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Guided bone regeneration with intentionally exposed membranes and its implications for implant dentistry. A 6 months re-entry randomized clinical trial

ABSTRACT

Aim Post-extraction alteration of the alveolar bone topography is one of the main problems associated with tooth loss. Guided bone regeneration (GBR) technique avoids in great part alveolar bone resorption after extractions This randomized controlled study aimed to evaluate the influence of early membrane exposure on GBR in humans.
Materials and methods The study involved 13 patients, each with 2 premolars with orthodontic indication for extraction. After extractions, clinical measurements were recorded for alveolar depth (AD), buccal-lingual (BL) and mesio-distal (MD) dimensions of the alveoli, and radiographic measurements for radiographic alveolar depth (RAD), width (AW), and total alveoli area (AA). Polytetrafluorethylene (e-PTFE) membranes were then adapted and fixed over the extraction sockets, and based on membrane coverage sockets were divided in: Group I - flap was rotated to completely cover the membrane; Group II - flap was conventionally replaced and membrane remained, intentionally, partially exposed. All patients received antibiotics and after 4 weeks all membranes were removed. Patients were followed up to 6 months, when new X-rays were taken and re-entry surgeries were performed to obtain final clinical and radiographic measurements.
Results Mean variation between pre and post-operative measurements for Group I were: AD=12.01; BL=9.16; MD=5.66; RAD=12.17; AW=5.45; AA=38.43; and for Group II were: AD=10.23; BL=8.41; MD=5.08; RAD=10.08; AW=4.94; AA=31.88. Group I presented significantly higher clinical and radiographic values (Mann-Whitney test, $p<0.05$) comparing to Group II, regarding all studied parameters.
Conclusions Early e-PTFE membrane exposure had a negative effect on alveolar bone formation in humans.

KEYWORDS e-PTFE membrane; Extraction socket; Guided bone regeneration; Membrane exposure.

INTRODUCTION

Dental loss is often associated with development of significant esthetical and/or functional problems. Post-extraction alteration of the alveolar bone topography is one of the main problems associated with tooth loss. During spontaneous socket healing process, even when a gentle extraction technique is applied, alveolar bone ridges decrease in height and thickness (1, 2), which may create difficulties in achieving proper dental rehabilitation, either with implants or with conventional prosthesis, normally due to insufficient amount of bone. The healing of the alveolar process after extraction is dependent on five subsequent stages, which are initiated by coagulum formation (3, 4, 5). The best results are achieved when this process is completed without disturbance (3, 5).
The use of membranes has avoided in great part alveolar bone resorption after extractions. Lekovic et al., in 1997, reported a considerable advantage in the preservation of alveolar bone when membranes were employed in fresh extraction sockets (2). The principle of Guided Bone Regeneration (GBR) is to use a barrier membrane to mechanically block migration of epithelial and connective tissue cells from the inner part of the flap into the extraction socket, and in turn allowing filling of the fresh socket with bone forming cells.
Although it may be more advantageous to place immediate implants into extraction sockets, this is not always feasible. In these cases, when immediate implant placement is not indicated, the appropriate procedure is to use a barrier membrane after extraction, associated or not to bone grafts, to avoid development of bone defects related to socket healing (6, 7), which may create difficulties in the future for placement of a dental implant. Bone regeneration in extraction sockets is often achieved

using membranes; however some factors have been shown to be important for the success of these procedures. One of the risk factors is membrane placement, that requires a very careful technique in order to achieve complete membrane coverage, which appears to be a critical step in the healing process (8). In fact, membrane exposure during healing has a major negative effect on GBR (9, 10).
Extracting a tooth results in soft tissue management difficulties regarding complete closure over a barrier membrane in GBR. One of the main problems after GBR is membrane exposure due to soft tissue dehiscence and/or collapse (11), which may result in the colonization of the membrane surface by oral bacteria, and this may lead to local infection (12). Nevertheless this infection may not necessarily manifest clinically, if appropriate pre and postoperatively measures are taken (13). Although bacterial contamination has been pointed as a drawback in GBR outcomes (15), the exact influence of early membrane exposure on bone formation in extraction sockets have not been fully established.
Some animal studies have been conducted to determine the role of early membrane exposure on the degree of disturbance in the healing process. Warrer et al., in an experimental study in monkeys, have histologically shown that early exposure affected negatively complete bone regeneration (15); Seibert and Nyman, in a study in dogs, found similar results: more bone was formed in sites where the membrane remained covered until second stage surgery for implant placement (6). Some clinical reports have also studied the effects of early membrane exposure in GBR. Nevins & Mellonig, reported four clinical cases in which complete bone formation was achieved after GBR even when early membrane exposure occurred (16). On the other hand, other reports have indicated a negative correlation between contamination on retrieved membranes and clinical outcomes of GBR (14, 17, 18). However, in addition to these clinical reports, no randomized controlled clinical study analyzed the effects of early membrane exposure on bone regeneration.
The purpose of the present study was to further evaluate if early exposure of expanded Polytetrafluorethylene (e-PTFE) membranes impairs bone formation in fresh extraction sockets following guided bone regeneration procedures in humans, through clinical (re-entry surgery) and radiographic parameters (digital radiographs), in a controlled randomized study using a split-mouth design.

MATERIAL AND METHODS

Fifteen patients, aged 18-30 years, were initially selected for the present study (9 women and 6 men, average age of 19.25 years). They received a detailed description about the nature of the study and all involved procedures, signed an informed consent form, and the study protocol was approved by the Ribeirao Preto School of Dentistry Human Research Committee. Comprehensive dental and medical histories were obtained. All participants were systemically healthy, non-smokers, had not used antibiotics in the last 6 months and presented no contra-indications for oral surgical procedures. Each patient had 2 premolars in the maxilla with orthodontic indication for extraction (Fig. 1A, B). Cast models were obtained after dental impression, and the teeth to be extracted were removed from the models. Acrylic stents were then provided in order to standardize the clinical measurements for alveolar depth (AD), buccal-lingual dimensions (BL) and mesio-distal dimensions (MD) of the alveoli.
All clinical and surgical procedures were performed by the same operator. Teeth were gently extracted under local anesthesia. Special care was taken to dislocate the teeth mesio-distally in order to preserve the buccal alveolar wall. The granulation tissue was carefully debrided and the alveoli were rinsed with a sterile saline solution. With the stent in position, clinical measurements for AD, BL and MD were then recorded. AD was measured inserting a periodontal probe (PCUNC 15, Hu-Friedy MFG. Co. Inc., Chicago, IL, USA) in the center of the alveolus in a straight line to its bottom (Fig. 2). Using a dry point compass and an endodontic ruler, the BL dimension was considered the distance between the buccal and the lingual alveolar wall, measured in a standardized position (Fig. 3); in a similar way, the MD distance was measured from the medial to the distal edge of the alveolus. In sequence,

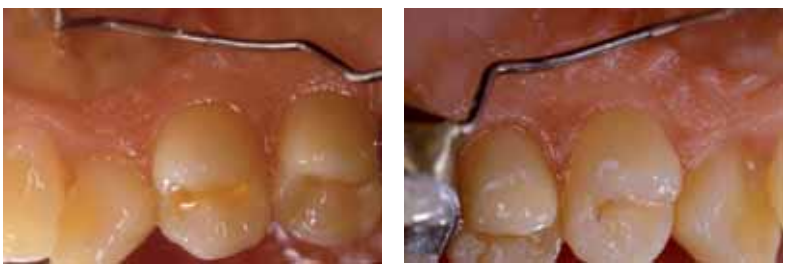

Fig. 1 *Preoperative view of right and left sides, respectively.*

Fig. 2 *Postextraction alveolus, buccal-lingual dimension measurement.*

digital radiographs (RVG, Trophy, Paris, France) were taken using individualized film holders (Fig. 4 A, B).
In one randomly defined site of each patient (alveoli from Group I), vertical incisions were performed, and a combination of full-thickness (more coronal portion) and split-thickness flap (more apical portion) was raised, according to Novaes Jr & Novaes (19). In the other site, buccal and palatal flaps were conventionally elevated (alveoli from Group II). Membranes (e-PTFE GT4 Gore Tex® membranes, Gore-Tex Periodontal Material, Flagstaff, AZ, USA) were then carefully adapted over the extraction sockets and held in position through titanium fixation screws (Frios System, Dentsply-Friadent, Mannhein, Germany). In the alveoli from Group I the flap was rotated and sutured to cover the entire membrane (Fig. 5), while in Group II the flap was conventionally replaced and sutured, and the membrane remained, intentionally, partially exposed (Fig. 6).
All patients were placed on antibiotics, as previously described (20): amoxicilin + clavulanic acid, 500 mg, every 8h, starting 24 hours before the surgery and continuing for 10 days; then doxycyclin 100mg once a day (twice in the first day) for another 21 days. All patients were instructed to discontinue tooth brushing and to avoid trauma or pressure at the surgical site, and also to use a 0.12% chlorhexidine digluconate solution twice a day for 4 weeks. Plaque control was maintained by weekly careful prophylaxis with ultrasonic points. After 4 weeks all sutures and membranes from both groups were removed. During the postoperative period, the adjacent teeth were maintained in position by the orthodontic appliances. The patients were recalled for control and prophylaxis monthly up to 6 months, when re-entry surgeries (Fig. 7A, B) and digital radiographs (Fig. 8A, B) were performed to obtain final measurements. Despite the invasive nature of a re-entry procedure, it has the important advantage of providing a three-dimensional analysis of the newly formed tissues in the alveoli, apart from enabling eventual correction of remaining defects (21).
Radiographic analysis (comparison of initial and final digital radiographs) provided measurements for radiographic alveolar depth (RAD) and width (AW), and total defect area (AA). For maximum RAD, the

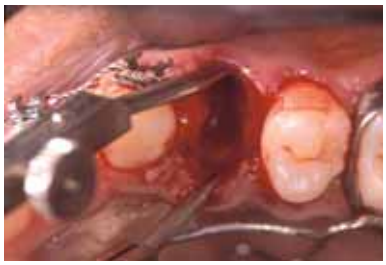

Fig. 3 *Post-extraction alveolus. Alveolar depth dimension measurement.*

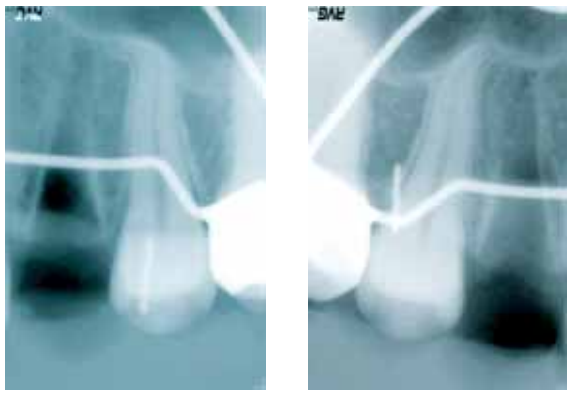

Fig. 4 *Immediate postextraction radiographies: A) Group I; B) Group II.*

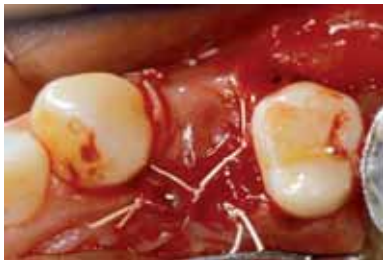

Fig. 5 *Group I - flap was rotated to cover the entire membrane.*

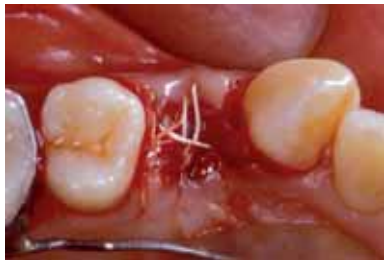

Fig. 6 *Group II - flap was conventionally replaced and membrane remained, intentionally, partially exposed.*

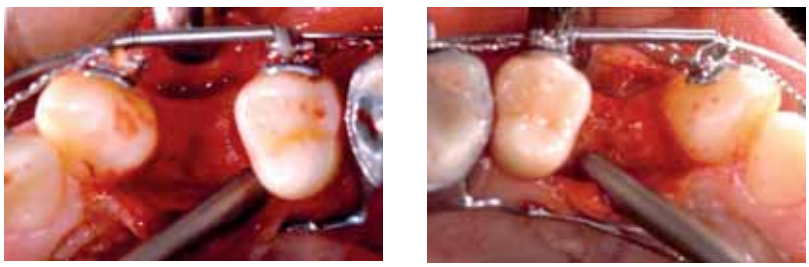

Fig. 7 *Re-entry surgery: A – Group I; B – Group II.*

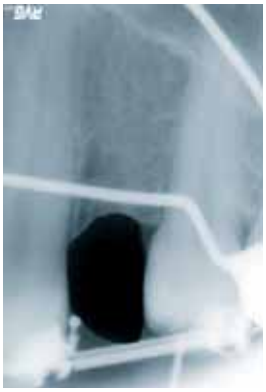

Fig. 8 *6-month post-operatively radiographies: A) Group I; B) Group II.*

Fig. 9 *Radiographic parameters: in yellow, line representing the maximum alveolar width (AW); in red, line representing the maximum alveolar depth (RAD).*

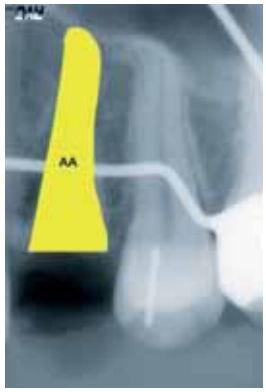

Fig. 10 *Radiographic parameters: in yellow, area used to calculate total defect area (AA).*

distance between an imaginary line, connecting mesial and distal osseous crests, and the most apical extent of the alveolus was measured. The maximum distance between mesial and distal alveolar crests was considered as the maximum AW (Fig. 9). In order to calculate AA, the "empty" area inside the alveolus was measured, i.e. the area between the alveolar walls and an imaginary line connecting mesial and distal crests (Fig. 10).

Data analysis

Each clinical measurement, namely AD, BL and MD dimensions, and each radiographic measure, namely radiographic RAD and AW and AA, were obtained in mm (and in mm^2 for AA), according to the following formulas:

¢= I – F (where ¢= measure variation; I= initial measure; F= final measure).

Then, the percentage values were calculated:

%= ¢ x 100/I (%= percentage value; ¢= measure variation; I= initial measure).

Mean values and standard-deviations for alveoli from Groups I (covered membranes) and II (exposed membranes) were obtained, and compared through the Mann-Whitney test ($p< 0.05$, $n=13$), to determine if the 2 groups had similar values preoperatively, and if one of the surgical procedures produced a better result after 6 months.

RESULTS

Fifteen patients were initially selected for the present study. In two patients, the membranes of Group I became exposed in the post-operative period – these patients were then discharged. The sample size, for statistical analysis, was of 13 patients (9 woman and 4 man, average age of 19.68 years). The pre-operative values for both groups were similar – there were no significant statistical differences between them (Mann-Whitney test, $p > 0.05$). The averages and standard-deviations for all pre-operative parameters are summarized in Table 1.

The healing process was uneventful for all 13 patients that concluded the study. No evidence of inflammation or infection was observed in any of the sites, even in those with exposed membranes. The systemic antibiotics and local antimicrobial regimen were well tolerated. However, as stated before, in two patients of the initial sample the membranes of Group I became exposed. Even though there were no signs of infection in these patients and sites, they were excluded from the sample because of the nature of comparisons that were made in this study, which requires a completely covered membrane during the entire period proposed (4 weeks).

Averages and standard-deviations for the 0-6 month variations of the clinical parameters of both groups are summarized in Table 2. Regarding all clinical measures, alveoli from Group I (covered membranes) presented significantly higher values ($p<0.05$) when compared to Group II (exposed membranes). The strongest difference between the groups was regarding AD, as alveoli from Group I presented almost 20% more vertical gain compared to Group II. For the other clinical measures, BL and MD dimensions (MD), Group I presented around 10 % more gain than Group II.

	Group I	Group II	P < 0.05*
AD	12.23 ± 1.74	11.15 ± 1.46	NO
BL	9.54 ± 0.78	8.92 ± 1.12	NO
MD	5.92 ± 0.64	5.77 ± 0.73	NO
RAD	12.69 ± 1.68	11.02 ± 1.21	NO
AW	6.12 ± 0.42	5.59 ± 0.55	NO
AA	38.79 ± 4.06	36.50 ± 4.17	NO

** Mann-Whitney test*

Table 1 *Averages and standard-deviations for pre-operative parameters.*

	Group I	Group II	p*
AD	12.01 ± 1.80	10.23 ± 1.94	0.03
BL	9.16 ± 0.71	8.41 ± 0.90	0.04
MD	5.66 ± 0.49	5.08 ± 0.51	0.02
RAD	12.17 ± 1.67	10.08 ± 1,75	0.001
AW	5.45 ± 0.43	4.94 ± 0.67	0.03
AA	38.43 ± 4.08	31.88 ± 4.32	0.008

** Mann-Whitney test*

Table 2 *Averages and standard-deviations for the 0-6 month variations of the clinical and radiographic parameters of both groups.*

Averages and standard-deviations for the 0-6 month variations of the radiographic parameters are shown in Table 2. Group I exhibited statistically better results ($p<0.05$), with 20% more gain in RAD, 10% more gain in total defect area and 20 % more gain in AW.

DISCUSSION

One of the most common clinical complications in GBR procedures is early membrane exposure (22). Results from the twenty-six sites evaluated in the present randomized controlled study demonstrated that fresh extraction sockets in which membranes were totally submerged during the whole healing process presented better clinical and radiographic results. Although evidence of a negative effect of membrane exposure in bone formation has been previously discussed (23, 24, 25), to our knowledge there are no prospective data regarding the effect of intentionally exposed e-PTFE membranes in fresh extraction sockets in humans on GBR results. Thus, as the majority of the studies have evaluated bone formation under membranes placed in conjunction with immediate implants, it becomes difficult to draw direct comparisons to the present controlled randomized clinical study in humans.

Gher et al. (26), in 1994, and Nowzari and Slots (14), in 1995, reported that, when membranes used in association to immediate implants became exposed, new bone formation was decreased in comparison to submerged membranes. Also in 1994, Celletti et al. evaluated the efficacy of guided tissue regeneration around exposed implant threads, in fresh extraction sockets in beagle dogs. The authors found that the greatest gain in bone levels was seen for two sites that received e-PTFE membranes and remained covered for the entire evaluation interval (10). Furthermore, Machtei, in 2001, showed that sites with submerged membranes presented 6 times more bone formation around implants than sites in which membranes became exposed, and the author highlighted that this finding was not only statistically significant, but had a clinical significance (9). Thus, our findings are in agreement with previous studies, as exposure had a detrimental effect on new bone formation (around 20% more bone formation was associated with submerged membranes).

Evaluating ridge defects treated with GBR, Lang et al. (27) concluded that membrane exposure is likely to be a risk factor for infection after verifying that sites with exposed and prematurely removed membranes presented up to 40% less defect fill. In 2002, Lorenzoni et al, a retrospective study in 41 patients with implants associated with GBR showed higher alveolar bone loss associated with premature membrane exposure up to 24 months after implant placement, when compared to the implants in which the membranes remained submerged. In 2004, a human study by Moses et al. (28) also showed that premature exposure of e-PTFE membranes resulted in a significant decrease in the amount of defect reduction around implants. In contrast, only the study of Nevins and Mellonig (16), in 1992, showed different results from GBR in ridge defects, where complete osseous formation was demonstrated in 4 patients, regardless of membrane exposure.

Despite the fact that our membranes were not submitted to microbiological analysis, based on previous studies on the relation between unsuccessful GBR procedures and microorganisms (14, 17), one of the possible explanations for less bone formation is the presence of bacterial colonization on exposed membranes which in turn might have hampered osteogenesis. e-PTFE membranes used for GBR present an inner occlusive and rigid surface to prevent migration of gingival cells into the defect and to maintain adequate space for bone formation, and a less occlusive and more flexible outer surface, in order to prevent epithelial proliferation (if exposed) and to provide good adaptation, tissue integration and wound stabilization (18). Interestingly, Simion et al. (17), in 1994, evaluating 10 sites in which immediate implants were associated with e-PTFE membranes, were able to detect the presence of potentially pathogenic bacteria in the outer as well as in the inner surfaces of membranes that became exposed. Another equally valid supposition is that an exposed non-absorbable membrane leads to compromised vascularity of the buccal and palatal flaps, which may have lead to a deficient coverage of the healing bone by the soft tissues.

It is important to emphasize that the surgical protocol used in this study, with membrane removal 4 weeks after placement, is not a proposal for clinical routine. The 6 month or greater time frame (2, 14) is clearly the more accepted practice. We had to remove the membranes 4 weeks after placement because the patient, due to ethical reasons, should not be maintained under antibiotics for a longer period,

which was necessary since the membrane was intentionally exposed. To guarantee that the only different parameter between groups was early membrane exposure, the membrane of the control group was also removed 4 weeks after placement.

The results from the present study indicate that achieving complete membrane coverage is a critical step, which optimizes bone formation in extraction sockets. It should be emphasized that in clinical practice, one or two millimeters of bone can make a big difference when planning the placement of osseointegrated implants. If the membrane is maintained without exposure for the entire healing period, the site that will receive an implant will probably present better conditions to comprise the esthetical and functional requirements of the treatment. A better contour of the alveolar bone will allow the ideal positioning of the implant. It will also make possible the placement of a longer and wider implant, which in some cases could be an important advantage, since it was demonstrated that the removal torque for wide diameter implants (4,5 mm) is 15 % greater than small diameter (3,25 mm), in bone of the same density (29); furthermore, the use of wider implants will lead to more implant-bone contact than narrow implants of the same length, and also allow the use of shorter implants in areas of adequate bone quality. This could be especially relevant in the posterior maxilla, since the use of shorter implants in many cases will avoid the need of more morbid surgeries, such as sinus floor elevations, and also in posterior mandible, where the inferior alveolar nerve is usually a limiting factor for the placement of longer implants.

Finally, the employed surgical technique, which results is relieved tension on the flaps, has been shown to be simple and effective in obtaining and maintaining primary closure over membranes placed over extraction sockets, without creating mucogingival or esthetical problems (19).

It can be concluded from this randomly controlled study that early e-PTFE membrane exposure leads to decreased bone formation in extraction sockets in humans. Efforts should be made to avoid membrane exposure and the surgical technique employed in this study to achieve primary membrane coverage is recommended, as it has been shown to be simple, effective and stable.

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