A Randomized, Controlled Clinical Evaluation of a Synthetic Gel Membrane for Guided Bone Regeneration Around Dental Implants: Clinical and Radiologic 1- and 3-Year Results

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Purpose: The objective of this study was to determine whether a synthetic bioresorbable polyethylene glycol (PEG) hydrogel membrane could provide similar clinical and radiographic outcomes as a standard collagen membrane, both in combination with a membrane-supporting material, during follow-up periods of 1 and 3 years.

Materials and Methods: This study enrolled patients requiring implant treatment with an expected osseous defect in the posterior maxilla or mandible. Defects around the implants were grafted with deproteinized bovine bone mineral and covered with either a collagen membrane or a PEG hydrogel membrane, which is applied as a liquid and becomes a solid gel in situ. Surgical re-entry was performed after 6 months, and fixed partial dentures were inserted subsequently. Patients were examined clinically and radiographically 1 and 3 years after loading. Results: Thirty-six of the 37 included patients were reexamined in the third year. The implant survival rate at 3 years was 100%. The peri-implant tissues were healthy, with no differences between the two groups. Compared to the time of surgery, the mean changes in the distance between the first bone-to-implant contact to the transition point (ie, rough implant surface to polished neck portion) were 0.43 ± 0.56 mm (PEG) and 0.21 ± 0.36 mm (collagen) at 1 year and 0.61 ± 0.89 mm (PEG) and 0.33 ± 0.64 mm (collagen) at 3 years. The respective differences between groups were 0.13 mm (1 year) and 0.31 mm (3 years), which were not significant at either time point (analysis of covariance). Conclusion: The tested PEG hydrogel was as successful as a standard collagen membrane for the treatment of bony dehiscence defects around dental implants after follow-up periods of 1 and 3 years. Int J Oral Maxillofac Implants 2012;27:435–441.

Key words: bone substitute, dental implant, graft material, guided bone regeneration, membranes, randomized controlled trial

As implant dentistry has evolved, it has become evident that implants cannot be placed directly into the jaw in all situations without prior or concomitant bone augmentation procedures. Therefore, the concept of guided bone regeneration (GBR) has been fundamental in optimizing implant dentistry.1,2 The main tool in GBR is a cell-occlusive membrane that can be manufactured from different natural or synthetic polymers. The properties of these membranes are clearly defined and fulfill the following specific criteria: biocompatibility, tissue integration, cellular occlusion, space preservation, and easy clinical handling.3,4

In the past decade, two types of membranes have been successfully investigated in preclinical and clinical trials. In the 1980s, nonresorbable membranes largely predominated, but since the 1990s, the biodegradable type has been favored by clinicians. Nonbiodegradable membranes consist of expanded polytetrafluoroethylene (e-PTFE) and are well documented in implant dentistry.2 However, e-PTFE presents several drawbacks, including the necessity for a second surgery for its removal and a high rate of complications, such as exposure of the membrane to the oral environment.
and subsequent infection. As a consequence, most clinicians use resorbable membranes in combination with filling materials to compensate for the lack of stiffness that is typical of this type of barrier membrane.

Collagen membranes of animal origin may be considered the standard resorbable membrane, with the clinically relevant advantage that no second surgery for removal is required. The application of resorbable membranes made of native collagen, in combination with a bone graft, has been judged as a useful alternative to the well-established e-PTFE membranes in small to moderate defects. Intrinsically to all animal-derived materials is the risk of immunogenic reactions or transmission of animal-derived pathogens. In addition, the vast majority of the membranes must be trimmed and cut with scissors to fit the individual site. Subsequently, the membrane can be placed intraorally and, if needed, further adapted to the respective defect dimensions.

To overcome these difficulties, a synthetic membrane that can be applied precisely to the defect dimension via direct intraoperative formation would enhance surgical convenience and efficacy as well as patient safety. Experimental studies have introduced a synthetic hydrogel made of polyethylene glycol (PEG) for use in bone regeneration therapy. 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 procedures. In an early randomized controlled clinical trial with this PEG membrane, Jung and coworkers assessed 6-month outcomes. Bone fill of moderate dehiscence-type defects (> 3 mm) was examined clinically after a flap was raised at reentry. The PEG membrane was as successful as a standard collagen membrane for the short-term treatment of bony dehiscence defects around dental implants, and it simplified clinical handling.

The aim of the present study was to evaluate and compare the clinical and radiologic outcomes of implants placed in bone augmented with a xenogenic bone substitute material and covered with a new PEG membrane hydrogel or a porcine collagen membrane 1 and 3 years after implant loading.

**MATERIAL AND METHODS**

The current study presents the 3-year follow-up findings of a prospective, single-center, randomized, controlled clinical investigation. The clinical study protocol and all procedures and materials were approved by the local ethical committee of the Canton of Zurich and by the Swiss health authority before the start of the study. Informed consent was obtained from all patients before any study procedures were performed. The study was overseen by an independent monitor to ensure consistency and accuracy.

**Patients**

The primary inclusion criterion was the need for at least one implant in the posterior mandible or maxilla with an expected osseous defect of at least 3 mm in the vertical dimension. Most of these defects were dehiscences, which means that at least 3 mm (vertically) of the implant surface at the buccocervical aspect would not be covered by pristine bone. Defect morphologies and measurements were provided in the earlier study. Thirty-seven patients fulfilled all the inclusion criteria, underwent comprehensive dental care, and were subsequently enrolled in the study.

Sites were randomized to receive either the collagen membrane (control) or the PEG hydrogel (test). The randomization envelope was opened only after primary implant stability was confirmed and the site was assigned to the respective treatment modality.

**Surgical and Prosthetic Procedures**

The surgical procedure was described previously. In brief, solid screw-type implants (Straumann Standard Plus Implants, Institut Straumann) were inserted following prosthetically driven standard protocols. Implants were set with the shoulder at the level of the crest, meaning that the polished neck was incorporated within pristine bone at the oral, mesial, and distal aspects. This was done to allow implants to heal submucosally. Osseous dehiscence defects around implants were grafted with a natural bone mineral of bovine origin (Bio-Oss Spongiosa Granules, particle size 0.25 to 1 mm; Geistlich Pharma). The bone substitute was covered, according to the randomization protocol, with either a test or a control membrane.

The test device is a synthetic biodegradable barrier membrane (MembraGel, Institut Straumann) composed of two multifunctional PEG molecules. The membrane is applied directly in a liquid state intraoperatively with a syringe, and it forms a hydrogel via a cross-linking reaction within approximately 90 seconds after application. After the in situ gelation, the membrane is approximately 1 mm thick; it was determined that it had to overlap the bone substitute by at least 2 mm. No fixation was needed, as the gel adhered to the surrounding hard tissues. The membrane degraded hydrolytically during the healing period.

As the positive control, a collagen membrane of porcine origin was used (BioGide membrane, Geistlich Pharma) following a standard procedure. Fixation was achieved with resorbable tacks (Resorpin, Geistlich Pharma).

Because healing was attempted with the implants in a submerged position, the implants were placed such
that the shoulder was epicrestal mesially and distally; consequently, the augmentation material reached the implant shoulder.

Periosteal releasing incisions were used to allow tension-free adaptation of the flap. The patients were given instructions postoperatively regarding antiseptic, analgesic, and antibiotic use.

Re-entry was performed 6 months after implant placement. The soft tissues were allowed to heal for at least another 2 weeks before impression taking. Thereafter, fixed partial dentures were incorporated.

**Follow-up Protocol**

All patients were enrolled in a strict maintenance care program at the clinic during the entire study period according to the individual needs of the patient. Clinical and radiographic measurements were recorded 1 and 3 years after insertion of the prosthetic reconstruction.

**Clinical Evaluation.** Form, color, and coverage of the peri-implant soft tissues were examined by visual assessment of the clinical appearance. Full-mouth bleeding scores and full-mouth plaque scores were recorded. 18,19

**Radiographic Evaluation.** To measure the interproximal marginal bone levels, radiographs were obtained on the day of surgery and 1 and 3 years after implant loading using the paralleling technique with individual mounts to obtain standardized images of each patient over time. Thereafter, the radiographs were digitized. The marginal bone level (ie, the distance from the abutment-implant junction to the first bone-to-implant contact) was measured at the mesial and the distal aspects at a magnification of 10× using an image analysis program (ImageJ 1.410, U.S. National Institutes of Health). The abutment-implant junction was defined as the reference point (0 mm). The augmentation materials reached the abutment-implant junction, as previously discussed. Consequently, the 1.8-mm polished neck portion was embedded in both pristine bone and the bone substitute. Since osseointegration does not occur on polished titanium surfaces, 20–22 measurements of the first bone-to-implant contact of less than 1.8 mm were corrected to that value (ie, the transition point from the rough to the polished surface) at all evaluation points.

All measurements were performed by a single examiner who was not aware of treatment (control versus test). The known distance between three to five implant threads was used for the purpose of calibration and determination of the exact magnification of the images. In case of uncertainty, two other experienced researchers assisted, and the values were rechecked and discussed until agreement was obtained. Before any measurements were made, interexaminer calibration with regard to radiographic interpretation was conducted.

**Statistical Analysis**

All statistical analyses were appropriate to the nature and distribution of the data collected. Categorical data were described as contingency tables with frequencies and percentages. Continuous data were summarized by means, standard deviations, minima, and maxima. Statistical analysis of the radiographic data was done using analysis of covariance models, including a factor for study membranes and the covariate baseline value. The hypothesis of no difference regarding radiographic outcome between the two membranes was tested with a two-sided significance level (α) of 5%. All statistical calculations and analyses were performed using the statistical software SAS (version 9.1.3, SAS Institute) within the operating system Windows Server 2003 R2.

**RESULTS**

Thirty-seven patients participated in the study. All patients were assigned an individual recall interval at the clinic with the dentist and the dental hygienist beginning at the time of implant placement. One patient was lost to follow-up in the second year because of the patient’s wish to withdraw from the study. At the 3-year follow-up, all 36 implants in the remaining 36 patients were clinically stable and radiologically osseointegrated. Thus, the survival rate of the examined implants was 100% for both test and control sites. None of the implants showed peri-implant radiolucency, mobility, or pain.

**Clinical Observations**

Overall, the patients showed a good level of oral hygiene. The periodontal status of the entire dentition at the 3-year follow-up was normal (eg, probing depths of 1 to 3 mm) in all participants. The oral soft tissues at test and control sites showed normal architecture and a pink color at the evaluation dates. All implants were covered with soft tissue and did not show any clinical dehiscences or fenestrations (Fig 1).

**Radiographic Findings**

The marginal bone levels and changes observed during the investigation period are listed in Table 1 and illustrated in Figs 2 to 4.

The mean resorption of the first bone-to-implant contact during the initial remodeling phase (ie, surgery to the 12-month recall) amounted to 0.43 mm on test implants and 0.21 mm on control implants. Between the first and third year, further vertical bone resorption of 0.17 mm (test implants) and 0.12 mm (control implants) was measured. The respective differences between groups were 0.13 mm after 1 year and 0.31 mm after 3 years. None of the differences between groups were statistically significant (analysis of covariance).
Two of 18 control implants and three of 18 test implants showed more than 0.2 mm of bone resorption per year between the 1st and 3rd years. Of the 36 patients, three (two in the test group and one in the control group) showed bone resorption of more than 2 mm at the 3-year follow-up. However, these differences were not statistically significant.

Table 1  Marginal Bone Levels Over Time and with the Different Membranes

<table>
<thead>
<tr>
<th>Visit</th>
<th>Collagen membrane</th>
<th>PEG hydrogel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Min</td>
</tr>
<tr>
<td>Surgery</td>
<td>1.84 ± 0.10</td>
<td>1.80</td>
</tr>
<tr>
<td>12 mo</td>
<td>2.04 ± 0.35</td>
<td>1.80</td>
</tr>
<tr>
<td>36 mo</td>
<td>2.17 ± 0.63</td>
<td>1.80</td>
</tr>
<tr>
<td>12 mo vs surgery</td>
<td>0.21 ± 0.36</td>
<td>-0.29</td>
</tr>
<tr>
<td>36 mo vs surgery</td>
<td>0.33 ± 0.64</td>
<td>-0.29</td>
</tr>
<tr>
<td>36 mo vs 12 mo</td>
<td>0.12 ± 0.33</td>
<td>-0.26</td>
</tr>
</tbody>
</table>

The implant shoulder was used as the reference point.
DISCUSSION

The present randomized, controlled clinical study demonstrated similar clinical and radiologic outcomes for a new synthetic PEG gel membrane and a standard porcine collagen membrane used for GBR around dental implants after 3 years. A 100% survival rate for both test (PEG) and control (collagen) implants after 3 years was found. None of the implants showed peri-implant radiolucency, was mobile, or was painful. In a case series, in which peri-implant defects were treated with deproteinized bovine bone mineral and covered with a collagen membrane, a survival rate of 100% after 5 years was achieved. In a recent review on implant outcomes with GBR procedures to correct peri-implant dehiscences and fenestrations reported survival rates of 95.7% (range: 84.7% to 100%) after follow-up periods of 1 to 10 years. A rather short follow-up period, in conjunction with strict inclusion criteria (ie, no immediate implants, conventional [delayed] loading protocols, strict hygiene control), might be responsible for the high survival rate reported in the present study.

From an esthetic point of view, all GBR procedures were successful, as no soft tissue dehiscences or fenestrations were discovered at the reexaminations. In patients with a high lip line, soft tissue levels at upper premolars are well visible. These observations are in accordance with other studies reporting stable and healthy peri-implant soft tissues after GBR.

Marginal bone levels, as measured on standardized radiographs, were affected by bone remodeling of 0.43 mm (PEG test membrane) and 0.21 mm (natural collagen control membrane) after 1 year; a further reduction of the first bone-to-implant contact was seen during the following 2 years of 0.17 mm (test) and 0.12 mm (control). The respective differences between test and control groups from the analysis of covariance models were 0.13 mm (year 1) and 0.31 mm (year 3). In the control group, 2 of 18 and, in the test group, 3 of 18 implants showed more than 0.2 mm bone resorption per year between the 1- and 3-year follow-up examinations. None of the differences were statistically significant. It may be asked whether the success of buccal bone augmentations may legitimately be judged by periapical radiographs that focus only on the mesial and distal aspects of the first bone-to-implant contact. It is obvious that the amount of bone regeneration at the buccal aspect of an implant cannot be reassessed without being invasive. However, a re-entry procedure was performed after 6 months, and the ethical committee did not permit an additional reentry procedure or cone beam computed tomography after 3 years. The findings at the reentry procedure and the treatment evaluation after 6 months are documented elsewhere. At the 2009 European Workshop on Periodontology, the issue of appropriate methods to evaluate bone regeneration was discussed extensively. It was not possible to identify one technique that fulfilled all the requirements. The two-dimensional radiograph does not aim to assess buccal bone volume but implant integration and bone alteration mesial and distal to the implant. Because GBR has the overall goal of enabling implant integration and bone alteration mesial and distal to the implant, the ethical committee did not permit an additional reentry procedure or cone beam computed tomography after 3 years. The findings at the reentry procedure and the treatment evaluation after 6 months are documented elsewhere. At the 2009 European Workshop on Periodontology, the issue of appropriate methods to evaluate bone regeneration was discussed extensively. It was not possible to identify one technique that fulfilled all the requirements. The two-dimensional radiograph does not aim to assess buccal bone volume but implant integration and bone alteration mesial and distal to the implant. Because GBR has the overall goal of enabling implant integration, it is a complementary treatment to implant placement. Hence, assessment of implant integration and peri-implant soft tissues is important for the evaluation of GBR procedures. Another study that examined bone remodeling processes at one-piece Straumann implants after concomitant bone augmentation found that approximately 72% of all implant sites were stable (minimal bone loss), while the remainder (approximately 28%) lost > 0.5 mm of bone; of the latter, 14.1% of implants that underwent simultaneous placement and bone augmentation lost up to 1.5 mm. Another clinical trial found an average of 0.3 mm bone loss after
5 years. With respect to the performance of other implant types in regenerated bone, Bränemark implants showed mean bone level changes of 0.06 mm after 3 years. In a recent review of clinical outcomes of implants following lateral bone augmentation, the authors found similar survival rates for implants placed into augmented versus native bone. However, in two of the included controlled clinical studies, slightly more radiographic bone loss was found at augmented sites, although this was not statistically significant. Compared with these studies, the present trial revealed similar stability of the marginal bone levels. Of the 36 patients, only three (two in the test group, one in the control group) showed bone resorption of more than 2 mm at the 3-year follow-up. One of the patients in the test group had developed a horizontal periodontal defect on an adjacent tooth, which affected the first bone-to-implant contact at the test implant. Another patient (test group) lost a neighboring tooth as a result of root caries. In addition, this patient was a smoker and underwent orthognathic surgery during the follow-up phase. These factors might be responsible for the increased bone resorption. The third patient, who received a control membrane, showed increased bone loss without any detectable reason.

Scientific efforts toward the improvement of GBR procedures should focus on the development of resorbable synthetic materials, which are as practical and predictable in clinical use as conventional grafts and membranes of animal and human origin. In a variety of preclinical studies in different animal models, the PEG membrane was proven to be safe and effective in different defect modalities. Whereas collagen disintegrates enzymatically, PEG is resolved in a hydrolytic process that breaks the PEG polymers into PEG constituent molecules that are resorbed and rapidly cleared by the kidneys and does not produce an acid environment. The tissue response was examined histologically in a previous dog study, and no statistically significant difference was seen between these two degradation processes. In other medical disciplines such as laparoscopic surgery, a sprayable, site-specific adhesion barrier system containing PEG has been used successfully to significantly reduce postoperative adhesions of soft tissues.

The cohort of patients in the present study had also been examined during the initial phase of the healing process; the amount of clinically visible defect fill was also observed at the re-entry operation 6 months after implant placement by elevating a full-thickness flap. The new PEG membrane was as successful as the control membrane in treating dehiscence defects around implants. In addition, it featured simplified clinical handling. Other clinical studies of GBR with synthetic membranes are scarce. One study used a polyglycolic acid/trimethylene carbonate membrane (Gore Resolut Adapt Membrane) and achieved clinically and histologically favorable results after 6 months of healing concerning broadening of the alveolar ridge prior to implant placement. A further histologic study in humans compared a polyactic/polyglycolic acid membrane (Inion GTR Biodegradable Membrane System) to BioGide (the same membrane used in the present study) without bone fillers regarding new bone formation after third molar extraction and observed similarly favorable clinical results with both devices. Clinical follow-up studies of GBR around implants with synthetic resorbable membranes are not available.

CONCLUSION

A bioresorbable polyethylene glycol membrane performed as successfully as a natural collagen membrane in treating bony dehiscences around dental implants regarding clinical soft tissue parameters and marginal bone levels after a follow-up period of 3 years.

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