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A randomized, controlled clinical trial to evaluate a new membrane for guided bone regeneration around dental implants

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Abstract

Objectives: The use of barrier membranes in guided bone regeneration (GBR) procedures for the treatment of alveolar bone defects is common practice. The objective of this study was to test whether a synthetic bioresorbable polyethylene glycol (PEG) hydrogel membrane could result in a similar amount of vertical bone fill as a standard collagen membrane, both combined with a membrane supporting material.

Material and methods: The study enrolled 37 patients requiring implant treatment with an expected osseous defect in the posterior maxilla or mandible. After raising a mucoperiosteal flap, the implant sites were prepared and dental implants placed. The defect height was then measured and defects <3 mm were excluded from the study. Defects were grafted with bovine bone mineral and randomly covered with either a collagen membrane (control group, 18 patients) or a PEG hydrogel membrane (test group, 19 patients), which is applied as a liquid. After a healing period of 6 months, surgical re-entry was performed and the change in vertical bone height from baseline evaluated. **Results:** Well-vascularized hard tissue was apparent at all sites and the regenerated bone was similar to the surrounding native bone. Mean vertical defect fill after 6 months was 5.63 ± 1.84 mm at test sites and 4.25 ± 1.16 mm at control sites, and the mean defect fills were 94.9% and 96.4% at test and control sites, respectively. More soft tissue complications were observed with the PEG membrane (e.g., delayed or incomplete wound healing) but all sites recovered uneventfully.

Conclusions: The new PEG hydrogel membrane was as successful as a standard collagen membrane in the treatment of bony dehiscence defects around dental implants with simplified clinical handling.

The method of guided bone regeneration (GBR) is most commonly used in clinical situations for the treatment of limited alveolar bone defects in the jaws. It is based on the concept of using a barrier to create a space into which the cells originating from bone tissue can grow without migration or interference of the faster proliferating cells of the connective or soft tissue (Gottlow et al. 1984; Nyman & Lang 1994).

The tool used to generate this is a cell occlusive membrane, which can be manufactured from different natural or synthetic polymers. Nowadays, biodegradable membranes made of collagen have become the standard of care in many clinical situations (Zitzmann et al. 1997; Hämmerle et al. 1998; Jung et al. 2003; Moses et al. 2005).

Common to all currently used membranes is the fact that their fabrication is

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completed before they are delivered for patient use. Consequently, they are made available in standard sizes and forms and need to be adapted to the patient's individual situation. The availability of a synthetic and resorbable membrane that could be directly custom-made intraoperatively for an individual defect would therefore represent an improvement for future GBR procedures.

Experimental studies have introduced a newly developed synthetic hydrogel made of polyethylene glycol (PEG) for use in bone regeneration therapy (Lutolf et al. 2003; Jung et al. 2006; Wechsler et al. 2007). PEG has been shown to be highly biocompatible and was investigated in other medicine disciplines, e.g. as a sprayable adhesion barrier (Vaage et al. 1997; Mettler et al. 2003). Several preclinical studies with different animal models have been conducted to evaluate the possibilities and limitations of this PEG material for its use as a barrier membrane or matrix in GBR procedure (Jung et al. 2006; Wechsler et al. 2007; Thoma et al., submitted). The promising results from these experimental studies have led to investigations of the efficacy and the feasibility of the PEG membrane for the first time in clinical situations.

The primary aim of the present study was to test whether a synthetic and biodegradable PEG membrane could result in a similar amount of vertical bone fill as a standard collagen membrane, both combined with a membrane supporting material.

Materials and methods

The present study was a prospective, controlled, randomized, clinical investigation. All procedures and materials were approved by the local ethical committee. Informed consent was obtained from all patients.

Patients

The study recruited 37 male or female patients in need of implant treatment in at least one site with an expected osseous defect in the posterior mandible or maxilla. All patients were in good general health and underwent comprehensive dental care.

Enrolled patients complied with all the inclusion and exclusion criteria. Two of the

inclusion criteria, such as primary stability of the dental implant and osseous defect ≥ 3 mm in vertical dimension could only be evaluated on the day of surgery. If two or more sites were still available fulfilling the defect criterion, one was selected by throwing a die. The selected site was assigned to a treatment according to the randomization envelope.

In the event that a patient was found to be ineligible for the study at the time of surgery, an alternative treatment following good clinical standards was offered to the patient.

PEG biodegradable hydrogel membrane

The investigational device is a synthetic biodegradable barrier membrane (Institut Straumann AG, Basel, Switzerland) composed of two multifunctional PEG molecules. The membrane material is applied as liquid and forms a hydrogel by a cross-linking reaction within a few seconds after application. The membrane is degraded hydrolytically during the healing period.

The PEG components and corresponding buffers are supplied in four separate syringes and have to be mixed immediately before use.

Surgical procedure

The implant placement was performed either as a delayed (between 6 weeks and 6 months after extraction) or a late procedure (more than 6 months after extraction). Before surgery, the patients received antibiotics (2×750 mg Clamoxyl[®]; GlaxoSmithKline AG, Münchenbuchsee, Switzerland) and analgesics/antiphlogistics (500 mg Mefenacid[®]; Streuli Pharma AG, Uznach, Switzerland). Surgery was performed under local anesthesia. The incision was placed at the mid-crest, with releasing incisions if necessary, and a mucoperiosteal flap was raised. The implant site was prepared according to current standard Straumann instructions and a Straumann SLA solid screw implant (Institut Straumann AG) was inserted.

Immediately after implantation, initial implant stability was assessed by hand testing. If any implant lacked primary stability at this assessment, the patient was excluded from further participation in the study.

The osseous defect of eligible sites was determined after implant placement with

the help of a calibrated periodontal probe. If the defect height was < 3 mm, the patient was excluded from the study. If the defect height was ≥ 3 mm, the site was assigned to a treatment according to the randomization envelope.

Measurement of defect size

- Defect height (mm) measured from the SLA surface border of the implant to the first bone-to-implant contact (BIC; Fig. 1a).
- Defect width (mm) measured from the mesial to the distal bone crests (Fig. 1b).
- Defect depth (mm) measured from the bone crest to the implant surface in a direction perpendicular to the long axis of the implant (Fig. 1c).
- Infrabony defect height (mm) measured from the bone crest to the first BIC (Fig. 1d).

Augmentation procedure

Osseous defects around implants were grafted with a natural bone mineral of bovine origin (BioOss[®] Spongiosa Granules, particle size 0.25–1 mm; Geistlich Pharma AG, Wolhusen, Switzerland). The defect was filled with the bone substitute without being overfilled. The natural bone mineral was used alone. Horizontal thickness after augmentation procedure was assessed; this value was 0 before the GBR procedure (Fig. 1e).

Afterwards, the xenogenic bone substitute was covered according to the randomization with either test or control membrane.

- *Test group (PEG membrane)*: The filled defect was covered with the PEG membrane. The prepared gel was applied directly over the bone substitute using the dental tip of the static mixer. After the *in situ* gelation, the membrane had to overlap the walls of the defect by at least 2 mm. The thickness was approximately 1 mm. No fixation was needed as the gel adheres to the surrounding tissues (Fig. 2).
- *Control group (BioGide[®] membrane; Geistlich Pharma AG)*: The filled defect was covered with a standard collagen membrane. The size of the membrane was adapted using scissors according to the exposed bone defect.

The membrane overlapped the walls of the defect by at least 2 mm to allow complete bone contact and to prevent gingival connective tissue invasion be-

low the material. The membrane was fixed by resorbable pins made of polylactic acid (Resor Pin[®]; Geistlich AG, Wolhusen, Switzerland) to avoid mem-

brane displacement due to loading or mobilization.

For test and control sites, the time taken for extraoral membrane preparation and for surgical application was recorded. Extraoral membrane preparation included the opening of package and mixing of PEG membrane components, and cutting the collagen membrane with scissors. In the test group, surgical application included application and gelation of the PEG membrane. In the control group, application consisted of adapting and fixing the collagen membrane.

Wound closure

Periosteal-releasing incisions were used to allow tension-free adaptation of the mucoperiosteal flaps. Healing was attempted with the implants in a submerged position (except for two test sites with non-submerged healing). The sutures used were ePTFE non-absorbable monofilament sutures (Gore-Tex[®] suture; Gore, Flagstaff, AZ, USA).

Postoperative treatment

The patients were instructed to rinse twice daily with an aqueous solution of 0.2% chlorhexidine (Kantonsapotheke, Zurich, Switzerland) and to continue the antibiotic regimen for 5 days (750 mg Clamoxyl[®], three times a day). In addition, analgesics (500 mg Mefenacid) were prescribed for the next 2 days according to individual needs. Patients were also instructed to refrain from mechanical plaque removal in the area of implantation for 1 week. The sutures were removed 7–10 days following implantation.

Re-entry

Six months later, a re-entry surgery was performed to assess the result of the attempted regeneration. Mucoperiosteal

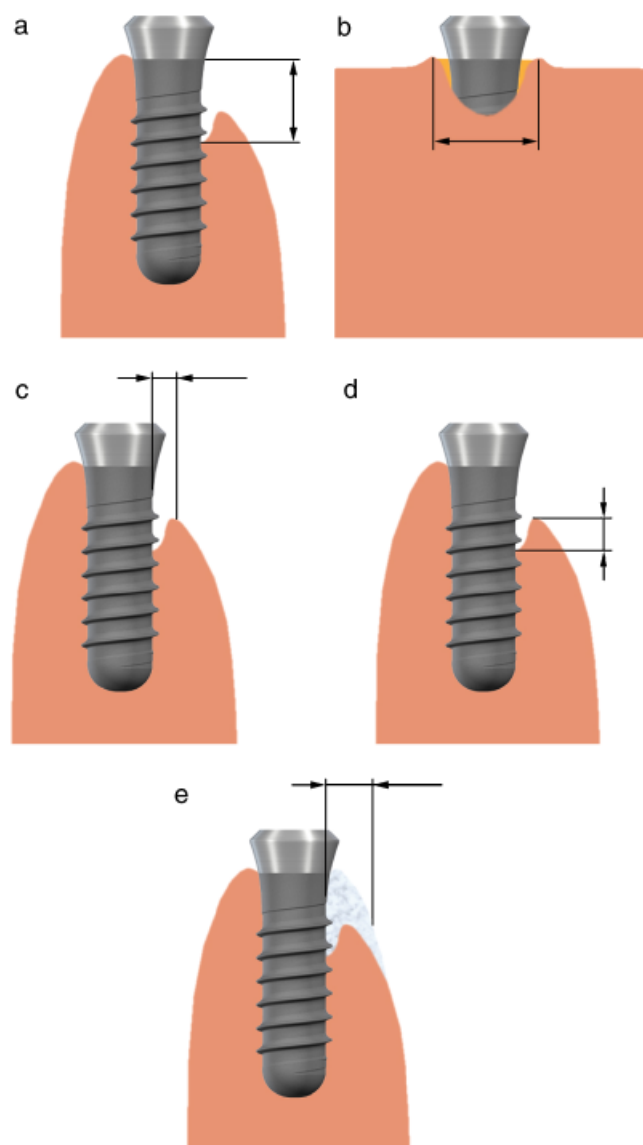


Fig. 1. (a) Defect height from SLA surface border to first bone-to-implant contact (BIC), (b) defect width from mesial to distal bone crests, (c) defect depth from bone crest to implant surface, (d) defect height from bone crest to first BIC, (e) horizontal thickness after filling with natural bone mineral.

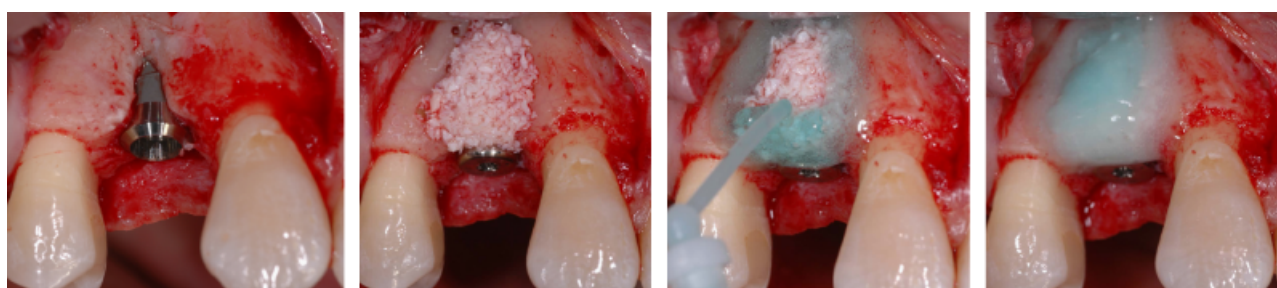


Fig. 2. In situ application of polyethylene glycol hydrogel membrane.

flaps were reflected to allow for exact evaluation. The same clinical measurements assessed at baseline were again recorded (Fig. 1a–d). To assess horizontal thickness after augmentation procedure (Fig. 1e), a special measuring abutment was placed on the implant. Cover screws were replaced by healing abutments. Subsequently, the flaps were adjusted to fit around the neck of the healing abutment and sutured. One week later, the sutures were removed.

Statistical evaluation

The change in vertical bone level after 6 months was the primary variable for this study. The power-analysis showed that with a minimum of 17 patients per group (total of 34 patients), it will be possible to detect a difference of 1 mm between the test and control group with a standard deviation (σ) = 1 and a significance level of $\alpha = 0.05$ with a power of 80%. To protect from possible drop-outs, the sample size was increased by 10% resulting in 18 patients per group (total of 36 patients). The secondary variables related to bone regeneration and consisted of measurements of the defect width, defect depth, infrabony defect and the horizontal thickness of the augmented bone. Data were reported using means and standard deviations (SDs). The two-sided *t*-test was selected to detect differences between the test and the control sites. The level of statistical significance was set at $P \leq 0.05$.

Soft tissue healing for both groups was clinically assessed and descriptively listed. A comparison of the times taken for the extraoral preparation and the intraoral application of the two membranes was made.

Results

Patients

Thirty-seven patients were enrolled and entered in the trial: 19 were randomized to test group (PEG Hydrogel) and 18 to the control group (collagen membrane). The mean age was 48 years (range 32–72 years) in the test group and 54 years (range 23–80 years) in the control group.

Clinical observations at baseline

Both treatment groups were homogeneous with regard to the baseline values of the

quantitative variables measured, with the exception of the defect height. At baseline, mean defect height was 5.95 ± 1.9 mm in the test group and 4.5 ± 1.54 mm in the control group, showing a statistically significant difference ($P = 0.016$).

Healing period, soft tissue

After an observation period of 6 months, no evidence of serious adverse local or systemic effects was observed in any of the groups.

During the healing period, nine patients treated with test membrane and six with the control membrane complained of mild to moderate adverse events. Of these, two patients in each group complained about pain or discomfort during the initial healing period. In the test group, six sites with a delayed wound healing and/or a remaining dehiscence on top of the cover screw were observed (Fig. 3). No special care was needed for these sites. In another three sites in the test group, the wound healing was primarily uneventful. However, after 5–7 weeks, these sites showed a slight buccal dehiscence defect with an exposure of the implant shoulder (Fig. 4). Local disinfection (rinsing with 0.2% chlorhexidine) was performed. All sites recovered



Fig. 3. Remaining dehiscence during the healing period observed in six sites in the test group.

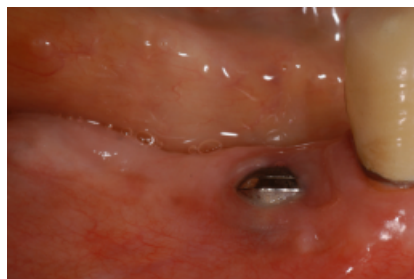


Fig. 4. Buccal dehiscence with exposure of implant shoulder observed in three sites in the test group after 5–7 weeks.



Fig. 5. Delayed/incomplete wound healing observed in four sites in the control group.

even though dehiscence remained until re-entry surgery. In the control group, four sites with delayed or incomplete wound healing were observed (Fig. 5). All of them recovered uneventfully.

Clinical observations at re-entry, bone volume and quality

After a healing period of 6 months, a re-entry operation was performed for abutment connection and to measure the residual defects. At this time point, all implants were stable.

The quality of the newly formed bone varied from very dense bone to more soft bone. In cases with dense bone, almost no graft particles could still be seen. The regenerated bone was very similar to the surrounding native bone. The majority of the cases showed a bone quality where the graft particles were still recognizable on the surface of the regenerated area but embedded in newly formed bone (Fig. 6).

Sufficient bone volume and quality was observed at all sites, even where soft tissue healing was delayed or incomplete.

In all sites, the defect heights had decreased. At the test and the control sites, vertical defect fills of 5.63 ± 1.84 and 4.25 ± 1.16 mm, respectively, were observed (Fig. 7a). This difference of vertical defect fill between test and control membrane was statistically significant. However, the percentage of vertical bone defect filling after 6 months did not reveal a statistically significant difference between the two groups (Fig. 7b). At the test and control sites, the calculated vertical defect fills were 94.9% and 96.4%, respectively.

Regarding change in defect depth (Fig. 8a) and defect width (Fig. 8b), no statistically significant differences between the two groups were observed.



Fig. 6. Graft particles on surface and embedded in newly formed bone.

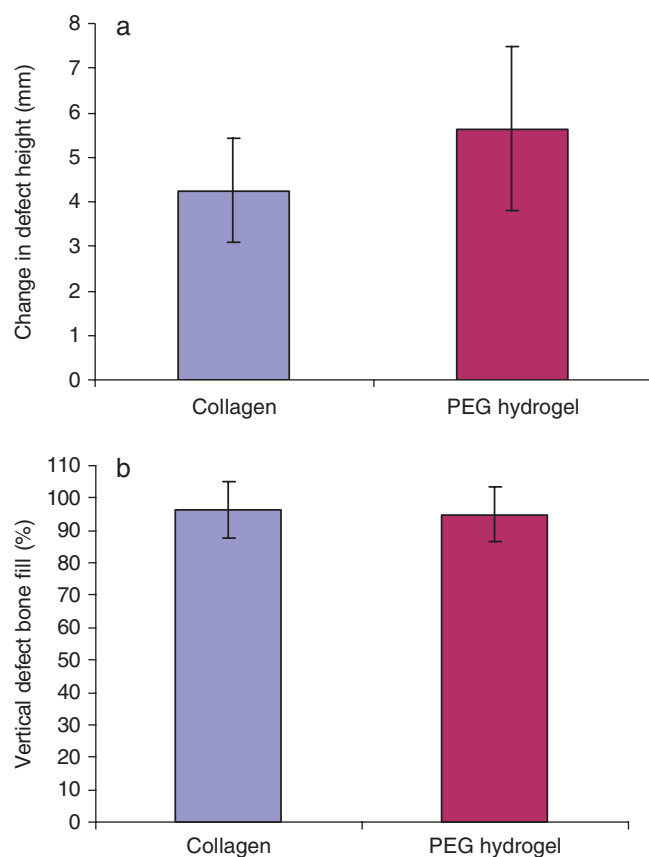


Fig. 7. (a) Change in defect height (mm), (b) vertical defect bone fill (%).

Time for membrane application

For test and control sites, the time taken for extraoral membrane preparation and for surgical application was recorded. The extraoral preparation time was slightly lower for the PEG hydrogel membrane, and the intraoral application time was significantly lower ($P < 0.001$; Table 1).

Discussion

The present study demonstrated that a synthetic *in situ* forming PEG membrane could successfully be used as a biodegradable barrier membrane for GBR in humans.

This was documented by a similar amount of defect resolution compared with defects treated with a standard collagen membrane.

This randomized controlled clinical study was designed in a similar way to a previous human study evaluating the effect of rhBMP-2 in dehiscence type bone defects around dental implants (Jung et al. 2003). Both studies reported similar initial defect heights ranging from 4.5 to 6 mm in the present study and from 5.8 to 7 mm in the previous study. In addition, the favorable data of the present study regarding mean vertical bone fill obtained at the control (96.4%) and at the test sites (94.9%) corre-

spond well with previous clinical studies using resorbable and non-resorbable membranes. These clinical studies reported mean vertical defect resolutions of 92% (Zitzmann et al. 1997), 86% (Hämmerle & Lang 2001) and 91% (Jung et al. 2003) using the same collagen membrane and the same xenogenic bone substitute mineral as the control sites in the present study. These comparable values reveal that the PEG membrane was at least as effective in treating dehiscence type bone defects around dental implants as a standard collagen membrane. This was also documented by the fact that the changes in defect height (in mm) were statistically significantly higher in the test group (5.63 mm) compared with the control group (4.25 mm). However, it has to be taken into account that the initial defect height was slightly higher in the test group compared with the control group. Hence, the normalized data (percentage changes against baseline) no longer revealed any statistically significant difference between the test and the control group. Regarding the changes in defect depth, the control group revealed a higher standard deviation than the test group, although no difference could be detected in the mean values. It might be speculated that the PEG membrane revealed a more consistent stability of the augmented volume. Therefore, the soft tissue pressure of the surrounding mucosa might not have the same negative influence to the regeneration volume for the PEG membrane compared with the collagen membrane.

The majority of the cases in both groups showed a bone quality where the graft particles were still recognizable on the surface of the new tissue. This is in line with other clinical studies treating bone defects simultaneously with dental implant placement reporting similar clinical observations (Zitzmann et al. 1997; Jung et al. 2003). On a histological level, one study stated that the individual particles of the xenogenic bone substitute mineral were clearly identifiable and they were found to be surrounded by varying amounts of newly formed bone, osteoid and bone marrow (Jung et al. 2003). This could possibly explain that some re-entry sites in the present study revealed a more softer bone than others.

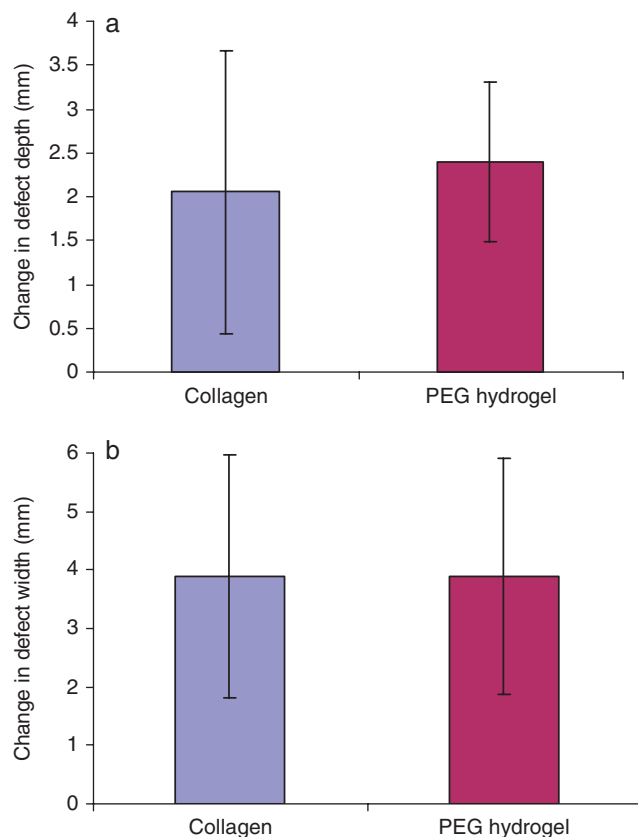


Fig. 8. (a) Change in defect depth (mm), (b) change in defect width (mm).

Table 1. Time taken for extraoral preparation and intraoral application of membranes

	Patients (N)	Mean (SD) (s)	P-value for differences between treatment groups
Extraoral			
PEG Hydrogel	19	96.79 (39.23)	0.115
Collagen	18	124.83 (63.95)	
Intraoral			
PEG Hydrogel	19	61. (25.54)	0
Collagen	18	194.83 (122.5)	
PEG, polyethylene glycol.			

Future developments of GBR membranes can either be related to increasing the safety and predictability of the membranes and/or simplifying the clinical handling. Collagen membranes are the most often used resorbable membranes and have been extensively tested in human and animal studies (Zitzmann et al. 2001; Jung et al. 2003; Moses et al. 2005). However, collagen is derived from animal materials and carries the potential risk of immunogenic reactions and transmission of animal-derived pathogens (Schwartzmann 2000). In order to overcome these difficulties, a synthetic membrane made of

PEG has been developed. The PEG material has been successfully investigated in several preclinical studies for use as a matrix system to release bioactive molecules (Lutolf et al. 2003; Jung et al. 2007a, 2007b) and as a GBR membrane (Jung et al. 2006). In addition to these indications, PEG is presently used in other medical disciplines. The safety and effectiveness of a sprayable PEG material used as a barrier system in laparoscopic surgery has been assessed in a randomized, prospective, controlled, clinical trial (Mettler et al. 2004). It was demonstrated that the PEG material was safe and well tolerated, with no ad-

verse effects attributed to the material and no patients in whom it could not be applied. In the present study, no serious adverse events were reported during the 6-month study period. However, nine patients treated with PEG hydrogel and six with collagen membrane complained of mild to moderate adverse events ranging from pain and discomfort to soft tissue dehiscence.

The clinical evaluation of the soft tissue coverage at the time of suture removal revealed six instances of small to moderate soft tissue dehiscence at the test sites (31%) and four of moderate soft tissue dehiscence at the control sites (22%). All had an uneventful recovery without removing the membrane. However, only one site per group healed completely whereas the others remained with an exposure of the cover screw. At the test sites, the exposures were generally very small (<1 mm) whereas at the control sites, almost the entire cover screw was exposed after 30 days. This is in agreement with another clinical study comparing two different collagen membranes with an ePTFE membrane (Moses et al. 2005). The authors reported 32.1% wound dehiscence at the time of suture removal using the same collagen membrane as in the present study. Soft tissue healing over these exposed barriers were noticed only in one out of nine patients. Regarding the amount of soft tissue complications, a previous study evaluated the same resorbable collagen membrane and a non-resorbable ePTFE membrane for GBR at dehiscence type bone defects (Zitzmann et al. 1997). The authors reported a total of incomplete wound closure after 7–10 days of 16% for the collagen membrane and of 22% for the ePTFE membrane. Another study investigated a newly developed cross-linked collagen membrane (Friedmann et al. 2002). In this study, only five out of 14 sites healed uneventfully. In nine patients (64%), soft tissue dehiscence occurred within the first 14 postoperative days. However, within the following 4 weeks, the healing by secondary epithelialization was completed in all nine exposed sites. The reasons for these generally high values of soft tissue complications remain unclear. In the present study, one reason for the relatively high numbers of complications might be that the patients have been

treated in the postgraduate clinic with less experienced surgeons. An additional reason may be that very small dehiscence with diameters <1 mm that recovered after 1–2 weeks have also been recorded as adverse events. In contrast to the control sites, three out of 19 test sites revealed a late soft tissue dehiscence. These complications occurred mainly in the posterior mandible with very little or no keratinized mucosa exposing the buccal implant shoulder. It is unclear whether this delayed dehiscence after 5–7 weeks is attributed to the lack of keratinized mucosa and the perforating implant shoulder or to the PEG membrane itself. After the implant shoulder was exposed, no further complications occurred. It would be interesting to further evaluate the soft tissue integration properties of the PEG material.

An additional development in future GBR procedures may be a simplification of the clinical handling. Common to all presently used membranes is the fact that their fabrication is completed before they are delivered for patient use. Consequently, they are made available in standard sizes and forms and need to be adapted to the patient's individual situation. In contrast to the control membrane, the presently used PEG membrane can be custom-made for an individual defect directly intraoperatively. This allowed a reduction of the intraoral application time by more than three times compared with the control membranes. There are no other studies available describing the time needed for GBR procedures.

It can be concluded that the *in situ* formed PEG membrane could be successfully used to treat bony dehiscence defects

around dental implants with similar amounts of defect resolutions as achieved with a standard collagen membrane. The test membrane revealed more soft tissue complications than the collagen membrane. The PEG membrane showed a favorable and simplified clinical handling as well as a decreased intraoral application time.

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