CLINICAL OUTCOMES OF THE ENTIRE PAPILLA PRESERVATION TECHNIQUE WITH AND WITHOUT BIOMATERIALS IN THE TREATMENT OF ISOLATED INTRABONY DEFECTS: A RANDOMISED-CONTROLLED CLINICAL TRIAL

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Running title: Entire papilla preservation technique with and without biomaterials

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Abstract

Background: This randomised clinical trial compared the clinical efficacy of the entire papilla preservation technique (EPP) alone and in combination with enamel matrix proteins plus bovine-derived bone substitutes (EMD+BS) in the treatment of isolated interdental intrabony defects.

Material and methods: A total of 30 patients with one isolated deep intrabony defects were enrolled 15 of them were randomly assigned to EPP alone while the other 15 to EPP EMD+BS. Access to the intrabony defect for debridement was provided by a single vertical incision positioned in the buccal gingiva of the neighbouring interdental space. Following the elevation of a buccal flap, an inter-dental tunnel was prepared undermining the defect-associated papilla. Granulation tissue was removed and root surfaces were carefully debrided. In the EPP EMD+BS group, bone substitutes and EMD were applied. EPP group did not receive any regenerative biomaterials. Microsurgical suturing technique was used for optimal wound closure. Outcome measures included gain in clinical attachment level (CAL), probing depth (PD) reduction, and gingival recession (REC).

Results: Early healing phase was uneventful in all cases and 100% primary wound closure was maintained throughout the study period. Intragroup differences between baseline and 1-year were statistically significant in both groups in terms of CAL gain and PD reduction ($p \leq 0.001$), no statistically significant differences were detected in REC ($p > 0.05$). There were no statistically significant differences in mean ± SD CAL gain (6.3 ± 2.5 mm *versus* 5.83 ± 1.12 mm), PD reduction (6.5 ± 2.65 mm *versus* 6.2 ± 1.33 mm), and increase in gingival recession (0.2 ± 0.25 mm *versus* 0.36 ± 0.54 mm) between the EPP EMD+BS and EPP groups.

Conclusions: EPP with and without regenerative biomaterials can provide significant amount of CAL gain and PD reduction, with negligible increase in gingival recession.

Within the limits of the present study, it can be concluded that addition of regenerative biomaterials do not improve the overall clinical outcomes.

Introduction

The ultimate end-point of treatment following the completion of initial periodontal therapy is accomplishing regeneration of the lost periodontal tissues. Various surgical techniques and biomaterials have been investigated to achieve periodontal regeneration since the very first inception of guided tissue regeneration (GTR) technique (Nyman et al. 1982). Barrier membranes in combination with bovine-derived bone substitutes, enamel matrix proteins (EMD), demineralized freeze-dried bone allografts have been used for the formation of new cementum, new periodontal ligament and new alveolar bone (Heijl 1997, Sculean et al. 1999, Camelo et al. 2001). Various factors such as plaque control, percentage of bleeding on probing, location and morphology of the defect, smoking habit, and exposure of the barrier membrane significantly influence the clinical outcomes following the implantation of these biomaterials (Tonetti et al. 1993, Machtei 1994, De Sanctis et al. 1996a, Kornman & Robertson 2000, Farina et al. 2013). Exposure of the applied biomaterials is the major issue in the field of regeneration, as this event may lead to contamination of the surgical site and jeopardizes wound stability. To overcome this clinical issue, different approaches have been proposed to provide an ideal environment for early as well as late wound stability. Instead of using GTR technique, researchers have focused on biologics such as EMD and this shift significantly decreased the incidence of early wound healing complication (Sanz et al. 2004). On the other hand, implementation of microsurgical technique and its principles into the regenerative periodontal surgery increased the rate of primary healing by minimizing the trauma to the soft tissues (Tibbets & Shanelec 1998, Cortellini & Tonetti 2001). Moreover, evolution of the surgical flap design improved early wound healing and stability that are critical factors for the clinical outcomes. Papilla preservation technique (Takei et al. 1985), modified papilla preservation technique (Cortellini et al. 1995), simplified papilla preservation technique (Cortellini et al. 1999), minimally invasive surgical approaches with papilla elevation (Cortellini & Tonetti 2007) or without palatal papilla elevation (Cortellini & Tonetti 2009, Trombelli et al. 2009) aim at preserving the interdental papillary complex and enhancing wound stability. All the aforementioned techniques, however, entail an incision over the defect-associated interdental papilla that may jeopardize the volume and complex vascular integrity of the interdental tissues.

Recently, a novel surgical approach, the ‘‘entire papilla preservation (EPP)’’ technique has been proposed for regenerative treatment of isolated deep intrabony defects (Aslan et al. 2017a). This novel concept provides an intact gingival chamber over the intrabony defect, with completely preserved interdental papilla. One-year prospective cohort study (Aslan et al. 2017b) with twelve isolated deep non-contained intrabony defects treated with EMD+bone substitutes, revealed 100% primary closure during all stages of wound healing and documented 6.83 mm of mean clinical attachment gain. However, the efficacy of this novel surgical concept when combined with biomaterials remains unclear. Therefore, the aim of the present randomised and controlled clinical trial was to investigate the clinical efficacy of “EPP” alone in comparison to EPP combined with regenerative biomaterials.

Material and Methods

Experimental design

The present study is designed as a single-centre, parallel group, and randomised, controlled clinical trial comparing the efficacy of two treatment modalities in 30 patients. The present paper is written according to the CONSORT statement for improving the quality of reports of parallel-group randomised trials. The study protocol was approved by the Institutional Review Board of School of Medicine, Ege University, İzmir, Turkey (protocol no. 15-4.1/10). A single defect was treated in each patient and all the experimental sites were accessed with the "EPP" technique (Aslan 2017a) and debrided carefully. EDTA gel was applied on the instrumented root surfaces. EMD+bone substitutes were applied in one group (EPP EMD+BS, 15 defects), while the other group (EPP, 15 defects) did not receive any regenerative biomaterials. The single vertical incision was sutured with single interrupted sutures. Patients were enrolled in a stringent maintenance programme with recalls on a weekly basis for the first month and then monthly controls for professional tooth cleaning for the 12 months postoperatively. Clinical periodontal parameters were recorded at baseline, which is 3 months after completion of initial periodontal therapy. Periodontal probing was avoided in the experimental site during the 12-month study period. Final clinical outcomes were recorded 12 months after the regenerative periodontal surgery.

Study population

Inclusion criteria were; being systemically healthy, having the clinical diagnosis of advanced periodontitis, willing to receive regenerative periodontal surgery after completion of non-surgical periodontal therapy and giving a written informed consent. Eligible patients had one isolated intrabony defect with probing depth (PD) ≥7 mm, clinical attachment level (CAL) ≥8 mm and at least 4 mm intrabony component involving predominantly the interproximal area of the affected tooth. Moreover, the patients had to exhibit full-mouth plaque score (FMPS) and full-mouth bleeding score ≤20%. Current smokers, patients with known systemic diseases such as diabetes and cardiovascular diseases or using medications that affect periodontal tissues, pregnant or lactating women were excluded from the study. Local exclusion criteria were; one-wall intrabony defects, defects that involve buccal and lingual sites, presence of inadequate endodontic treatment and/or restoration in the relevant teeth.

Surgical procedures

All surgical procedures were performed by one experienced periodontal surgeon (S.A.). The surgical site was anesthetized using articaine-epinephrine 1:100,000. Trans-papillary infiltration was avoided to prevent physical (needle penetration) and chemical (in terms of prolonged vasoconstriction) trauma to the gingival tissues. Bone sounding was performed following the onset of anesthesia.

The "Entire papilla preservation" technique is a tunnel-like approach of the defect-associated interdental papilla. An operating microscope (x6 to x21 magnification) was used to increase the visibility of the surgical site (Cortellini & Tonetti 2001). Following a buccal intra-crevicular incision, a bevelled vertical releasing incision was performed in the buccal gingiva of the neighbouring interdental space and extended just beyond the mucogingival line to provide appropriate mechanical access to the intrabony defect. A microsurgical periosteal elevator was used to elevate a buccal full-thickness muco-periosteal flap extending from the vertical incision to the defect-associated papilla. A specifically designed angled tunnel

elevator facilitated the interdental tunnel preparation under the papillary tissue. Utmost care was taken to elevate the interdental papilla in full-thickness manner up to the intact lingual bone crest. A microsurgical scissor was used to remove the granulation tissue from the inner aspect of the defect-associated interdental papilla. Excessive thinning of the papilla was avoided not to compromise the blood supply. The granulation tissue was removed with a mini-curette. Any residual subgingival plaque or calculus was gently removed from the exposed root surface with an ultrasonic scaler. The surgical area was thoroughly rinsed with sterile saline and root conditioning of the exposed surface was done applying 24% EDTA gel (Pref-Gel, Institut Straumann, AG, Basel, Switzerland) for 2 minutes to remove the smear layer. Then, the exposed root surface was rinsed with sterile saline just before opening the randomisation envelope and treatment was continued basing on the group assignment. In the EPP EMD+BS group, EMD (Emdogain, Institut Straumann, AG, Basel, Switzerland) was applied to the exposed root surface. Subsequently, a deproteinized bovine-derived bone substitute (Cerabone, Botiss Biomaterials GmbH, Berlin, Germany) was placed into the intrabony defect. Contamination with blood or saliva was prevented during biomaterial application. In the EPP group, the intrabony defect was left to fill with a blood clot, as a result of bleeding from the residual bone walls. No periosteal releasing incision was performed. Gentle pressure was applied to the surgical area using saline-wetted gauze for 1 min to readapt the mucoperiosteal flap. Microsurgical suturing technique with 6-0 or 7-0 monofilament suture materials was performed for optimal wound closure of the surgical area.

Post-surgical care

After the surgery, patients received 600 mg ibuprofen and were instructed to take a subsequent dose 8 hours later. If necessary, patients were advised to take additional tablet and to report. Systemic doxycycline (100 mg b.i.d.) was prescribed during the first post-operative week. The patients were asked to refrain from using mechanical oral hygiene measures for a period of 4-weeks. During this period, the patients were requested to rinse with 0.12% chlorhexidine digluconate mouthrinse for 1 min twice daily. The sutures were removed 2 weeks after the surgery. Each patient received professional tooth cleaning (performed by S.A.) during the monthly control appointments for the following 12 months.

Clinical parameters

Clinical periodontal parameters were recorded at baseline, which is 3 months after completion of initial periodontal therapy. Final clinical outcomes were recorded 12 months after the regenerative periodontal surgery. Clinical periodontal parameters were recorded at 4 sites (mesial, buccal, distal, and oral) of each tooth present except the third molars. All clinical measurements at baseline and also 1-year after the surgery were carried out by the same examiner blinded to the study group (N.B.). Before the study, the examiner was calibrated for the intra-examiner reproducibility and accuracy. Full-mouth plaque scores (FMPS) were recorded as the percentage of total surfaces exhibiting plaque (O'Leary 1972). Bleeding on probing (BOP) was assessed dichotomously (as present or absent) and BOP was deemed positive if it occurred within 15 seconds after periodontal probing. Full-mouth bleeding scores (FMBS) were then calculated (Cortellini 1993a). PD and recession of the gingival margin (REC) were rounded to the nearest 0.5 mm at the deepest location of the experimental interproximal site. CAL was calculated as the sum of PD and REC. Primary closure of the surgical sites was evaluated on a weekly basis for the first

month after the surgery. Any adverse effects such as haematoma, pain, discomfort, oedema, and additional painkiller intake were recorded.

Clinical characterization of the intrabony defects during the surgery
Defects were described as 1-,2-,3-wall or combination defects according to Papapanou et al. (2000). Depth of the intrabony component (INFRA) was measured as the distance between the crest of the marginal bone and the deepest location of the osseous defect, and width of the intrabony defect as the horizontal distance between the crest of the marginal bone and root surface.

Surgical and patient-centered outcomes
Operation time was measured with a chronograph, starting at delivery of local anaesthesia till the final suture. Primary closure of the surgical site was checked with magnification at the end of surgery and then weekly for 6 weeks. Presence of a discontinuity in the soft tissues was registered as wound failure. Patients were asked to fill the questionnaire at the end of the surgery to report about intraoperative pain and subjective opinion for the discomfort of the procedure. A visual analogue scale (VAS) of 100 mm long was used to evaluate the degree of discomfort (0=no pain/hardship; 100=unbearable pain/hardship). Patients were asked at week 1 for their experience with post-operative pain and discomfort using a standard questionnaire; pain intensity was quantified with a VAS essentially as described (Cortellini et al. 2001, Tonetti et al. 2002).

Data analysis
CAL gains, residual PD and REC change were the outcome variables. Data within each group were expressed as mean ± standard deviation of 15 defects in 15 patients. All calculations were performed using the software IBM SPSS Statistics version 25.0. To assess normality, the Shapiro-Wilk test was applied. Repeated measures ANOVA (baseline and 1-year) and Independent samples Student t-test were used for normally distributed parameters. Wilcoxon's test for intragroup comparisons and Mann-Whitney U test for intergroup comparisons were used for parameters that were not normally distributed.
The level of significance used in the statistical analyses was set at 5% ($\alpha \leq 0.05$). Assuming a standard deviation in CAL gain of 1.0 mm, a sample size of 28 patients (14 patients per group) was estimated to have an 83% power to detect a difference of 1.0 mm in CAL gain between groups by using a parametric test with a 0.05 two-sided significance level (Trombelli et al. 2010).

Results
Experimental population and characteristics of surgical sites
Thirty patients were enrolled in this randomised-controlled clinical trial. The EPP alone was applied in 15 subjects (mean age 43.93 ± 12.85 years, range 21-63 years, 7 females). The EPP EMD+BS was applied in other 15 subjects (mean age 44.93 ± 13.06 years, range 22-60 years, 5 females). There was no drop-out throughout the study protocol and no missing data for the statistical analysis.
The two experimental groups were homogeneous and well-balanced, with no statistically significant differences according to age, gender, tooth type, severity, and morphology of the intrabony defects (Table 1). The experimental defects were mainly combination of 2-wall components (86% of defects for the EPP EMD+BS group; 93% of defects for the EPP group).

Post-surgical and early healing phase
The surgical time for EPP alone was rather short (55.07 ± 7.86 min, range 39-68 min). Slightly longer surgical time was required for EPP EMD+BS that accounted for 65.4 ± 10.94 min on average (range 50-93 min). The difference between the two groups was statistically significant ($p<0.01$).
Primary closure of the defect-associated papilla and single vertical incision was obtained in all treated sites (100% primary closure rate), irrespective of regenerative biomaterial application or not. No adverse events (e.g. oedema or haematoma) were noted in any of the treated sites.
None of the subjects reported severe intraoperative pain or subjective feeling of hardship of the surgical procedure at the end of the intervention. On day-4, none of the patients reported any post-operative pain. A slight discomfort was reported by two patients (13.3%) of the EPP EMD+BS group (mean VAS 9.33 ± 9.03) and by one patient (6.7%) of the EPP group (mean VAS 8.33 ± 9.38). The difference between the two groups did not reach statistical significance ($p=0.757$). The mean additional painkiller intake was 0.87 ± 0.74 tablets for the EPP EMD+BS group and 0.73 ± 0.88 tablets for the EPP group, without inter-group significant differences ($p=0.296$).

Clinical outcomes at 1-year
Clinical characteristics at baseline and 1-year are shown in Table 2. Both groups presented with low levels of FMPS and FMBS, shallow residual probing depths, significant amounts of CAL gains and very limited increase in gingival recession.
CAL significantly decreased from baseline to 1-year for both groups; however, no statistically significant differences were found in CAL change between groups ($p=0.983$). Eight EPP EMD+BS defects (53%) showed a gain ≥6 mm; five defects (33%) 5 mm; and two defects (14%) 4 mm. Seven EPP defects (47%) showed a gain ≥6 mm; five defects (33%) 3 to 4 mm; and three defect (20%) 4 mm.
PD significantly decreased from baseline to 1-year for both groups; however, no significant differences were found in PD reduction between the groups ($p=0.866$). Five EPP EMD+BS defects (33%) showed residual PD of 2 mm, eight defects (53%) 3 mm; and two defects (14%) ≥4 mm. Three EPP defects (20%) showed residual PD of 2 mm, nine defects (60%) 3 mm; and three defects (20%) ≥4 mm.
REC increased from baseline to 1-year for both groups. No statistically significant differences were found in REC increase between the two groups ($p=0.523$). No gingival recession occurred in nine of EPP EMD+BS defects (60%) and eight of EPP defects (53%).

Conclusions
Within the limits of the present study:
-EPP with and without regenerative biomaterials seems to provide ideal conditions during the early and late wound healing phases. However, the addition of the regenerative biomaterials did not improve the overall clinical outcomes, statistically. Long-term results are needed to confirm the stability of the present findings.
-Completely preserved interdental papilla revealed 100% primary closure in all treated sites. This phenomenon probably further enhanced the stability of the blood clot and no soft tissue complication or wound failure was observed.
-Patient-centered outcome measures clearly demonstrated the clinical applicability of the EPP, as a minimally invasive surgical approach.

-Based on the obtained results, it can be concluded that improvements in flap design and execution seem to be more efficient than the regenerative biomaterials when applied in appropriate intrabony defect configuration.

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Figure 1. Representative case treated with the entire papilla preservation technique (EPP group) without regenerative materials. (a) Ten mm preoperative probing depth at the distal side of the maxillary left lateral incisor. (b) Interdental tunnel preparation by undermining the defect-associated papilla. Note the elasticity of alveolar mucosa and full access to the defect area by the help of a single vertical incision. (c) Defect measurement with UNC-15 periodontal probe. (d) After the application of 24% EDTA gel, bleeding from residual bone walls. (e) Primary closure of surgical area following the blood clot formation using microsurgical knots and intact interdental papilla. (f) 14 days after the surgery. (g) Excellent wound healing and integrity of defect-associated interdental papilla. (h) The 1-year photograph shows a 3 mm of residual probing depth and a CAL gain of 7 mm. No gingival recession occurred (i) Baseline radiograph. (j) 1-year radiograph.

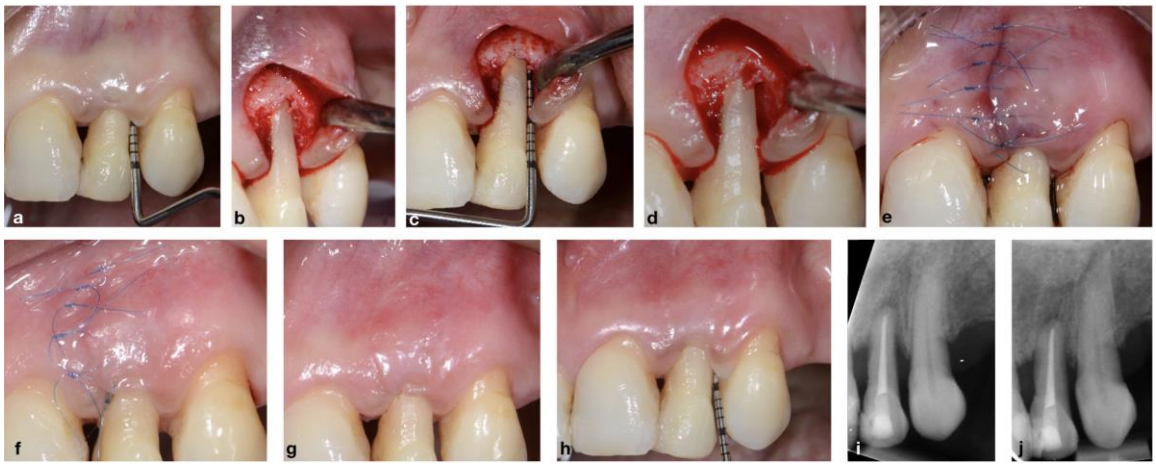

Table 1. Patient characteristics and clinical parameters measured at baseline.

	EPP EMD+BS (N=15)	EPP (N=15)	Significance (*p*)
Gender (female/ male)	5/ 10	7/ 8	0.456
Age (mean ± SD)	44.93 ± 13.06	43.93 ± 12.85	0.755
Tooth type (*incisor/ canine/ premolar/ molar)*	10/ 1/ 2 / 2	6/ 1/ 4/ 4	0.263
FMPS (%)	13.93 ± 2.31	13.13 ± 1.55	0.517
FMBS (%)	9.4 ± 1.95	10.2 ± 1.32	0.452
PD (mm)	9.33 ± 2.87	9.26 ± 1.65	0.409
CAL (mm)	11.66 ± 3.45	11.4 ± 2.17	0.690
REC (mm)	2.33 ± 1.23	2.13 ± 1.12	0.697
INFRA (mm)	6.63 ± 2.74	6.7 ± 1.62	0.329
Intrabony width (mm)	3.08 ± 0.81	3.04 ± 0.63	0.901
CEJ-BD (mm)	12.8 ± 3.5	12.48 ± 2.12	0.648
X-ray angle (deg.)	28.8 ± 8.76	29.33 ± 9.48	0.874
Main defect configuration (-1/ -2/ -3 wall)	0/ 13/ 2	0/ 14/ 1	1

FMPS, full-mouth plaque score; FMBS, full-mouth bleeding score; PD, probing depth; CAL, clinical attachment level; REC; gingival recession; INFRA, depth of the intrabony component of the defect; CEJ-BD, cemento-enamel junction and the bottom of the defect; Intrabony width, horizontal distance from the root surface to the alveolar bone crest.

Table 2. Clinical outcomes at baseline and 1-year after treatment.

Parameter	**Baseline**	**1-year**	**Change**	***p***
CAL				
EPP EMD+BS	11.66 ± 3.45	5.36 ± 1.85	6.3 ± 2.5	<0.001
EPP	11.4 ± 2.17	5.56 ± 1.74	5.83 ± 1.12	<0.001
p	0.690	0.6	0.983	
PD				
EPP EMD+BS	9.33 ± 2.87	2.83 ± 0.74	6.5 ± 2.65	<0.001
EPP	9.26 ± 1.65	3.06 ± 0.79	6.2 ± 1.33	<0.001
p	0.409	0.404	0.866	
REC				
EPP EMD+BS	2.33 ± 1.23	2.53 ± 1.36	-0.2 ± 0.25	0.14
EPP	2.13 ± 1.12	2.5 ± 1.4	-0.36 ± 0.54	0.14
p	0.697	0.932	0.523	

CAL, clinical attachment level; PD, probing depth; REC; gingival recession.

Table 3. Surgery-related outcomes.

	EPP EMD+BS(N=15)	**EPP (N=15)**	**Significance (*p*)**
Time	65.4 ± 10.94	55.07 ± 7.86	<0.01
Hardship (VAS)	18.33 ± 6.17	17.67 ± 5.62	0.812
Pain intensity (VAS)	9.33 ± 9.03	8.33 ± 9.38	0.757
Painkiller tablets (n)	0.87 ± 0.74	0.73 ± 0.88	0.296
Post-operative discomfort (n)	2 (13.3%)	1 (6.7%)	1
Post-operative pain (n)	1 (6.7%)	1 (6.7%)	1

Time, chair-time measured from delivery of anesthesia to completion of the surgical procedures, in minutes; Hardship, personal opinion of the patient for the hardship of the procedure, in 100 mm VAS scale; Painkillers, the number of pain killers taken in addition to the 2 compulsory ones delivered after the surgery; Post-operative discomfort and pain, as questioned at 1-week recall visit; the intensity of pain measured with VAS scale.