.0	2.6 ± 1.0	<0.001	2.2 ± 1.1	NS
	OFD mean (± SD)	1.8 ± 1.1	3.5 ± 1.3	<0.001	3.5 ± 1.2	NS
CAL						
	EMD mean (± SD)	10.4 ± 1.6	7.0 ± 1.3	<0.001	7.5 ± 1.4	NS
	GTR mean (± SD)	10.3 ± 1.6	7.1 ± 1.2	<0.001	7.5 ± 1.2	NS
	EMD+GTR mean (± SD)	10.2 ± 1.4	6.9 ± 1.1	<0.001	7.3 ± 1.2	NS
	OFD mean (± SD)	10.4 ± 1.3	8.4 ± 1.2	<0.001	8.6 ± 1.0	NS

At both 1 and 10 years, treatment with EMD, GTR, and EMD+GTR resulted in statistically significant ($p<0.05$) higher CAL gain compared with OFD.

EMD, enamel matrix protein derivative; GTR, guided tissue regeneration; OFD, open flap debridement; PPD, probing pocket depth; GR, gingival recession; CAL, clinical attachment level.

The results obtained with GTR are also in agreement with those from previous clinical studies, which indicate that the clinical improvements obtained following this regenerative approach can be maintained over a longer period of time, provided that an optimal patient and defect selection are accomplished and that the patients are enrolled in an strict maintenance programme (Gottlow et al. 1992, Cortellini et al. 1996b, De Sanctis & Zucchelli 2000, Sculean et al. 2001c, 2006, Eicholz & Hausmann 2002, Cortellini & Tonetti 2004, Eickholz et al. 2004, Stavropoulos & Karring 2004, Nygaard-Østby et al. 2008). The present results are in line with those of a retrospective study that has evaluated a total of 175 patients treated with GTR (Cortellini & Tonetti 2004). These findings have suggested that the clinical improvements obtained with GTR can be maintained over a period of up to 16 years, and thus, this treatment approach represents an important modality for the long-term maintenance of severely compromised teeth.

It is interesting to note that in the present study, treatment with EMD+GTR has led to significant clinical improvements on both a short- and a long-term basis, although the improvements were not significantly higher when compared with those obtained with EMD or GTR alone. Comparable results were reported in an experimental study in monkeys, evaluating treatment of experimentally created intra-bony defects with EMD, GTR, EMD+GTR, or OFD (Sculean et al. 2000b). The histological evaluation has indicated that treatment with EMD+GTR may enhance formation of new attachment and new bone, but the amount of the newly formed tissues was not superior to treatment with EMD alone or GTR alone. All these data taken together seem to suggest that a combination of EMD+GTR may not additionally improve the results.

An important aspect of the present study is the finding that the improvements obtained with OFD were also maintained over 10 years. Although observations from histological studies have failed to show predictable regeneration of the attachment apparatus following OFD (Caton et al. 1980, Bowers et al. 1989, Sculean et al. 2000b), our results indicate that this treatment option may also lead to significant and stable clinical results on a long-term basis. These findings are in agreement with previous data, suggesting that OFD may still be considered a valuable option for treating certain intra-bony defects, if an optimal plaque control level is ensured (Rosling et al. 1976, Polson & Heijl 1978, Tonetti et al. 2002, Eickholz et al. 2008).

In all four groups, a slight, statistically non-significant loss of mean CAL was measured between the 1- and 10-year evaluation period, which, in turn, was probably because of the slight increase (statistically non-significant) of mean PPD. Although at 10 years the increase in PlI, GI, and BOP did not reach statistical significance compared with the baseline and 1-year values, it cannot be excluded that plaque accumulation might have led to inflammation and loss of CAL. The fact that no differences were found in the four groups in terms of PlI, GI, and BOP between the 1- and 10-year results seems to indicate that these patients displayed a good level of oral hygiene. On the other hand, it should be noted that in the present analysis only 38 out of the 56 patients were included, and obviously, these 38 patients were those who regularly attended the maintenance care programme. These findings are in line with previous results, which have demonstrated that the clinical outcomes obtained with GTR can only be maintained if the patients are enrolled in a regular maintenance programme (Cortellini et al. 1996b). Therefore, it cannot be excluded that, if data were available, the rest of 18 patients might have led to different clinical results at 10 years.

Another important factor that has been shown to strongly influence the outcome of regenerative periodontal treatment is smoking (Tonetti et al. 1995). In the present patient population, only two out of the 38 patients were smokers, and therefore, no further analysis was possible. Furthermore, it should be kept in mind that because of the low number of patients, the study has a low statistical power, and thus the findings need to be interpreted with caution. Despite that, we figured on an ''intention to treat analysis'', and a full application of the intention to treat approach is possible only when complete outcome data are available for all randomized subjects. However, in the present study, it was not possible to follow-up those who withdrew from treatment, and this is particularly important for the implementation of an intention to treat analysis (Lachin 2000). On the other hand, it needs to be pointed out that currently, no consensus exists about how missing responses should be handled in an intention-to-treat analysis (Hollis & Campbell 1999).

In conclusion, within its limits, the present study has shown that in non-smoking patients on a strict plaque control programme, the clinical outcomes obtained with all four approaches can be maintained over a period of 10 years.

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Clinical Relevance

Scientific rationale for the study: The data on the long-term outcomes following treatment with EMD, GTR, EMD+EMD, or OFD are limited.
Principal findings: At 1 and 10 years after surgery, all four treatments resulted in statistically significantly higher CAL compared with baseline. The three regenerative modalities resulted in higher CAL gains than OFD. The combination of EMD+GTR has failed to yield any additional improvement compared with EMD or GTR alone.
Practical implications: The clinical results obtained with all four treatments can be maintained over a period of 10 years.