A randomized, controlled clinical trial to evaluate a synthetic gel-membrane for GBR around dental implants – clinical and radiological 1- and 3-year results

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Abstract

Purpose
The objective of this study was to test whether a synthetic bioresorbable polyethylene glycol (PEG) hydrogel membrane could result in a similar clinical and radiographic outcome as a standard collagen membrane, both combined with a membrane supporting material, a follow-up period of 1 and 3 years.

Materials and Methods
This study enrolled 37 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 (DBBM) 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. After a healing period of 6 months, surgical re-entry was performed and subsequently fixed partial dentures were inserted. Patients were examined clinically and radiographically 1 and 3 years after loading.

Results
All patients could be reexamined in the third year with the exception of one drop-out giving a total number of 36. The implant survival rate at 3 years was 100%. The peri-implant tissues were healthy showing no differences between the two groups. Compared to the time of surgery the mean change in the distance between the first bone-to-implant contact to the transition point (i.e. rough implant surface to polished neck portion) at 1 year was $0.43 \pm 0.56$ mm (test) and $0.21 \pm 0.36$ mm (control) and $0.61 \pm 0.89$ mm (test) and $0.33 \pm 0.64$ mm (control) at 3 years. The respective differences between groups from the analysis of covariance models were $0.13$ mm (1 year) and $0.31$ mm (3 years). The differences between the groups were not significant at either 1 year or 3 years.

Conclusion
The tested PEG hydrogel was as successful as a standard collagen membrane in the treatment of bony dehiscence defects around dental implants after a follow-up period of 1 and 3 years.

Key words: GBR, membranes, graft material, bone substitute, dental implant, RCT

Introduction

As an adjunct to the evolving development of tooth replacements with titanium implants, it became evident that implants could not be placed directly into the jaw in all situations without prior or concomitant bone augmentation procedures. Therefore, the concept and practice of guided bone regeneration (GBR) was 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 occlusiveness, 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 non-resorbable membranes largely predominated, but since the 1990s the biodegradable type has been favoured by clinicians.

Non-biodegradable membranes consist of expanded polytetrafluoroethylene (ePTFE) and are well documented in implant dentistry.2 However, ePTFE presents several drawbacks, including the necessity for a second surgery for removal and a high rate of complications, such as exposure of the membrane to the oral environment with
subsequent infection. As a consequence of this, most clinicians use resorbable membranes combined with filling materials to compensate for the lack of stiffness found in 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. Resorbable membranes made of native collagen in combination with a bone graft have been judged as a useful alternative to the well-established ePTFE membranes in small-to-moderate defect situations. Intrinsic 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 in order to fit the individual patient situation. Subsequently, the membrane can be intraorally placed and may be further adapted to the respective defect dimensions.

In order to overcome these difficulties, a synthetic membrane that can be applied precisely to the defect dimension by a 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 the 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 a first randomized, controlled clinical trial with this PEG membrane Jung and coworkers assessed 6-month outcomes. Bone fill of moderate dehiscence type defects (e.g. > 3 mm) was examined clinically after raising a flap at re-entry. The results showed that the PEG membrane was as successful as a standard collagen membrane in the short-term treatment of bony dehiscence defects around dental implants with simplified clinical handling.

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

Material and Methods
The present study shows the 3-year follow-up 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 monitored by an independent study monitor to ensure consistency and accuracy.

Patients
The primary inclusion criterion was the necessity of at least one implant in the posterior mandible or maxilla with an expected osseous defect of at least 3 mm in vertical dimension. Thirty-seven patients fulfilled all the inclusion criteria, underwent comprehensive dental care and were subsequently enrolled in the study. The randomization envelope was opened only after primary implant stability was reached and the site was assigned to the respective treatment modality.

Surgical procedure
The surgical procedure has previously been described. In brief, solid screw implants (Straumann Standard Plus Implants, Institut Straumann AG Basel, Switzerland) were inserted following prosthetically driven standard protocols. Osseous dehiscence defects around implants were grafted solely with a natural bone mineral of bovine origin (BioOss Spongiosa Granules, particle size 0.25-1 mm; Geistlich Pharma AG, Wolhusen, Switzerland). Afterwards, the bone substitute was covered according to the randomization with either a test or a control membrane.

**Test group (PEG membrane):**
- The test device is a synthetic biodegradable barrier membrane (MembraGel, Institut Straumann AG, Basel, Switzerland) composed of two multifunctional PEG molecules. The membrane is applied in a liquid state directly intraoperatively using a syringe and forms a hydrogel by a cross-linking reaction within approximately 90 seconds after application. After the in situ gelation, the membrane thickness was approximately 1 mm and had to overlap the bone substitute by at least 2 mm. No fixation was needed as the gel adheres to the surrounding hard tissues. The membrane is degraded hydrolytically during the healing period.

**Control group:**
- As the positive control a collagen membrane of porcine origin was used (BioGide membrane, Geistlich Pharma AG, Wolhusen, Switzerland) following a standard procedure with fixation using resorbable tags (Resorpin, Geistlich Pharma AG, Wolhusen, Switzerland).

Since 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 bone augmentation was performed up to the implant shoulder.

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

**Prosthetic reconstruction**

After the re-entry procedure 6 months following 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 examinations**

All patients were enrolled in a strict maintenance care program at the clinic during the entire study period according to the individual need of the patient. Clinical and radiographic measurements were taken 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 score (FMBS) and full-mouth plaque score (FMPS) were recorded.\(^\text{18,19}\)

**Radiographic evaluation**

For the measurement of the interproximal marginal bone level, radiographs were taken at the day of surgery and 1 and 3 years after implant loading using the parallel technique with individual mounts for each patient in order to enable standardized X-rays over time. Thereafter, the radiographs were digitalized. The marginal bone level (i.e. the distance from the abutment-implant junction to the first bone-to-implant contact) was measured at the mesial
and the distal aspect at a magnification of 10 times using an image analysis program (ImageJ 1.410, Wayne Rasband, National Institute of Health, USA). The abutment-implant junction was defined as a reference point (0 mm).

Augmentations were performed up to the abutment-implant junction, as previously discussed. Consequently, the 1.8 mm polished neck portion was embedded in the pristine bone and the bone substitute as well. No osseointegration occurs on polished titanium surfaces. Therefore, measurements of the first bone-to-implant contact of less than 1.8 mm were corrected to that value (i.e. transition point of rough to polished surface) at all times of evaluation.

All measurements were performed by one single examiner not aware of groups. 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 uncertainties, two other experienced researchers assisted, and the values were rechecked and discussed until agreement was obtained.

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 (n, %). Continuous data were summarized by mean, standard deviation, minimum and maximum. The 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 testing of no difference regarding radiographic outcome between the two membranes was carried out at a two-sided significance level α of 5%. All statistical calculations and analyses were performed using the statistical software SAS version 9.1.3 under the operating system Windows Server 2003 R2.

Results

Follow-up outcomes

All patients were assigned an individual recall interval at the clinic with the dentist and the dental hygienist since the time of implant installation. One patient was lost to follow-up in the second year due to 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 the test and the control sites.

Clinical examinations

The patients showed an overall good level of oral hygiene, the periodontal status of the whole dentition at the 3-year follow-up was normal (e.g. probing depths 1-3 mm) in all participants (table 1). The oral soft tissues at test and control sites showed a normal form and a pink color at the evaluation dates. All implants were covered with soft tissue and did not reveal any clinical dehiscence or fenestration.

Radiographic examinations

The marginal bone levels and alterations during the investigation period are listed in table 2 and illustrated in figures 1-3. Of the 36 patients, 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.

The mean reduction of the first bone-to-implant contact during the initial remodeling phase (i. e. surgery to 12-month result) amounts to 0.43 mm (test implants) and 0.21 mm (control implants). Between the first and third year assessments, further vertical bone reduction of 0.17 mm (test implants) and 0.12 mm (control implants) was
measured. The respective differences between groups from the analysis of covariance models were 0.13 mm after 1 year and 0.31 mm after 3 years. None of the differences between groups were statistically significant.

Discussion
The present randomized, controlled clinical study demonstrated similar clinical and radiological outcomes for a new synthetic PEG gel membrane and a standard porcine collagen membrane used for GBR around dental implants after 3 years.

In this study a 100% survival rate of both test and control implants after 3 years was found. A case series study treating periimplant defects with DBBM, covered with a collagen membrane revealed a survival rate of 100% after 5 years. A recent review on implant outcomes with GBR procedures to correct peri-implant dehiscences and fenestrations reported survival rates of 95.7% (range: 84.7-100%) after follow-up periods of 1-10 years. A rather short follow-up duration in conjunction with strict inclusion criteria (i.e. no immediate implants as well as conventional loading protocols plus a strict hygiene control) might be responsible for the good survival rate reported in the present study.

From an aesthetic point of view all GBR procedures were successful as no soft tissue dehiscences and fenestrations were discovered in the reexaminations. These observations are in accordance with other studies reporting stable and healthy periimplant soft tissues after GBR procedures.

Marginal bone levels measured on standardized X-rays show bone remodeling of 0.43 mm (PEG test membrane) and 0.21 mm (natural collagen control membrane) after 1 year and a further reduction of the first BIC during the following two years of 0.17 mm at the test and 0.12 mm at the control implants. The respective differences between test and control group from the analysis of covariance models were 0.13 mm (year 1) and 0.31 mm (year 3). None of the differences were statistically significant. Looking at other studies examining bone remodeling processes at one-piece Straumann implants after concomitant bone augmentation, one found that approximately 72% of all implant sites were stable (minimal bone loss), while the remainder (approximately 28%) lost > 0.5 mm; of the latter, 14.1% of implants with simultaneous implant 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. When focusing on the performance of other implant types in regenerated bone, a study on Branemark implants found mean bone level changes after 3 years of 0.06 mm. In a recent review on clinical outcomes of implants following lateral bone augmentation, the authors found a similar survival rate of implants placed into augmented versus solely pristine bone. In two of the included controlled clinical studies however, 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, 3 (2 in the test group, 1 in the control group) showed bone resorption of more than 2 mm at the 3-year follow-up. One of these patients in the test group developed a horizontal periodontal defect at the adjacent tooth, affecting the first bone-to-implant contact (BIC) at the adjacent test implant. Another patient lost the neighboring tooth due to root caries just adjacent to the test implant. 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 with a control implant showed an increased bone loss without any detectable reason.

Scientific effort in 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 including different animals, the PEG membrane has been proven to be safe and effective in different defect modalities. In other medical disciplines such as
laparoscopic surgery a sprayable, site-specific adhesion barrier system containing PEG is successfully used to significantly reduce postoperative adherence of soft tissues.\textsuperscript{31} The same cohort of patients in the present study was also examined during the initial phase of the healing process and focused as well on the amount of clinically visible defect fill at the re-entry operation 6 months after implant installation by elevating a full-thickness flap.\textsuperscript{17} The new PEG membrane was as successful as the control membrane in treating dehiscence defects around implants. In addition, it showed a simplified clinical handling. Other clinical studies on GBR with synthetic membranes are scarce. One study used a polyglycolic acid/trimethylene carbonate membrane (Gore Resolut Adapt Membrane) and found clinically and histologically favorable results after 6 months healing time concerning broadening of the alveolar ridge prior to implant installation.\textsuperscript{32} A further histologic study in humans compared a poly lacta/ polylactid membrane (Inion GTR Biodegradable Membrane System) to BioGide without bone fillers regarding new bone formation after wisdom-tooth extraction and found similarly favorable clinical results with both devices.\textsuperscript{33} Clinical follow-up studies on GBR around implants with synthetic resorbable membranes are not available.

Conclusion
It can be concluded that the PEG membrane performed as successfully as the 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.

Acknowledgements
The authors express their special thanks to Michael Hotze (Institut Straumann AG, Basel, Switzerland) for constructive discussions and contributions. This study has been supported by the Clinic for Fixed and Removable Prosthodontics and Dental Material Science, University of Zurich and by a research grant of the Institut Straumann AG.

References


Tables & Figures

Table 1  Mean values and changes of oral hygiene levels (FMBS, FMPS), standard deviations (SD), minimum and maximum values (%) between the different follow-ups

<table>
<thead>
<tr>
<th></th>
<th>Collagen Membrane</th>
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<th>PEG Hydrogel</th>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Min – Max</td>
<td>Mean ± SD</td>
<td>Min – Max</td>
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<tr>
<td><strong>Visit</strong></td>
<td></td>
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<tr>
<td>Full mouth bleeding score</td>
<td></td>
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<tr>
<td>Baseline Evaluation</td>
<td>7.28 ± 3.91</td>
<td>0.0 – 15.0</td>
<td>12.63 ± 5.21</td>
<td>5.0 – 23.0</td>
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<tr>
<td>Month 12</td>
<td>6.61 ± 2.30</td>
<td>4.0 – 12.0</td>
<td>13.05 ± 15.64</td>
<td>1.0 – 50.0</td>
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<tr>
<td>Month 36</td>
<td>8.50 ± 4.22</td>
<td>3.0 – 16.0</td>
<td>6.78 ± 3.17</td>
<td>2.0 – 16.0</td>
</tr>
<tr>
<td>Month 12 vs. Baseline</td>
<td>-0.67 ± 4.56</td>
<td>-10.0 – 16.0</td>
<td>0.42 ± 16.55</td>
<td>-19.0 – 39.0</td>
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<tr>
<td>Month 36 vs. Baseline</td>
<td>1.22 ± 4.98</td>
<td>-5.0 – 10.0</td>
<td>-5.78 ± 5.41</td>
<td>-16.0 – 2.0</td>
</tr>
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<td>Month 36 vs. Month 12</td>
<td>1.89 ± 4.74</td>
<td>-6.0 – 10.0</td>
<td>-6.33 ± 14.87</td>
<td>-40.0 – 6.0</td>
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<tr>
<td><strong>Full mouth plaque score</strong></td>
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<tr>
<td>Baseline Evaluation</td>
<td>12.06 ± 3.749</td>
<td>7.0 – 22.0</td>
<td>18.00 ± 4.702</td>
<td>9.0 – 28.0</td>
</tr>
<tr>
<td>Month 12</td>
<td>14.00 ± 8.324</td>
<td>3.0 – 31.0</td>
<td>18.63 ± 11.300</td>
<td>5.0 – 56.0</td>
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<tr>
<td>Month 36</td>
<td>17.72 ± 14.233</td>
<td>4.0 – 60.0</td>
<td>10.00 ± 5.064</td>
<td>3.0 – 19.0</td>
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<td>Month 12 vs. Baseline</td>
<td>1.94 ± 8.861</td>
<td>-12.0 – 20.0</td>
<td>0.63 ± 14.504</td>
<td>-23.0 – 47.0</td>
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<tr>
<td>Month 36 vs. Baseline</td>
<td>5.67 ± 14.876</td>
<td>-11.0 – 48.0</td>
<td>-8.00 ± 6.155</td>
<td>-21.0 – 5.0</td>
</tr>
<tr>
<td>Month 36 vs. Month 12</td>
<td>3.72 ± 13.424</td>
<td>-18.0 – 41.0</td>
<td>-8.83 ± 13.342</td>
<td>-51.0 – 14.0</td>
</tr>
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Table 2  Mean values and changes of marginal bone levels, standard deviations (SD), minimum and maximum values (mm) between the different follow-ups. Reference point is the implant shoulder

<table>
<thead>
<tr>
<th></th>
<th>Collagen Membrane</th>
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<th>PEG Hydrogel</th>
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<tr>
<td></td>
<td>Mean ± SD</td>
<td>Min – Max</td>
<td>Mean ± SD</td>
<td>Min – Max</td>
</tr>
<tr>
<td><strong>Visit</strong></td>
<td></td>
<td></td>
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<tr>
<td>Surgery</td>
<td>1.84 ± 0.10</td>
<td>1.80 – 2.15</td>
<td>1.80 ± 0.02</td>
<td>1.80 – 1.88</td>
</tr>
<tr>
<td>Month 12</td>
<td>2.04 ± 0.35</td>
<td>1.80 – 2.93</td>
<td>2.24 ± 0.57</td>
<td>1.80 – 4.11</td>
</tr>
<tr>
<td>Month 36</td>
<td>2.17 ± 0.63</td>
<td>1.80 – 4.09</td>
<td>2.41 ± 0.89</td>
<td>1.80 – 5.07</td>
</tr>
<tr>
<td>Month 12 vs. Surgery</td>
<td>0.21 ± 0.36</td>
<td>-0.29 – 1.12</td>
<td>0.43 ± 0.56</td>
<td>0.0 – 2.31</td>
</tr>
<tr>
<td>Month 36 vs. Surgery</td>
<td>0.33 ± 0.64</td>
<td>-0.29 – 2.29</td>
<td>0.61 ± 0.89</td>
<td>0.0 – 3.27</td>
</tr>
<tr>
<td>Month 36 vs. Month 12</td>
<td>0.12 ± 0.33</td>
<td>-0.26 – 1.25</td>
<td>0.17 ± 0.58</td>
<td>-0.76 – 2.08</td>
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</table>
Figure 1 Periapical radiographs showing a test implant (site 25) at surgery, 1 and 3 years after loading.

Figure 2 Periapical radiographs showing a control implant at surgery, 1 and 3 years after loading.

Figure 3 shows the marginal bone level over time.