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A clinical study evaluating the treatment of supra-alveolar-type defects with access flap surgery with and without an enamel matrix protein derivative: a pilot study

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Abstract

Aim: There is evidence that regenerative treatment of intra-bony and mandibular class II furcation defects with access flap and an application of an enamel matrix protein derivative (EMD) can result in a clinical benefit compared with access flap alone. The aim of this pilot study was to check if the results of access flap surgery in suprabony defects are improved by additional application of EMD.

Material and Methods: Thirty-nine adult subjects with supra-alveolar-type defects were randomly assigned to a test ($n = 25$) and a control group ($n = 14$). Seventy teeth were treated with EMD; 28 teeth were treated by access flap. Probing depth (PD), clinical attachment level and bleeding on probing were evaluated at baseline and after 12 months.

Results: PD of the operated teeth was improved in both groups ($p < 0.001$ to $p = 0.041$) but always better in the test group. The attachment gain was 2.72 ± 1.80 mm at sites with an initial PD $\geqslant 7$ mm in the test group and 0.78 ± 0.62 mm in the control group ($p = 0.004$). In the test group the mean attachment gain was 0.97 ± 0.92 mm ($p < 0.001$); the mean reduction of PD was 1.55 ± 0.90 mm ($p < 0.001$).

Conclusions: The data suggest a significant clinical benefit of supplementary application of EMD during surgical treatment of periodontitis of supra-alveolar pockets, especially in deeper pockets.

Key words: enamel matrix proteins; flap operation; periodontitis; suprabony defects; surgical treatment

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The basic treatment of chronic periodontitis consists of mechanical removal of the subgingival biofilm to arrest the inflammatory process and to establish a non-periodonto-pathogenic microflora. The reduction of the periodontal pocket is a decisive aim in this context. In severe periodontitis, the surgical treatment was shown to be superior compared with a conventional scaling and root planing. In a meta-analysis, Heitz-Mayfield et al. (2002) reported a 0.6 mm higher probing depth (PD) reduction and a 0.2 mm higher clinical attachment level (CAL) gain after 12 months following surgical treatment of deep pockets in comparison with non-surgical therapy. Because osteoclast activation may occur after raising a mucoperiostal flap, the decision for surgical therapy has to be taken with care (Binderman et al. 2001). Several modifications of the surgical procedure like the modified Widman flap technique (Ramfjord & Nissle 1974) as well as access flap or papilla preservation techniques (Takei et al.

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1985, Cortellini et al. 1995, Zucchelli et al. 2006) and recently the minimally invasive surgical technique (Cortellini & Tonetti 2007a, b) have been suggested. The recent procedures enable a defect-specific and tissue-preserving approach to improve primary wound closure and clinical outcome because usually limited regeneration of the periodontal ligament occurs.

The use of enamel matrix derivatives has been described to have a regenerative effect on periodontal tissues (Gestrelius et al. 1997, Brett et al. 2002, Wang et al. 2005, Nemcovsky et al. 2006). When treated with enamel matrix derivatives, sites with intra-bony defects or furcations with class II involvement showed significantly better results (Francetti et al. 2004, Jepsen et al. 2004). Human histological studies revealed newly formed cementum, periodontal ligament and the formation of new bone (Sculean et al. 2000, Yukna & Mellonig 2000). An attachment gain of 4.1 mm and a pocket depth reduction of 5.3 mm for intra-bony pockets $\geqslant$4 mm after 1 year was reported by Silvestri et al. (2003) in a multicentre controlled clinical trial. In another study, the mean attachment gain for intra-bony pockets was 3.1 mm (Tonetti et al. 2002). A mean reduction of 5.7 mm in pocket depths was shown after application of enamel matrix proteins (Sculean et al. 1999), and 5 years, later the mean clinical attachment gain of 3.4 mm was reduced to 2.9 mm (Sculean et al. 2004). Yilmaz et al. (2003) found better results at maxillary incisors and canines with horizontal-type bone loss 8 months after application of enamel matrix proteins. A high degree of heterogeneity of the results has to be considered, but comparing with a placebo or control the mean improvements of attachment level and PD are given with 1.2 and 0.8 mm, respectively (Esposito et al. 2005). On the other hand, procedure sensitivity, a so-called centre effect, and bias due to decision making by the dentist have been noted.

Angiogenic effects of enamel matrix derivatives could be shown in vitro and in animal studies (Yuan et al. 2003). Positive effects of enamel matrix derivatives on primary wound healing have also been observed (Wennström & Lindhe 2002, Grayson et al. 2006). Wennström and Lindhe described a better early wound healing of the soft tissues after scaling and root planing with supplementary topical application of enamel matrix proteins. A higher frequency of sites without clinical signs of inflammation and bleeding after probing of the residual pocket was observed.

Based on the existing knowledge about enamel matrix derivatives, it was plausible to check if enamel matrix derivatives have a beneficial effect not only in intra-bony or furcation defects but also for results of the surgical procedure in general, because an improvement of fibroblast proliferation on the root surface has been described in vitro (Lyngstadaas et al. 2001, Davenport et al. 2003). To our knowledge a study like ours, considering also premolars and molars, has not been undertaken until now. The aim of this randomized prospective clinical pilot study was to compare the results for PD, attachment level and bleeding on probing (BOP) after flap operation with and without supplementary application of enamel matrix derivatives in supra-alveolar-type defects 1 year after surgical intervention.

Material and Methods

Patients

Thirty-nine subjects (29 women and 10 men) recruited from the Department of Conservative Dentistry and Periodontology at the University of Leipzig gave their written informed consent and participated in the prospective non-blinded clinical study. The sample size was fixed after model calculations for attachment level and PD using $\alpha = 5\%$ for the level of significance and a test power of 80% (Jones & Payne 1997). The primary outcome variable was improvement of attachment level; the secondary outcome variable was PD reduction. At the baseline visit, patients were randomly assigned by toss of a coin by the surgeons to one of two treatment groups. Twenty-five volunteers (20 women, five men, mean age 44.4 ± 8.8 years, range 25–56) were assigned to the test group. Fourteen volunteers (nine women, five men, mean age 52.1 ± 9.2 years, range 37–63) were assigned to the control group. All subjects were scheduled for periodontal flap surgery, diagnosed as suffering from chronic periodontitis with supra-alveolar-type defects. Anterior initial therapy had been performed during 3months before surgery. All patients had improved levels of oral hygiene after the initial therapy (interproximal plaque index $<35\%$, Lange et al. 1977). Surgical therapy was considered necessary in the case that PD was $\geqslant$5 mm after initial therapy and BOP still existed. Criteria for inclusion in the study were as follows: general good health, no intake of antibiotics within the last 6 months, teeth be to treated were with pulp vitality, teeth with a maximum mobility of degree 2, and moderate or severe periodontitis.

Surgical and post-surgical treatment

All patients received local anaesthesia. After intra-sulcular incision, mucoperiostal access flaps were raised and granulation tissue and pocket epithelium were removed. Subgingival calculus and plaque were removed by scaling and root planing using an ultrasonic scaler and curettes. No modification of the bone outline has been performed. The area of surgery was rinsed with saline and the mucoperiostal flap was replaced. Proximal single sutures were made with monofil suture material (4/0 Prolene, Ethicon, Norderstedt, Germany). Before suturing, in the test group enamel matrix proteins (Emdogain®, Straumann, Freiburg, Germany) were placed with a short blunt-ended needle after the application of 24% EDTA (Pref-Gel, Biora AB, Straumann Group, Malmö, Sweden) in the sites for 2 min. The EDTA was carefully removed by irrigation with saline. During application of the enamel matrix proteins, contamination with saliva or blood was avoided. A 0.2% chlorhexidine digluconate solution and a 1% chlorhexidine digluconate gel for application in the area of surgical intervention were prescribed. The sutures were removed after 14 days in the test group and after 10–14 days in the control group.

Every 3 months, all subjects underwent standardized, supportive periodontal care with professional biofilm and calculus removal, re-instruction and re-motivation by an experienced prophylaxis assistant. An interproximal plaque index of $<35\%$ could be maintained during the study period.

Clinical examination and statistical analysis

PD, CAL as well as BOP were recorded at six sites per tooth before surgery (baseline) as well as 12 months after surgery using a North Carolina probe (HuFriedy, Leimen, Germany). Data were recorded for all sites of operated teeth, for sites with 4–6 mm and for sites

⩾7 mm of PD in the operated area. All values are given as means ± SD and medians. Identical treatment was performed by both authors, surgeons and examiners. Both examiners participated in repeated formal calibrations of six patients; the intra-class correlation coefficient was 0.79 for AL and 0.78 for PD. The statistical unit was the patient. Statistical analysis was performed using the Mann–Whitney *U*-test and the Wilcoxon test. The Mann–Whitney *U*-test was used for testing differences between the groups. Within-group differences were checked using the Wilcoxon test. A level of $\alpha \leqslant 0.05$ was considered to be significant.

Results

In total, 70 teeth were treated with enamel matrix derivatives; 28 teeth were in the control group. Twenty-five molar teeth, 20 premolar teeth and 25 incisors were treated in the test group. In the control group, 19 molar teeth, six premolar teeth and three incisors were treated. All volunteers from the baseline measurements could be examined after 12 months; no adverse effects were seen. The six-point measurements are given as mean value and SD per group. The results for PD, attachment level as well as BOP of both groups before and after the treatment are given together with the statistical results in Table 1. The improvements calculated as the differences between baseline and final results are given in Table 3. It can be seen that the PD is significantly improved in both groups, but the PDs are significantly different between the groups at the end of the study ($p<0.001$). A significant reduction in PD occurred in the test group (1.55 mm after 12 months for overall measurements while in the control group a difference of 0.41 mm was measured). These results are significantly different ($p<0.001$). The overall changes of the CAL are significant only in the test group ($p<0.001$). Here, the improvement after 12 months is 0.97 mm in the test group and 0.07 mm in the control group. These changes are significantly different between both groups ($p<0.001$). PD as well as attachment level and BOP were without significant difference at baseline. A significant improvement of BOP occurred in both groups (0.22 and 0.13, $p=0.001$ and 0.020), but there was no significant difference between both groups at the end of the study.

Table 1. Probing depth (PD, mm), attachment level (AL, mm) and bleeding on probing (BOP, %) of operated teeth and statistical analysis for the study (E) and control (F) group at baseline and after 12 months

	Baseline			End of the study			Wilcoxon's test
	mean	SD	median	mean	SD	median	*p*
PD-E	4.30	0.95	4.25	2.75	0.44	2.61	<0.001
PD-F	4.07	0.67	4.01	3.66	0.83	3.67	0.041
U-test		NS			<0.001		
AL-E	4.92	1.18	5.00	3.95	0.97	3.67	<0.001
AL-F	4.41	0.82	4.38	4.34	1.03	4.13	NS
U-test		NS			NS		
BOP-E	0.41	0.20	0.42	0.19	0.16	0.17	0.001
BOP-F	0.42	0.21	0.46	0.29	0.19	0.26	0.020
U-test		NS			NS		

Table 2. Probing depth (PD, mm), attachment level (AL, mm) and bleeding on probing (BOP, %) of operated sites with initial probing depths of 4–6 mm and ⩾7 mm; statistical analysis for the study (E) and control (F) group at baseline and after 12 months

	Baseline			End of the study			Wilcoxon's test
	mean	SD	median	mean	SD	median	*p*
Considering recordings at sites with PD 4–6 mm of the operated teeth							
PD-E	4.80	0.41	4.75	3.02	0.56	2.89	<0.001
PD-F	4.53	0.34	4.50	3.92	0.95	3.77	0.028
U-test		NS			0.002		
AL-E	5.44	1.23	5.00	4.24	1.17	4.19	<0.001
AL-F	4.71	0.55	4.50	4.35	1.01	4.15	NS
U-test		0.043			NS		
BOP-E	0.50	0.24	0.50	0.24	0.22	0.22	0.001
BOP-F	0.48	0.36	0.55	0.32	0.36	0.22	NS
U-test		NS			NS		
Considering recordings at sites with PD ⩾7 mm of the operated teeth							
PD-E	7.92	1.04	7.60	3.73	1.31	3.50	0.001
PD-F	7.75	1.14	7.17	5.80	1.90	5.25	0.018
U-test		NS			0.001		
AL-E	7.95	1.58	8.00	5.23	1.55	5.00	0.001
AL-F	7.74	1.99	7.63	6.96	2.01	6.83	0.012
U-test		NS			0.027		
BOP-E	0.56	0.38	0.50	0.17	0.30	0.00	0.003
BOP-F	0.78	0.26	0.88	0.59	0.35	0.67	NS
U-test		NS			0.011		

To get more information the results were split considering different initial PDs. Groups of sites of the operated area with PDs of 4–6 mm or ⩾7 mm, respectively, at baseline were formed. This separate analysis has been performed because at buccal and lingual sites, relatively low PDs and attachment levels can occur with confounding influence on the mean values. Mean values as well as standard deviation and medians are given in Table 2.

It can be seen again that the supplementary use of enamel matrix derivative is superior to flap procedure alone. Significant improvements occurred in the test group at PD, CAL and BOP after 12 months for the categories 4–6 mm and ⩾7 mm ($p<0.001$–$p=0.003$). Starting with no significant difference, the PD is significantly different between both groups for both categories at the end of the study (0.002 and 0.001). There was no significant difference at the end of the study for attachment level at the sites with an initial PD of 4–6 mm, but a significant difference was seen for sites ⩾7 mm ($p=0.027$). BOP is not significantly better after flap operation alone. Taken together with the dramatic decrease of BOP for initially deep pockets in the test group, there is a significant difference between both groups regarding BOP for sites ⩾7 mm ($p=0.011$).

The real benefit of the operation in both groups is given as the mean difference (Δ) between baseline and final results in Table 3. Improved results

Table 3. Comparison of the mean differences (Δ) of probing depth (PD), attachment level (AL) and bleeding on probing (BOP) between the study and control groups

	Test group			Control group			*U*-test *p*
	mean	SD	median	mean	SD	median	
Considering all six recordings per tooth of the operated teeth							
ΔPD	1.55	0.90	1.17	0.41	0.66	0.58	<0.001
ΔAL	0.97	0.92	0.92	0.07	0.55	0.00	<0.001
ΔBOP	0.22	0.24	0.17	0.13	0.18	0.11	NS
Considering recordings at sites with PD 4–6 mm of the operated teeth							
ΔPD	1.78	0.72	1.67	0.61	0.95	0.79	<0.001
ΔAL	1.20	1.02	1.20	0.36	0.78	0.00	0.009
ΔBOP	0.26	0.32	0.24	0.16	0.33	0.00	NS
Considering recordings at sites with PD ⩾7 mm of the operated teeth							
ΔPD	4.19	1.62	4.38	1.95	1.17	2.25	0.001
ΔAL	2.72	1.80	2.50	0.78	0.62	0.50	0.004
ΔBOP	0.39	0.36	0.42	0.19	0.27	0.00	NS

can be seen for all sites of the operated teeth, for sites with initial PDs 4–6 or ⩾7 mm, respectively. No significant difference between the groups could be found for BOP. At initially higher PDs, a greater benefit of the use of enamel matrix protein derivative (EMD) with respect to PD reduction and attachment gain was seen. The improvement was 1.78 mm for PD and 1.20 mm for attachment level in the test group for sites with an initial PD of 4–6 mm. The corresponding results for sites ⩾7 mm are 4.19 and 2.72 mm. The results for PD reduction and attachment gain are significantly better in the test group than in the control group. In the control group, the PD reduction was 0.61 and 1.95 mm and the attachment gain 0.36 and 0.78 mm, respectively. The differences between both groups are always significant for PD reduction and attachment level gain ($p<0.001$–$p=0.009$).

Discussion

During the treatment of periodontitis, flap operation has positive effects on the attachment level when a minimum of PD is respected (Heitz-Mayfield et al. 2002). Lindhe et al. (1982) found that surgical treatment by flap operation at pocket depths between 1 and 3 mm was followed by an attachment loss of up to 0.2 mm. Supplementary application of enamel matrix derivative in intra-bony pockets had a positive effect on PD and attachment level after surgical periodontal therapy (Francetti et al. 2004). The use of specific biomaterials/biologicals is more effective than an open flap debridement in improving attachment levels in intra-osseous defects (Trombelli et al. 2002a). GTR is consistently more effective than flap operation in mandibular or maxillary class II furcation defects (Jepsen et al. 2002).

Esposito et al. (2005) conclude from their systematic review on enamel matrix derivatives used during periodontal surgery in intra-bony defects, that 1 year after application, emdogain-treated sites had statistically significant attachment improvements when compared with placebo or control sites. They add that the results have to be interpreted with great caution because of the observed heterogeneity of the studies included into the meta-analysis.

Positive effects of enamel matrix derivatives on wound healing are described (Wennström & Lindhe 2002, Grayson et al. 2006). The idea of our study was to check the beneficial effect on clinical results in flap operation, where no treatment of furcation or infrabony defects was intended. That means, is there a general superior effect of the use of enamel matrix derivatives during flap operation? A lower frequency of clinical signs of inflammation after the use of enamel matrix derivatives (Wennström & Lindhe 2002) would favour the opinion that supplementary attachment gain and pocket reduction could occur. The results of our clinical pilot study were able to demonstrate that the same procedure of flap operation had better results regarding CAL and PD when enamel matrix derivatives were applied during the operation. This can be seen when all sites of the operated area are considered. It can be seen clearly when sites of the operated area with an initial PD of 4–6 mm are considered for calculation and is even more impressive for sites ⩾7 mm. It is not a result of chance because the level of significance could be reached. Of course a non-blinded study can have some bias. As in other studies regarding the outcome of different surgical procedures, no placebo material was used. Because both authors operated the patients of the test and control group, the influence of subjective factors on the results is the same. Some bias could occur while measuring attachment level and PD by the surgeon. Also from the ethical point of view it does not make sense to record clinical variables in a different manner in function of the treatment procedure. The randomization by toss of coin in this study had the disadvantage that unequal distribution of the patients occurred; for future studies a randomization table should be used. Model calculations have been performed using existing data. Because in the present study the SD was higher than expected and used for model calculation, the power of the study has been recalculated and is now 82% for the primary outcome variable and 89% for the secondary outcome variable. The primary outcome variable for studies on periodontal regeneration should be improvement of attachment. As a secondary outcome variable, PD reduction was considered in this study because not only attachment gain alone has an influence on further stability after operation. PD is also of importance because it influences the conditions for anaerobic bacterial growth. Because our study was self-supported, no placebo has been used in this unblinded study. A multilevel analysis to combine the influence of several factors on the outcome of the study was not recommended because some patients contributed more than one tooth to the study.

All participants underwent the same regime of supportive periodontal maintenance with intervals of 3 months. One may speculate about the reason for the significant advantage of the use of enamel matrix derivatives during the flap operation. First, it could be an antibacterial effect, because in an observer-blind randomized study, a direct influence of Emdogain® on the vitality of supragingival plaque has been described (Arweiler et al. 2002). On the other hand, early wound healing could be positively influenced as described by Wennström & Lindhe (2002). These authors also applied enamel matrix derivatives during flap operation. No differences for PD were found in comparison with the controls after 3 weeks, but significantly higher frequencies of sites without clinical signs of inflammation and BOP were registered after 1 and 2 weeks. One may speculate that the better results in deeper pockets are explained in this manner. The stimulation of fibroblasts with a consecutive release of transforming growth factor β 1 and a more rapid attachment of the fibroblasts could be another explanation (van der Pauw et al. 2000). The clinical results may be explained by the selective outgrowth and colonization of the root surface by the fibroblasts. It is also plausible that this occurs in the relatively undisturbed conditions of deeper pockets.

Our results, 0.9 mm higher attachment gain and 1.1 mm higher PD reduction, are comparable to the results from the meta-analysis on enamel matrix derivative used in infrabony defects. We do not wonder that our overall sites results are lower than 1.2 mm for the improvement of the attachment level in infrabony defects (Esposito et al. 2005). This could be explained in the same manner as the correlation between attachment level gain and defect morphology and depth in infrabony defects (Silvestri et al. 2003); here our results are also lower in shallow pockets.

It is clearly visible that most PD reduction is caused by attachment gain. On the other hand, it is also clearly visible that in the test group, but more in the control group, high standard deviations occur. That means for us, the results are influenced not only by the use of a material or by a procedure but also by host factors. There seems to be no influence on the results for BOP by the use of enamel matrix derivative.

Studies exist on enamel matrix proteins in horizontal bone loss (Trombelli et al. 2002b, Yilmaz et al. 2003), that could be considered as matching pieces to our study. Better clinical improvements have been seen in comparison with the conventional flap technique. Trombelli et al. (2002b) studied 35 patients; the improvement of PD and attachment level was with 5.4 and 4.7 mm, respectively, better than our results in baseline pockets of 8.9 mm. While Yilmaz et al. (2003) studied the flap operation in upper frontal teeth, in our study all types of teeth have been included. The reduction of pocket depth of that study was with 2.87 and 2.92 mm for pockets deeper than 4 mm framed by our results (1.79 for pockets 4–6 mm, 4.19 mm for pockets $\geqslant$7 mm, respectively). In our study, the attachment gain was 1.20 for pockets initially between 4 and 6 mm and 2.72 mm for deeper pockets, and the results of Yilmaz et al. (2003) were 2.16 and 2.27 mm in the enamel matrix protein groups.

In contrast to these results, the application of enamel matrix proteins during coronally repositioned flap operation in the treatment of gingival recessions had not been followed by a significant better outcome than surgery without enamel matrix protein use (Hägewald et al. 2002). One may speculate if this type of operation is more procedure-sensitive. Positive results about the influence of enamel matrix derivative during root coverage procedures are reported, too (Cueva et al. 2004, Castellanos et al. 2006). The mean attachment gain of 0.90 mm is about at the level of attachment gain achieved in our study. On the other hand, it has to be recognized that the amount of attachment gain is not of immediate clinical importance. For the patient, the long-term maintenance of his own teeth is probably more important than the improvement of mm-scaled variables. However, within the limits of this pilot study it could be demonstrated that the supplemented access flap operation could be superior to the conventional access flap procedure without use of enamel matrix derivatives. The study could contribute to the conclusions of the review of Sculean et al. (2007) that surgical periodontal therapy with enamel matrix derivative may lead to higher improvements in clinical variables not only in treating deep intra-bony defects but also in treating periodontitis with supra-alveolar-type defects. Further research executed as a multicentre randomized clinical trial is needed.

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Clinical Relevance

Scientific rationale for the study: The application of EMDs is followed by superior results during access flaps for intra-bony or mandibular furcation defects. The present pilot study evaluates the general benefit of supplementary application of EMD during periodontal surgery in supra-alveolar-type defects for the clinical outcome after 12 months.

Principal findings: PD reduction and clinical attachment gain are significantly better after flap operation with enamel matrix derivatives. The benefit increases with higher initial PDs. It seems to be without any effect on the results of BOP after 1 year.

Practical implications: The supplementary use of EMD improves the clinical results of access flap surgery of supra-alveolar pockets.