

# Microsurgical access flap in conjunction with enamel matrix derivative for the treatment of intra-bony defects: a controlled clinical trial

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## Abstract

**Objectives:** The aims of this controlled study were to clinically and radiographically evaluate the effect of a microsurgical approach for the treatment of intra-bony defects with and without an enamel matrix derivative (EMD). Parts of this study population were already published by Wachtel and colleagues in 2003.

**Material and Methods:** Seventy intra-bony defects were randomly assigned to a microsurgical access flap with application of EMD (test group) and on the contralateral side to a microsurgical access flap alone (control group). Clinical and radiographic parameters were assessed at baseline and after 6 and 12 months.

**Results:** Both test and control treatments resulted in a statistically significant mean clinical attachment level (CAL) gain, probing pocket depth (PPD) reduction and radiographic bone fill. The test group yielded statistically significantly more CAL gain, PPD reduction and radiographic bone fill than the control group. Gingival recession increase after 12 months averaged 0.5 and 0.7 mm for the test and control groups, and did not reach statistical significance. Two weeks after surgery, primary wound closure was maintained in 91% of the test sites and 97% of the control sites.

**Conclusion:** The combination of a microsurgical access flap with EMD seems to be superior to open flap debridement in terms of PPD reduction, CAL gain and radiographic bone fill. In the test as well as the control group, primary wound closure was successfully achieved.

Key words: enamel matrix derivative; intra-bony defect; microsurgical access flap

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## Conflict of interest and sources of funding statement

The authors declare that they have no conflicts of interests.

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Guided tissue regeneration (GTR) of lost periodontal attachment has been proven to be a successful treatment of intra-bony defects (Becker & Becker 1993, Cortellini et al. 1993a, b, Weltman et al. 1997). In

a recent review, Needleman et al. (2005) demonstrated that GTR had a greater effect on probing measures of periodontal treatment than open flap debridement. However, most of the studies also report on a high variation of the clinical results (Chung et al. 1990, Cortellini et al. 1990, Selvig et al. 1992, Needleman et al. 2001); few studies found no clinical difference between open flap debridement and GTR treatment (Pritlove-Carson et al. 1995, Mayfield et al. 1998).

The systematic assessment of the relevant factors associated with heterogeneity of periodontal regenerative outcomes provided evidence that besides patient and defect factors surgical factors also had an enormous impact on the outcome of periodontal regeneration (Tonetti et al. 1993, 1995, 1996, Machtei et al. 1994, Falk et al. 1997). In particular, the need to preserve soft tissues in order to attempt primary closure to submerge grafts, biologic active

substances and the blood clot became evident. Exposure of barrier membranes to the oral environment is described as a frequent complication, being present in 50–100% of the sites treated with traditional flap techniques and barrier membranes (Selvig et al. 1993, Murphy 1995). The inevitable bacterial contamination of the exposed barriers and subsequently of the underlying healing tissues were found to be one of the reasons for a reduced clinical response of these sites compared with those areas that remained completely closed during the entire healing process. Several studies indicate that the outcome of GTR procedures can be negatively altered by bacterial contamination of non-resorbable or resorbable membranes (Selvig et al. 1992, Nowzari et al. 1995, De Sanctis et al. 1996a, b, Zucchelli et al. 1997).

In contrast, Cortellini & Tonetti (2005) achieved clinical attachment level (CAL) gains between 5.4 and 6.8 mm and primary flap closure in over 90% of the cases when following a microsurgical approach strategy in combination with a papilla preservation flap. In a clinical study, Wachtel et al. (2003b) corroborated the results, obtaining over 90% of primary wound closure using a microsurgical procedure.

Scientific effort has elucidated another option for periodontal tissue regeneration: enamel matrix proteins play a major role in the development of periodontal tissues and show effectiveness in the regeneration of the periodontium (Gestrelus et al. 1997, Hammarstrom 1997a, b, Heijl et al. 1997, Mellonig 1999). Human histologic studies further revealed that improvements in clinical parameters after the application of enamel matrix proteins in part correlated with the formation of new cementum, new periodontal ligament and new bone (Mellonig 1999, Sculean et al. 1999b, 2000). Results from controlled clinical studies have also shown that treatment outcomes after application of enamel matrix derivative (EMD) may be comparable with those achieved by the GTR technique in intra-bony defects and stable over a long-term follow-up (Sculean et al. 1999a, b, 2008, Esposito et al. 2004, 2005).

Cortellini and colleagues showed that according to the results from GTR procedures a greater wound stability and limitation in patient morbidity can be achieved by using a minimally invasive, high-power magnification-assisted surgical technique (Cortellini & Tonetti

2007a, b). Wachtel et al. (2003b) presented preliminary data from a prospective clinical trial, demonstrating that when a microsurgical approach was used, primary wound closure could be reached in over 90% of all the cases. Furthermore, in terms of probing pocket depth (PPD) reduction and CAL gain, the combination of a microsurgical access flap with EMD yielded better results when compared with the microsurgical access flap alone (Wachtel et al. 2003b).

This study reports on the use of a microsurgical papilla preservation technique with and without the use of EMD. The results presented represent a second analysis on a larger group of patients comprising additional radiographic evaluation that also includes original data previously published by Wachtel et al. (2003b).

## Material and Methods

### Study population

The study population consisted of 19 patients (13 females, six males) with a mean age of 46.1 years (ranging from 28 to 63 years), who gave their informed consent. An original study was published 6 years ago and included part of this population (11 patients) (Wachtel et al. 2003b). All patients were recruited by the principal investigator and one co-investigator and treated at the Institute for Periodontology and Implantology Munich, Germany. All patients completed the 12-month follow-up examination.

The inclusion criteria were:

- (1) good general health;
- (2) no use of antibiotics during the past 6 months;
- (3) good oral hygiene standard;
- (4) smoking status of <10 cigarettes/day;
- (5) presence of advanced periodontal tissue destruction;
- (6) presence of a minimum of one pair of similar, contra-lateral, intra-bony defects located in the inter-proximal area in the anterior and premolar teeth in either the maxilla or the mandible (the mesial aspect of the first molar, without furcation involvement, was also accepted by the study protocol);
- (7) the selected defects had to exhibit a PPD of  $\geq 6$  mm and a depth of the intra-bony defect component of  $\geq 3$  mm, as assessed by intra-oral

radiographs. One-, 2- and 3-wall defects were included.

Altogether, 70 intra-bony defects with a pre-surgical pocket depth  $\geq 6$  mm were included.

Before the start of the study, each patient received initial periodontal therapy consisting of thorough oral hygiene instructions and full-mouth scaling and root planing under local anaesthesia. Six weeks after completion of the initial therapy, a re-evaluation was performed to confirm that the patients met all the inclusion criteria for the study.

### Clinical parameters

The following measurements were obtained by one blinded investigator at baseline and at 6 and 12 months after surgery according to Wachtel et al. (2003b).

### PPD

The depths of the periodontal pockets were measured as the distance from the gingival margin to the base of the pocket to the nearest 1 mm with a manual pressure-sensitive periodontal probe (DB 764 R, Aesculap, Tuttlingen, Germany) calibrated at a force of 0.2 N.

### CAL

Probing CAL was measured with the same periodontal probe as the distance from the cemento-enamel junction to the base of the pocket.

The PPD and CAL measurements were performed both from the buccal and the lingual aspects of the inter-proximal sites. For each parameter, the larger of the two values was identified and recorded.

### Gingival recession (GR)

The amount of GR at the experimental site was measured with the periodontal probe as the distance from the cemento-enamel junction to the gingival margin.

### Oral hygiene status

Full-mouth plaque scores were recorded as the percentage of inter-proximal surfaces, which revealed the presence of plaque using the approximal plaque index (API) (Lange et al. 1977).

### Gingival inflammation

Bleeding on probing to the base of the pocket (BOP) was determined and the % of BOP-positive sites was recorded.

### Early wound-healing index (EHI)

Postoperative healing was assessed using the EHI (Wachtel et al. 2003b). Five stages of healing can be distinguished:

- 1 Complete flap closure – no fibrin line in the inter-proximal area.
- 2 Complete flap closure – fine fibrin line in the inter-proximal area.
- 3 Complete flap closure – fibrin clot in the inter-proximal area.
- 4 Incomplete flap closure – partial necrosis of the inter-proximal tissue.
- 5 Incomplete flap closure – complete necrosis of the inter-proximal tissue.

The EHI was recorded at 1 and 2 weeks postoperatively.

### Treatment procedures

The paired intra-bony defects were randomly assigned by the surgeon (flipping a coin) to receive either the test or the control treatment, which both consisted of a microsurgical access flap procedure aiming at maximal tissue preservation (Figs 1–6). In patients contributing more than one pair of defects, all defects located in one quadrant were assigned to the same treatment modality. Both the test and the control sites were treated during the same surgical session. All surgeries were performed by the same



Fig. 1. Pre-operative measurement of the intra-bony pocket.



Fig. 2. Intra-sulcular incision on the buccal aspect.



Fig. 3. Preparation of the inter-proximal soft tissue to the lingual side.

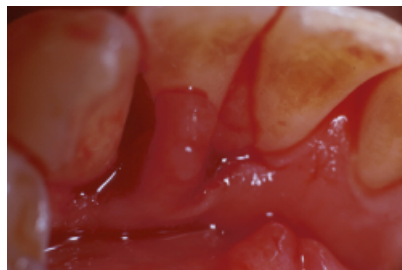


Fig. 4. The inter-proximal soft tissue is mobilized to the lingual aspect.

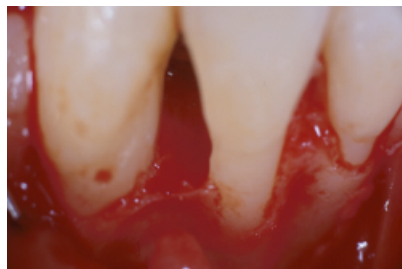


Fig. 5. Evaluation and cleaning of the intra-bony defect.



Fig. 6. Primary wound closure with a 7-0 polypropylene suture.

surgeon using microsurgical instruments (Mamadent, ADsystems, Vaterstetten, Germany) according to the modified papilla preservation technique (Cortellini et al. 1995b). During surgery, the intra-bony defect component was measured as the distance from the crest of the marginal bone to the deepest point of the bone defect. The exposed root sur-

faces of the test sites were conditioned with a 24% EDTA gel (Prefgel<sup>®</sup>, Straumann, Basel, Switzerland), followed by EMD (Emdogain<sup>®</sup>, Straumann) application while the control sites were left with its blood clot. Primary flap closure was achieved by a microsurgical two-layered suturing technique with a 7-0 polypropylene suture material (Seralene<sup>®</sup>, Serag-Wiesner AG, Naila, Germany). Postoperative healing was evaluated by the EHI (Wachtel et al. 2003b) at 1 and 2 weeks after surgery.

### Radiological evaluation

Standardized peri-apical radiographs were obtained immediately before surgery, and at 6 and 12 months of follow-up. Individually customized bite blocks were used to obtain reproducible films at each radiographic control. The X-rays served to evaluate the intra-bony radiographic parameters. The standardized X-rays were scanned, digitalized and corrected for grey levels according to the methods described by Fourmoussis et al. (1994a, b). All radiographs were evaluated by a single examiner blind to the treatment. Intra-bony defect depth was assessed from peri-apical radiographs using the computer-aided technique, using image analysis software (Image Tool, University of Texas, TX, USA). The defect depth was considered a primary outcome and measured as the distance between the cemento-enamel junction or the margin of the restoration and the deepest point of the intra-bony defect.

### Statistical evaluation

The values of PPD, CAL, GR and the radiological measurements were expressed as means  $\pm$  SEM of 35 pairs of defects in 19 patients at baseline, 6 and 12 months after surgery. Because several patients contributed with more than one pair of defects, the means for test and control sites were calculated in every patient, and the resulting 19 pairs were subjected to two-tailed *t*-tests for paired comparisons. To correct for multiple testing, a *p*-value of 0.025 was considered statistically significant.

### Results

#### EHI (Table 1, Fig. 7)

One week after surgery, the mean EHI values were  $1.77 \pm 0.84/0.69$  for both

Table 1. Early wound healing index at 1 and 2 weeks post-operative

n = 35	1 week	2 weeks
EMD	1.77 ± 0.84	1.37 ± 0.88
Control	1.77 ± 0.69	1.17 ± 0.57
p-values	1.0	0.128

EMD, enamel matrix derivative.

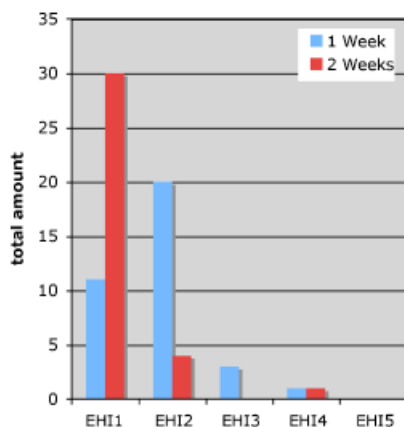


Fig. 7. Schematic drawing of the early wound healing index (EHI) after 1 and 2 weeks. Note that primary wound closure (EHI1, EHI2, EHI3) could be obtained in 91% of the test and 97% of the control sites.

the test and the control group. After 2 weeks, these values were reduced to  $1.37 \pm 0.88$  in the test and  $1.17 \pm 0.57$  in the control sites. None of the sites demonstrated complete necrosis of the inter-proximal tissue. Incomplete flap closure resulting in a negative architecture of the inter-proximal tissue was present in three EMD-sites and in one control site after 2 weeks. In 91% of the test sites and in 97% of the control sites, treatment resulted in a complete flap closure that was maintained up to 2 weeks.

#### Plaque and bleeding scores (Tables 2 and 3)

The success of initial periodontal therapy can be demonstrated, when the API is reduced <35%. This was accomplished at the time of surgery. Twelve months after surgery, the API values could be further reduced <25%. This difference was statistically significant ( $p < 0.001$ ). Full-mouth bleeding scores averaged 26% at baseline and 6% and 0% after 6 and 12 months in the test group. In the control group, the bleeding scores could be maintained from 29% at

Table 2. API at baseline, 6- and 12-month post-operative

n = 35	Baseline	6 months	12 months	p-value
API	$30.53 \pm 3.89$	$27.16 \pm 7.71$	$24.68 \pm 5.88$	<0.001

The difference between baseline and 12-month follow-up was statistically significant. API, approximal plaque index.

Table 3. Percentage of BOP-positive sites at different treatment intervals

n = 35	Baseline (%)	6 months (%)	12 months (%)
EMD	26	6	0
Control	29	29	37

BOP, base of the pocket; EMD, enamel matrix derivative.

Table 4. Results at 6- and 12 month after EMD and control treatment expressed in mm (mean ± SEM)

n = 35	6 months	12 months
PPD-reduction		
EMD	$3.5 \pm 0.2$	$4.2 \pm 0.3$
Control	$2.1 \pm 0.2$	$2.4 \pm 0.3$
p-values	<0.001	<0.001
CAL		
EMD	$2.7 \pm 0.3$	$3.7 \pm 0.4$
Control	$1.6 \pm 0.3$	$1.7 \pm 0.3$
p-values	0.0015	<0.0001
GR increase		
EMD	$0.6 \pm 0.2$	$0.5 \pm 0.2$
Control	$0.5 \pm 0.2$	$0.7 \pm 0.2$
p-values	>0.0025	>0.0025
Bone fill		
EMD	$1.4 \pm 0.2$	$2.5 \pm 0.4$
Control	$0.7 \pm 0.1$	$1.1 \pm 0.1$
p-values	0.039	<0.001

PPD, probing pocket depth; EMD, enamel matrix derivative; GR, gingival recession; CAL, clinical attachment level.

baseline to 29% after 6 months and increased to 37% at 12 months.

#### Reduction of PPD (Table 4, Fig. 11)

In comparison with the baseline data, both the test and the control sites showed a marked and statistically significant reduction of PPD. The mean PPD reduction was  $3.5 \pm 0.2$  and  $4.2 \pm 0.3$  mm for the test sites and  $2.1 \pm 0.2$  and  $2.4 \pm 0.3$  mm for the control sites after 6 and 12 months, respectively. The difference between PPD reductions after 6 and 12 months was statistically significant in the EMD-treated group ( $p < 0.001$ ), indicating an additional pocket reduction between 6 and 12 months. The PPD reduction in the test sites was significantly higher

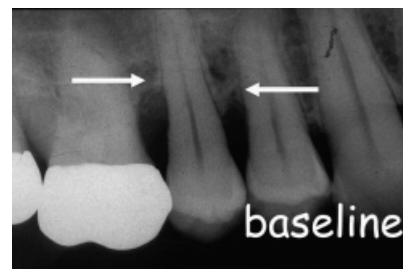


Fig. 8. Pre-operative X-ray of the intra-bony defect.

than in the control sites at both re-evaluation assessments ( $p < 0.001$ ).

#### Gain of clinical attachment (Table 4, Fig. 11)

Both groups showed a statistically significant gain of clinical attachment when compared with baseline after 6 and 12 months. CAL gains were  $2.7 \pm 0.3$  and  $3.7 \pm 0.4$  mm for the EMD-treated sites, and  $1.6 \pm 0.3$  and  $1.7 \pm 0.3$  mm for the control sites after 6 and 12 months, respectively. After 12 months, the test treatment resulted in an additional significant gain in clinical attachment compared with the CAL gain achieved 6 months after EMD application. In the control group, however, CAL gains did not improve between the two time points. Interestingly, both treatment modalities resulted in significantly improved ( $p < 0.001$ ) attachment levels after both 6 and 12 months compared with baseline. However, CAL gain was significantly higher in the test than in the control group at both time points ( $p = 0.0015$ / $p < 0.0001$ ).

#### GR (Table 4, Fig. 11)

The baseline values for GR (distance between the gingival margin and the cemento-enamel junction) were measured <1 mm at baseline and did not differ significantly between the test and the control group. In comparison with the baseline data, both the test and the control treatment resulted in a statistically significant increase in GR after

both 6 and 12 months (test:  $p = 0.0027/0.0081$ ; control:  $p = 0.021/0.0023$ ). The amount of GR increase for the test group measured  $0.6 \pm 0.2$  and  $0.5 \pm 0.2$  mm for the control group after 6 months. Twelve months after surgery, the GR

increase over baseline amounted to  $0.5 \pm 0.2$  mm for the test group and to  $0.7 \pm 0.2$  mm for the control group. No statistically significant differences could be evaluated between the test and the control group.

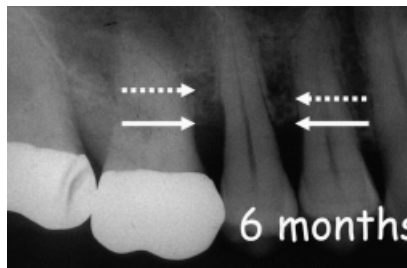


Fig. 9. X-ray at 6-month follow-up. Note the amount radiographic bone fill.

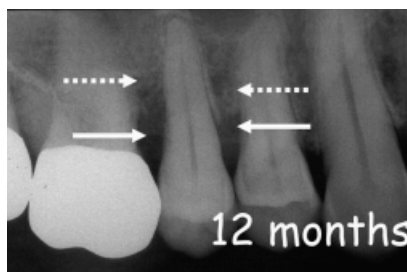


Fig. 10. X-ray at 12-month follow-up. Compared with the baseline radiograph, bone fill can be observed.

#### Radiological data (Table 4, Figs 8–11)

Both the test and the control group revealed a significant bone fill after 6 and 12 months. The test group displayed a radiographic bone fill from baseline to 6 months of  $1.4 \pm 0.2$  and  $2.5 \pm 0.4$  mm after 12 months, respectively. In the control group, a radiographic bone fill of  $0.7 \pm 0.1$  mm after 6 months and  $1.1 \pm 0.1$  mm after 12 months, respectively, was detected. The test group showed statistically significantly more radiographic bone fill than the control group after 6 months as well as after 12 months ( $p = 0.039/p < 0.001$ ). In both groups, a significant gain in bone fill was observed between the 6-month and the 12-month time points.

#### Discussion

The present investigation is a second larger analysis of a previous clinical trial (Wachtel et al. 2003b) reporting on eight additional patients and presenting

radiographical data of the study population. This study confirms that the use of an EMD is able to lead to better clinical outcomes with respect to CAL-reduction, PPD-reduction and radiographic bone fill when compared with open flap debridement alone. Furthermore, both the test and the control group could successfully limit the amount of post-operative GR and predictably achieve primary inter-proximal wound closure 1 and 2 weeks after surgery. Yet a limitation of the study is the limited amount of sites, a short duration of the follow-up and a lack of control group using a macrosurgical approach in conjunction with the treatment of EMD.

Primary wound closure seems to be of major clinical importance as secondary wound closure is associated with membrane exposure and irreversible tissue loss. These consequences are regarded as the chief shortfall of GTR procedures occurring in over 50% of all treated cases (Hugoson et al. 1995, De Sanctis et al. 1996a, b, Falk et al. 1997). Based on this knowledge, refined flap designs with respect to the preservation of the inter-proximal tissue have been developed (Takei et al. 1985, Cortellini et al. 1995b, 1999). As a consequence, the rate of primary wound closure in the inter-proximal area could be improved significantly (Cortellini et al. 1995a, b, 1999). Yet membrane exposure and dehiscence of inter-proximal tissues was still present in up to one-third of all treated cases occurring in the first postoperative weeks (Cortellini et al. 1995a, b, 1999). Consequently, a microsurgical approach for periodontal regeneration was introduced and it was reported that the rate of secondary wound closure could be further limited to <8% of all reported cases (Cortellini & Tonetti 2001, Wachtel et al. 2003a).

Cortellini and colleagues showed in two recent case series with a total of 53 deep intra-bony defects that a minimal-invasive, high-power magnification-assisted surgical technique using EMD yielded clinically significant improvements (CAL gains of  $4.8 \pm 1.9$  mm) (Cortellini & Tonetti 2007a, b). The present investigation corroborates these results, obtaining CAL gains of  $3.7 \pm 0.4$  mm and reporting primary wound closure in 91% of the test and 97% of the control sites. It can be concluded that the refined techniques developed for the GTR procedures also seem to be applicable on regenerative strategies with EMD.

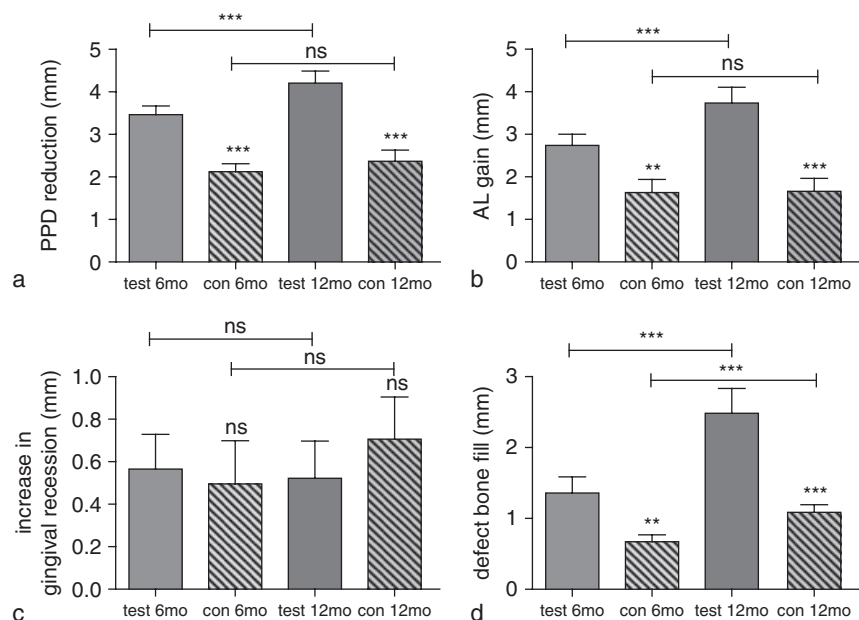


Fig. 11. Clinical outcomes after 6- and 12-month: PPD reductions (a), AL gain (b), increase in gingival recession (c), and bone fill (d) for test and control groups. Data are presented as means  $\pm$  SEM, 19 pairs of defects (in subjects contributing > 1 pair, data for each treatment group was summarized before statistical analyses) were analysed using *t*-tests for paired comparisons

A further objective of using a microsurgical approach was to limit GR occurring after a surgical intervention and to preserve a positive inter-proximal tissue architecture. Yet surgical approaches for the treatment of intra-bony defects were often accompanied by major tissue recession following the surgical intervention. Becker et al. (1988) showed that when a modified Widman-Flap was used, 1.8 mm of GR has to be expected in pockets of 7 mm and more. Surgical techniques with respect to EMD were associated with up to 1.7 mm of GR after the surgical intervention (Pontoriero et al. 1999, Froum et al. 2001). The present investigation reveals that when an EMD was used along with a microsurgical approach, 0.7 mm of GR has to be expected 12 months after the surgical intervention. Also, recession values from control sites are considerably lower compared with the mean change in recession of 1.2–1.7 mm observed after open flap debridement (Okuda et al. 2000, Sculean et al. 2001).

It can be concluded that the use of a microsurgical approach seems to be applicable on regenerative strategies dealing with EMD. In this context, primary wound closure can be achieved in the majority of the cases, leading to a significant clinical and radiographic improvement without compromising the aesthetic appearance of the treated site. Yet multicentre studies with a larger sample size need to confirm the results presented.

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### Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Supporting information in accordance with the CONSORT Statement 2001 checklist used in reporting randomized trials.

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### Clinical Relevance

*Scientific rationale for the study:* The goal of this study was to determine the effect of EMD in combination with a microsurgical approach for the treatment of intra-bony defects.

*Principal findings:* The test group (EMD) displayed significantly more CAL gain, PPD reduction and radiographic defect resolution. Furthermore, both the treatment groups were successful in limiting post-

operative GR and in achieving primary flap closure.

*Practical implications:* EMD seems to be superior with respect to regeneration of periodontal tissues when compared with open flap debridement alone.