Clinical Safety of a New Synthetic Resorbable Dental Membrane: A Case Series Study

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Dental membranes are commonly used in oral and maxillofacial surgery for the regeneration of small osseous defects. A new synthetic resorbable membrane has recently demonstrated its biocompatibility and bone regeneration capacity in preclinical studies. This membrane is made of poly(D,L-lactic/glycolic acid 85/15), has a bi-layered structure with a dense film to prevent gingival epithelial cell invasion, and a microfibrinous layer to support osteogenic cells and bone healing. This membrane completely degrades by hydrolysis in 4 to 6 months without signs of inflammation. Based on this research, a clinical study was conducted to evaluate the safety of the new membrane in guided tissue regeneration (GTR). In total, 26 patients (age: 50.5 ± 12.4, min-max 31–72 years; male/female 42/58%) were operated on at 7 independent private dental practices. Dental surgeons used the membrane together with various bone fillers in GTR for immediate and delayed implant placement (23 cases, 88%) and, to a lesser extent, socket preservation (2 cases, 8%) and alveolar crest augmentation (1 case, 4%). Surgeons reported an easy placement of the membrane (satisfaction index: 3.8/5). Fourteen days postsurgery, 15 patients had no pain while the others declared minimal pain (verbal rating scale: 2.2/10), and none had minor or serious complications related to the membrane. Exposure of the membrane without loosening the biomaterial granules was observed in 3 cases while mucosa healed normally over time. At 4 months postimplantation, no infection or mucosal inflammation was reported, and the overall dentist satisfaction with the clinical performance of the membrane was 4.5/5 on average. This clinical study demonstrated that the new synthetic resorbable membrane is safe for guided bone tissue regeneration in various dental surgery indications.

Key Words: guided bone regeneration, membrane, poly-lactic-glycolic acid, clinical study, alveolar preservation, dehiscence of dental implants, guided tissue regeneration

INTRODUCTION

Between 4 and 6 million dental implants are placed every year in Europe, and the numbers are increasing with the aging population. However, in approximately 30% of cases, bone volume is not sufficient to support a dental implant with a prosthetic rehabilitation. Such bone defects may have resulted from periodontal diseases such as gingivitis or periodontitis, infected roots, or alveolar bone crest resorption in edentulous areas. In these cases, different methods of bone regeneration are used before or during the placement of dental implants. Current bone regeneration techniques include bone block grafts, alveolar distraction osteogenesis, sandwich osteotomy, the use of growth factors, and bone substitute biomaterials. The choice of a bone regeneration method depends on the size of bone defect. For the regeneration of small osseous defects, bone substitute biomaterials covered by a membrane are commonly used in oral and maxillofacial surgery.

Guided bone regeneration (GBR) membranes were introduced in the 1980s to compensate for differences in the healing rates between epithelial and bone tissues. Indeed, gingival tissue heals in approximately 2 to 3 weeks while bone that is in contact with osteoconductive calcium phosphate biomaterials requires 16 to 24 weeks to regenerate. The role of a GBR membrane is triple: (1) to provide a physical barrier for maintaining the biomaterial granules in situ during soft tissue closure, (2) to prevent the invasion of epithelial cells, and (3) to isolate a space for bone regeneration. However, the majority of GBR membranes do not fulfill these requirements because...
they are made of animal-derived collagen with uncontrolled resorption rates. For instance, studies have reported that collagen membranes have inadequate mechanical integrity and barrier function over time.\textsuperscript{12–14} In case of oral exposure, these collagen membranes have insufficient strength to maintain the granules.\textsuperscript{15} Moreover, depending on their origin (eg, porcine skin, bovine pericardium) and processing methods (eg, chemical cross-linking), collagen membranes are completely degraded between 2 to 16 weeks, a period too short for a proper barrier function. Furthermore, their structures are variable by nature, leading to uncontrollable permeability of cells and tissues.\textsuperscript{16,17}

Since the current generation of GBR membranes is not adequate in many aspects, a new synthetic resorbable membrane was developed. This new membrane is made of synthetic poly lactic-co-glycolic acid (PLGA), a biodegradable polymer that is well documented and widely used in medical devices such as resorbable sutures.\textsuperscript{18} The PLGA 85/15 copolymer formulation was selected to manufacture the dental membrane, based on its degradation time, to match the kinetics of gingival and bone tissue healing. This GBR membrane has a bi-layered structure with a dense film to prevent gingival fibroblast ingrowth and ensure mechanical function, and a microfibrous layer to support colonization by osteogenic cells and promote guided bone regeneration. The biofunctionality of this membrane was evidenced in different animal models of bone regeneration of critical size defects.\textsuperscript{19}

On the basis of these research results, a multicentric clinical trial was conducted with the new synthetic resorbable bi-layered membrane. The rationale of this study was to demonstrate the safety of the clinical use of the synthetic resorbable membrane in a case series. Several indications were considered, such as the preservation of alveolar bone after tooth extraction, the coverage of bone defects in immediate or delayed implant placement, and bone augmentation of the alveolar crest. After approval by the ethical committees, this clinical study was conducted by 7 independent private dental practices and involved 26 patients following signatures of informed consent. However, this study was not a randomized comparative study aiming at demonstrating efficacy in bone gain.

### Design of the clinical study

This multicentre clinical study was designed to demonstrate safety and performance of the use of the synthetic resorbable bi-layered PLGA Tisseos membrane in patients. The principal investigator was Dr Guillaume Campard, and the clinical study was sponsored by Biomedical Tissues SAS. The main purpose of this clinical study was verification of the safety of use of the new synthetic resorbable dental membrane when implanted with or without synthetic bone substitutes in periodontal defects, socket preservation, the coverage of bone defects in immediate or delayed implant placement, and bone augmentation of the alveolar crest. The study was designed to include 36 patients recruited in 7 different private dental practices. In addition, each of the patients met the following inclusion criteria:

- >18 years of age
- Signed informed consent

The following exclusion criteria were used:

- Pregnancy or lactation
- Heavy smoking of >10 cigarettes per day
- Diseases or the use of medications that interfered with bone metabolism (eg, leukemia, diabetes, immunological deficiency, severe hepatothropy, renal disorders and heart diseases, bisphosphonates and corticoids)
- History of neoplasia due to head and neck radiotherapy
- Concurrent participation in another trial within 3 months prior to study entry

### Ethical approvals of the clinical study

The study was conducted in full accordance with the declared ethical principles of the World Medical Association Declaration of Helsinki. The protocol of the clinical trial was submitted and approved by the following ethical committees. On November 3, 2014, the French committee for health research (Comité Consultatif sur le traitement de l’information de Recherche dans le domaine de la Santé [CCTIRS]) approved the study under reference number 14632. On December 23, 2014, the committee for anonymous research (Commission Nationale de l’Informatique et des Libertés [CNIL]) gave permission under reference number DR2014520. On January 28, 2015, the National Committee of Dental Surgeon (Ordre National des Chirurgiens Dentistes [ONCD]) approved the study under reference number AMO/ES/49192. Anonymous Clinical Record Forms (CRF) were designed and distributed to surgeons and collected at the end of the study by an independent Clinical Research Associate (POL’ARC, La Chevrolière, France). During the first consultation, dental surgeons informed patients about the clinical study, the use of the synthetic resorbable membrane, and asked for age, body weight, height, smoking history, pregnancy or lactation, past and current diseases, and medication. After verification of the inclusion criteria and signature of informed consent, 26 patients were operated on from February 2015 to November 2015 by 7 independent private practices.

### Material and Methods

#### Manufacturing of the synthetic resorbable bi-layered PLGA membrane

The synthetic resorbable bi-layered PLGA membrane (Tisseos, Biomedical Tissues SAS, Nantes, France) was manufactured in an ISO 6 clean room according to the ISO 13485 certification for medical devices.\textsuperscript{15} The PLGA membrane had a bi-layered structure with a dense layer of 25 µm to prevent epithelial tissue ingrowth and a microfibrous layer of 400 µm to guide bone regeneration. The synthetic bi-layered membrane was cut into 15 × 25 mm pieces, packaged in double-sealed pouches, and sterilized with gamma irradiation at 25 kGy (Ionisos SA, Dagneux, France). The synthetic resorbable PLGA membrane Tisseos received a Certification European mark on May 6, 2014, from the notified body LNE G-MED (Paris, France).
**Surgical procedure**

Periodontal treatment consisting of dental scaling and education on oral hygiene was carried out on patients prior to surgery. The oral hygiene of patients was then assessed by dentists as good, average, or poor using the following criteria: Good: no plaque, no inflammation visible. Average: some plaque and some gingival inflammation without visible calculus. Poor: sign of gingivitis with visible calculus. Patients having severe chronic and acute periodontitis were not considered in this study. Prior to and after surgery, patients received antibiotics, analgesics and, in some cases, corticoids. On the day of surgery, patients were required to use a mouth rinse with chlorhexidine 0.2% for 1 minute. A sterile field was prepared, and periocular disinfection was done with polyvidone iodine 10% (Demicum Isobetadine, Mundipharma, Basel, Switzerland) or chlorhexidine gluconate 0.5 mg/mL (Hibidil, Regent Medical, Manchester, UK). Surgery was performed under local anesthesia by using articaine supplemented with adrenaline. The dental surgeons used the synthetic resorbable membrane together with various bone fillers in 3 types of indications: guided tissue regeneration (GTR) for immediate and delayed implant placement, socket preservation, and alveolar crest augmentation.

**Use of the Membrane in GTR for Immediate and Delayed Implant Placement**

In the cases of GTR around dental implants, the implants were inserted using standard operating procedures under saline irrigation. Dehiscences of implants were covered with biomaterial granules and the synthetic resorbable dental membrane. The dense film faced the gingival tissue while the microfibrous layer was in contact with the biomaterial granules and implant.

**Use of the Membrane in Socket Preservation After Tooth Extraction**

In the cases of socket preservation,atraumatic extractions were performed using a Luxator. If necessary, the remaining roots were separated using a dental bur. The sockets were rinsed with a saline solution, filled with biomaterial granules, and covered with the synthetic resorbable membrane as previously described.

**Use of the Membrane in Alveolar Crest Augmentation Prior to Dental Implants**

In the case of bone augmentation of the alveolar crest, the incision was placed at the mid-crest to expose the mandibular bone. Discharge incisions were performed at the buccal, mesial, and lingual areas. The cortical plate was perforated by means of a round bur to favor bleeding and access to the marrow cavity. Biomaterial granules were then placed on the alveolar bone and covered with the synthetic resorbable membrane.

At the end of the above procedures, the connective tissue was sutured using nonresorbable or resorbable sutures sizing from 3.0 to 5.0, depending on surgeon preference. After surgery, patients were advised to use mouthwash with chlorhexidine solution twice per day and avoid tooth brushing at the surgical sites for 10 days. The postoperative medication consisted of paracetamol (1 g every 6 hr) and in some cases corticoids (prednisone, 1.2 mg/kg/d) and antibiotics (amoxicillin 2 g/d) were prescribed for 5 days. Following surgery, the dental surgeons evaluated the ease of placement, stability over the site, and satisfaction for handling the synthetic resorbable membrane using an analogic scale from 1 (poor) to 5 (excellent).

**Post-operative clinical and radiographic assessment**

Safety assessment was performed by examining the clinical course and the presence or absence of adverse events. Performance was assessed by questioning patients for pain at 14 days postoperatively and surgeons for satisfaction scores on handling at time of surgery and on the overall clinical use of the membrane at 4 months. The information was reported in the anonymous CRFs. Fourteen days after surgery, patients were questioned about postsurgical pain using the verbal rating scale (VRS) from 0 (no pain) to 10 (extremely severe pain). Surgeons evaluated the signs of infection, mucosa inflammation, edema, membrane exposure, and loosening of biomaterial. The nonresorbable sutures were removed 14 days after surgery. Four months after implantation, the surgeons evaluated again any signs of infection and inflammation and completed a dentist satisfaction score with an analogic scale from 0 (poor) to 5 (excellent) for use of the membrane. Macrophotographs of the main surgical steps as well as the healed sites were taken by surgeons. Radiographs were made immediately after the surgical procedure and 4 months after implantation of the membrane.

**Statistical analyses**

The data collected in the CRFs were independently analyzed by a Contract Research Organization specializing in clinical evaluation of medical devices (Evamed, Caen, France). Data were expressed as average ± SD and MIN-MAX values for the continuous variables and as numbers and percentages for the categorical variables. Analyses of variances followed by least significant difference post hoc assessments were applied to compare the groups using GraphPad Prism 5.0 software (GraphPad Software Inc, La Jolla, Calif). Differences were considered significant if their P-values were less than 5% (*P < .05).

**Results**

Overall, 26 subjects—including 15 women and 11 men, age 31 to 72 years with an average of 50.5 years—met the inclusion criteria and were enrolled in the study (Table 1). These 26 patients were operated on at 7 private practices by different dental surgeons. The oral hygiene was evaluated as good for most patients and 2 patients declared to be smokers. The dental surgeons used the synthetic resorbable membrane together with various bone fillers, mostly in GTR for immediate and delayed implant placement (23 cases, 88%) and to a lesser extent in socket preservation (2 cases) and alveolar crest augmentation (1 case).

Fourteen days after surgery, patients were examined and questioned for pain according to the CRFs and the outlines, as reported in Table 2. Regarding safety of the use the synthetic
resorbable membrane in 26 patients by 7 independent dentists, only 1 minor adverse event was reported and concerned a lymph node observation unrelated to the surgery. While the internal analgesics were taken for 5 days after surgery in only 9 out of 26 patients (34%), 15 patients (58%) reported no pain at 14 days. Among those who reported pain, the VRS score was 2.2 ± 1.1/5 in average and did not exceed 5. Postoperative ecchymosis, swelling, and gingival inflammation were detected in some cases, commonly seen after surgery for tooth extraction, dental implantation, or alveolar crest augmentation. Membrane exposure was observed in 3 patients but was not accompanied by leakage of the biomaterial granules or infection of the site. Re-epithelialization and normal wound closure was observed on these exposed membranes in 2 to 3 weeks postimplantation. Patients were again examined 4 months after surgery. The epithelial tissues appeared normal without sign of inflammation or infection in all patients. As the synthetic membrane was completely resorbed in 4 to 6 months, with no need for its removal prior to dental implant insertion.

Figure 1 shows a case of fenestration at tooth #21. The size of the bone defect was large and required a bone regeneration procedure to prevent future exposure of the implant (Figure 1a and b). After removing the granulation tissues in the cavity using a curette and saline rinsing, the defect was filled with biomaterial granules. The membrane was easily placed with the dense film facing the gingival soft tissue and the microfibrous biomaterial granules. The membrane was easily placed with the dense film facing the gingival soft tissue and the microfibrous layers facing soft and hard tissues, respectively (Figure 3b). The alveolar bone defect was thinned with granules of biomaterial before covering with the membrane and closure of the gingival flap (Figure 3c). After 14 days, the gingiva healed properly without sign of inflammation (Figure 3d). After 4 months, the site was exposed, and two dental implants were inserted to replace incisor teeth #11 and #21. The membrane was not visible while the biomaterial granules were partly surrounded by a fibrous tissue (Figure 3e). After 6 months, the dental implants were well osseointegrated, and the final prostheses were placed, resulting in a proper aesthetic rehabilitation of the anterior sector (Figure 3f).

A case of alveolar ridge augmentation prior to dental implant is shown in Figure 3. After extraction of tooth #11 and healing for 4 months, the alveolar bone defect in the anterior vestibular area was exposed by raising the mucoperiosteal flap (Figure 3a). The bi-layered synthetic resorbable membrane was easily placed between the gingival flap and the bone wall with the dense and microfibrous layers facing soft and hard tissues, respectively (Figure 3b). The alveolar bone defect was thinned with granules of biomaterial before covering with the membrane and closure of the gingival flap (Figure 3c). After 14 days, the gingiva healed properly without sign of inflammation (Figure 3d). After 4 months, the site was exposed, and two dental implants were inserted to replace incisor teeth #11 and #21. The membrane was not visible while the biomaterial granules were partly surrounded by a fibrous tissue (Figure 3e). After 6 months, the dental implants were well osseointegrated, and the final prostheses were placed, resulting in a proper aesthetic rehabilitation of the anterior sector (Figure 3f).

All surgeons reported an easy placement of the membrane in different indications with a satisfaction score averaging 3.8/5. The dentist satisfaction score at 4 months postsurgery for using the synthetic resorbable membrane increased to 4.5/5 as reported by the 7 independent surgeons in 26 patients (Figure 4).

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**TABLE 1**

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Number</th>
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<tr>
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</tr>
<tr>
<td>Dental practices</td>
<td></td>
<td>7</td>
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<tr>
<td>Age (Years)</td>
<td>Mean ± SD</td>
<td>50.5 ± 12.4</td>
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<td></td>
<td>Min-Max</td>
<td>31–72</td>
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<tr>
<td>Gender</td>
<td>Male</td>
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</tr>
<tr>
<td></td>
<td>Female</td>
<td>15 (57.7%)</td>
</tr>
<tr>
<td>Oral hygiene</td>
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<td>15 (57.7%)</td>
</tr>
<tr>
<td></td>
<td>Average</td>
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</tr>
<tr>
<td></td>
<td>Poor</td>
<td>0 (0%)</td>
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<td>Smoking</td>
<td>No</td>
<td>24 (92.3%)</td>
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<td></td>
<td>Yes</td>
<td>2 (7.7%)</td>
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<td>Indication for using the</td>
<td>Guided tissue regeneration</td>
<td>23 (88%)</td>
</tr>
<tr>
<td>membrane</td>
<td>in immediate or delayed implant placement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Socket preservation</td>
<td>2 (8%)</td>
</tr>
<tr>
<td></td>
<td>Alveolar crest augmentation</td>
<td>1 (4%)</td>
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**TABLE 2**

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<th>Variable</th>
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<tr>
<td>Safety</td>
<td>Minor adverse event</td>
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<tr>
<td></td>
<td>Serious adverse event</td>
<td>None</td>
</tr>
<tr>
<td>Patient pain at day 14</td>
<td>Yes (VRS Mean ± SD)</td>
<td>2.2 ± 1.1/10</td>
</tr>
<tr>
<td></td>
<td>VRS Min-Max</td>
<td>1–5</td>
</tr>
<tr>
<td>Observation at day 14</td>
<td>Ecchymosis</td>
<td>4/6 (15%)</td>
</tr>
<tr>
<td></td>
<td>Edema</td>
<td>12/6 (46%)</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
<td>10/6 (38%)</td>
</tr>
<tr>
<td></td>
<td>Membrane exposure</td>
<td>3/6 (12%)</td>
</tr>
<tr>
<td></td>
<td>Biomaterial leakage</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>None</td>
</tr>
<tr>
<td>Observation at month 4</td>
<td>Inflammation</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>None</td>
</tr>
<tr>
<td>Dentist satisfaction</td>
<td>At surgery (mean ± SD)</td>
<td>3.8 ± 1.0/5 (76%)</td>
</tr>
<tr>
<td></td>
<td>At 4 months (mean ± SD)</td>
<td>4.5 ± 0.6/5 (90%)</td>
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*VRS indicates verbal rating scale.
DISCUSSION

This study reported the clinical safety of a new synthetic resorbable dental membrane. This membrane had a bi-layered structure with a thin dense film to prevent epithelial tissue invasion and microfibrils layer to guide bone regeneration. Preclinical studies have shown that the PLGA membrane maintained its structural integrity up to 16 weeks and was completely degraded in 26 weeks without sign of inflammation. The membrane was made of synthetic poly-lactic glycolic acid, a polymer widely used in medical devices such as resorbable sutures and surgical mesh.

In this clinical study, the new synthetic resorbable membrane was evaluated by 7 dental practices involving 26 patients. Dental surgeons used the membrane together with

Figure 1. Use of the synthetic resorbable dental membrane together with bone filler granules in a fenestration at the implant apex site. (a) Preoperative view. (b) Intra-operative view showing the fenestration. (c) Implantation of the membrane after filling the defect with biomaterial granules. (d) 14 days postsurgery view of soft tissue healing. (e) 4 months postsurgery view. (f) Retro-aveolar radiograph at 4 months postsurgery.

Figure 2. Use of the synthetic resorbable dental membrane together with bone filler granules in a bone dehiscence during implant insertion. (a) Preoperative view. (b) Intra-operative view showing the dehiscence. (c) Implantation of the membrane after filling the defect with biomaterial granules. (d) Sutures at end of surgery. (e) 14 days postsurgery view of soft tissue healing. (f) Retro-alveolar radiograph at 4 months postsurgery.
various bone fillers in GTR around dental implants, secondly in alveolar bone (socket) preservation and in augmentation of the alveolar crest (Table 1). Surgeons reported an easy placement of the membrane at the time of surgery (Figure 4). Fourteen days postsurgery, patients had no pain or declared minimal pain while ecchymosis, edema, and inflammation resulting from the surgery were sometimes noticed by the dental surgeons (Table 2). Exposure of the membrane without loosening of the biomaterial granules was also observed in 3 cases while mucosa normally healed over time. At 4 months postimplantation, no infection or mucosal inflammation was reported, and the overall dentist satisfaction with the clinical performance of the membrane increased (Figure 4). In terms of safety, no adverse event was reported with the use of this membrane (Table 2).

This synthetic resorbable membrane presented several advantages over standard collagen membranes.22 First, its surgical handling appeared to be well adapted to dental applications. The membrane was easily cut to fit the defect. Further, the physical properties did not change during surgery, whether dry or impregnated by blood. This property allowed for an easy placement on the site both prior to and after filling the bone defect with biomaterial granules (Figures 1c, 2c, and 3b). The membrane was then easily placed over the granules. There was no need to fix the membrane with pins or sutures because its adhesion to bone tissue was suitable. During suturing, the flap easily slid over the synthetic membrane without any displacement. In a contrasting approach, collagen membranes are difficult to handle, repositioning as they lose rigidity in wet conditions. Since collagen membranes often collapse on the biomaterial granules, some studies have reported the superposition of two collagen membranes.23,24

In this study, patients reported almost no pain after the implantation of the synthetic membrane (Table 2). The pain scores were comparable to those reported in other studies with similar surgeries.25,26 There was no need for use of a specific analgesic medication apart from recommendations following oral surgery for 5 days. Although no infection was reported, the use of a broad-spectrum antibiotic is recommended after oral surgery. At 14 days postsurgery, the primary healing of soft tissue over the membrane appeared normal without clinical inflammation (Figures 1d, 2e, and 3d). At 4 months postimplantation, the time frame corresponding to its degradation, no inflammation was reported with the synthetic membrane (Figure 1e).

Three cases of membrane exposure (3/26, 12%; Table 2) were reported in this study. This rate of exposure may be regarded as a disadvantage of the synthetic resorbable membrane but is in the range of exposure reported in the literature for other GTR membranes. For instance, a randomized controlled trial comparing bioabsorbable collagen membrane
membrane in different GTR indications. The surgical handling, physical barrier, and resorption rate of this membrane were satisfactory with various biomaterial fillers and dental implants. At 4 months postimplantation, no infection or mucosal inflammation was reported, and the overall dentist satisfaction with the clinical performance of the membrane was high. The results of this clinical study suggest that this new membrane can be used to achieve successful GTR at dehiscence when placing implants or in cases of alveolar bone crest augmentation prior to the insertion of dental implants.

**Abbreviations**

- CRFs: clinical record forms
- GBR: guided bone regeneration
- GTR: guided tissue regeneration
- PLGA: poly(D,L-lactic/glycolic acid)
- VRS: verbal rating scale

**ACKNOWLEDGMENT**

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**NOTE**

The authors have no conflict of interest.

**REFERENCES**

10. Sculean A, Nikolaidakis D, Nikou G, Ivanovic A, Chapple ILC, Stavropoulos A. Biomaterials for promoting periodontal regeneration in...