The Simplified Papilla Preservation Flap in the Regenerative Treatment of Deep Intrabony Defects: Clinical Outcomes and Postoperative Morbidity

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Background: The aims of the present multi-center, randomized, controlled clinical trial were: 1) to compare the efficacy of the simplified papilla preservation flap with and without a barrier membrane in deep intrabony defects; 2) to evaluate the postoperative morbidity and surgical complications; and 3) to preliminarily test the impact of baseline tooth mobility on clinical outcomes.

Methods: This parallel group, randomized, multi-center, controlled clinical trial involved 112 patients in 8 periodontal practices in 4 countries. A deep intrabony defect in each patient was accessed with the simplified papilla preservation flap. In the test defects, a bioabsorbable membrane was positioned. Patients’ experiences with the surgical procedure and postoperative period were evaluated with a questionnaire. Clinical outcomes included clinical attachment level (CAL) and probing depth (PD) changes.

Results: Complete observations were available for 55 test and 54 control defects. CAL gains at 1 year were 3.5 ± 2.1 mm in the guided tissue regeneration (GTR) group and 2.6 ± 1.8 mm in the control group (P = 0.0117). CAL gains ≥4 mm were observed in 50.9% of GTR sites and 33.3% of control sites. A significant center effect of 2.1 mm was observed (P = 0.01). Initial PD (P = 0.01) and baseline tooth mobility (P = 0.036) were significant covariates. During the procedure, 30.4% of test and 28.6% of controls reported feeling moderate pain, and subjects estimated the hardship of the procedure at 24 ± 25 visual analog scale (VAS) units in the test group, and at 22 ± 23 VAS in controls. In terms of the investigated outcomes, differences between test and control groups were not statistically significant. Among the postoperative complications, edema was most prevalent at week 1, and more frequently associated with the test treatment (P = 0.01). In the test group, 53.6% of membranes were exposed at week 3.

Conclusions: The present study further supports the added benefits of guided tissue regeneration with respect to access flap alone in the treatment of deep intrabony defects, as well as the general efficacy of GTR in different clinical settings. Furthermore, our study indicates a possible influence of baseline tooth mobility on clinical outcomes. J Periodontol 2001;72:1702-1712.

KEY WORDS
Guided tissue regeneration; periodontal diseases/surgery; periodontal diseases/therapy; surgical flaps; clinical trials, controlled; multi-center studies.

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The additional benefit of positioning a barrier membrane to promote clinical healing of a deep intrabony defect has been tested in many controlled clinical trials. A recent summary of the evidence derived from these trials (13 independent, controlled clinical trials) indicated that average clinical attachment level (CAL) gains of $3.4 \pm 1.8$ mm were observed in 243 guided tissue regeneration (GTR)-treated sites. This compares with $1.8 \pm 1.4$ mm of CAL gain in 213 controls. The frequency distribution of the expected CAL gain in 651 defects in 17 investigations indicates that 87.3% of sites gained $\geq 2$ mm of clinical attachment, and 62.5% gained 4 mm or more. More than 2 percent (2.7%) of sites lost clinical attachment following GTR therapy.

A recent randomized, controlled, multi-center, phase IV study explored the generalizability of the expected outcomes of GTR therapy. The results indicated that, despite the significant differences in the observed outcomes among the different centers and the substantial variability in the outcomes, GTR treatment was significantly better than access flap alone.

In the last decade, several studies have contributed in identifying patient, defect, and surgical factors associated with the observed variability in clinical outcomes. Control of these factors could increase efficacy and predictability. Among these factors, the ability to maintain a submerged subgingival environment has received much attention. In particular, a variety of studies have indicated that bacterial contamination of the membrane is associated with reduced clinical outcomes in terms of CAL gain and pocket reduction. To address this limitation, new surgical flaps have been designed to preserve the interdental tissue and thus decrease membrane contamination. These papilla preservation flaps have been used in several investigations, including a large multi-center trial. In these studies, the use of the improved flap design has resulted in a decrease in membrane exposures.

Taken together, this evidence is generally considered to support the concept that GTR therapy of intrabony defects is both effective and predictable. Efficacy and predictability of a procedure in terms of outcomes such as CAL gain have traditionally been the key parameters according to which periodontists have evaluated novel forms of therapy. With few exceptions, little consideration, however, has been given to other critical elements that contribute to the patient’s assessment of the cost-benefit ratio of a procedure and thus contribute to the final therapeutic choice. These include postoperative pain, discomfort, complications, and the perceived benefits from the treatment.

The aims of the present multi-center, randomized controlled clinical trial were: 1) to compare the efficacy of the simplified papilla preservation flap with and without the interposition of a barrier membrane in the treatment of deep intrabony defects; 2) to evaluate the postoperative morbidity and technical complications; and 3) to test the impact of baseline tooth mobility on clinical outcomes.

**MATERIALS AND METHODS**

**Experimental Design**

This was a parallel group, randomized, multi-center, and controlled clinical trial testing the efficacy of 2 treatment modalities in intrabony defects. The test treatment consisted of access to the defect with a papilla preservation flap, surgical debridement, and positioning of a specifically designed poly-D,L-lactide bioabsorbable membrane softened with acetyl-tributyl citrate to isolate the intrabony component of the defect. The same procedure was performed in the control group but with no barrier membrane. A single defect was treated in each patient. Patient outcomes were evaluated during the healing period, while clinical outcomes were evaluated at 1 year. The study scheme is illustrated in Figure 1. This investigation was performed at 8 periodontal practices constituting a practice-based research network; centers were located in Belgium, Holland, Italy, and the United States. Projected accrual

![Figure 1](1064_IPC_AAP_553361_12/19/01_9:38 AM_Page_1703.png)

Figure 1. Schematic illustration of the study outline.
included 14 subjects per center, for a total of 112 patients. Each clinical center was connected with and supervised by a central monitoring facility.

**Investigator Calibration**
An investigator meeting was held as previously described. In brief, a calibration exercise was performed to obtain acceptable intra- and interexaminer reproducibility for probing depth, recession of the gingival margin, and evaluation of defect anatomy. Intraexaminer reproducibility was evaluated as the standard deviation of the difference of triplicate measurements. All investigators reached the target of a standard deviation lower than 0.4 mm for attachment level. Interexaminer variability was evaluated as the standard deviation of the difference from the gold standard represented by Dr. Tonetti. The computed value for attachment level was less than 0.5 mm for all clinicians.

**Subject Population**
Inclusion and exclusion criteria were previously reported. In brief, patients younger than 21 years, with uncontrolled or poorly controlled diabetes, unstable or life-threatening conditions, requiring antibiotic prophylaxis, or who were heavy smokers (>20 cigarettes/day) were excluded. Only patients with a diagnosis of severe periodontitis previously treated by at least one cycle of scaling and root planing and oral hygiene instructions were invited to participate. These subjects had to present with full-mouth plaque scores (FMPS) and full-mouth bleeding scores (FMBS) <25% at study baseline (following completion of the initial periodontal treatment phase).

Entry criterion was the presence of a deep intrabony defect (≥4 mm), located in the interdental area, in anterior or premolar teeth. Depth was conservatively estimated by a combination of radiographic and clinical criteria. Defects extending into a furcation were not included. Depth of the intrabony component of the defect and absence of furcation involvement were preliminarily evaluated during the screening phase and confirmed during surgery. Inclusion of defects involving the mesial aspect of the lower first molar was individually evaluated for access and thickness of the alveolar ridge. The presence of a 2 to 3 mm band of keratinized tissue to allow surgical manipulation and suturing according to the protocol was also required.

After verification of the above criteria, 121 subjects gave informed consent and were enrolled into the study.

**Pre-Treatment**
Control of the periodontal infection was achieved prior to the experimental phase by an initial treatment consisting of scaling and root planing, patient motivation, and oral hygiene instructions. When indicated, clinicians supplemented mechanical debridement with antimicrobials and/or antibiotics.

**Randomization**
After having been entered into the study and assigned a patient number, all subjects were randomly assigned to one of the 2 treatment regimens. Assignment was performed by a central randomization facility using a custom-made program based on balanced, random, permuted blocks. Furthermore, to reduce the chance of unfavorable splits between test and control groups in terms of key prognostic factors, the randomization process balanced smoking status and location of the defect at upper first premolars in the test and control groups. All subsequent study appointments (surgery, controls, and maintenance) were booked at this point.

**Clinical Measurements**
Clinical parameters were evaluated before anesthesia on the day of surgery and 1 year later. Full-mouth plaque scores (FMPS) were recorded as the percentage of total surfaces (4 aspects per tooth) that revealed the presence of plaque. Bleeding on probing was assessed dichotomously at a force of 0.3 N with a manual pressure-sensitive probe; full-mouth bleeding scores (FMBS) were then calculated.

Probing depth (PD) and recession of the gingival margin (REC) were recorded to the nearest millimeter with a manual pressure-sensitive probe at 0.3 N by trained investigators at the deepest location of the selected interdental site. Clinical attachment levels (CAL), calculated as the sum of PD and REC, were the primary outcome variable. The position of the gingival margin was similarly evaluated on the buccal aspect of the affected tooth (REC-A) and of the adjacent tooth where a buccal suture was placed (REC-B). This is one of the sutures used to close the interdental papilla on top of the barrier membrane, the so-called “offset suture,” that finds its vestibular anchor age at the level of the buccal keratinized tissue of the tooth next to the experimental tooth. Tooth mobility was evaluated as damping characteristics of the periodontal ligament using a purpose-built electronic device as previously described and expressed as conventional units (PTU).

**Surgical Procedures**
Test defects were treated according to GTR principles placing a bioabsorbable membrane after having gained access to the defect using the simplified papilla preservation flap (SPPF), a surgical access flap specifically designed to preserve the interdental tissue for GTR procedures with bioabsorbable barrier membranes. A bioabsorbable membrane was positioned just coronal to the interdental alveolar crest to extend at least 3 mm beyond the margin of the defect; the membrane was firmly secured to the neighboring teeth.
with the enclosed absorbable ligatures. The flaps were then replaced and sutured employing non-absorbable e-PTFE sutures** as previously described.30

The control procedure was identical to the test procedure, apart from the omission of the membrane positioning steps.

**Intrasurgical Clinical Measurements**

The following defect morphology parameters were evaluated after debridement of the area as described:18,40 1) distance from the cemento-enamel junction (CEJ) to the bottom of the defect (CEJ-BD); and 2) distance from the CEJ to the most coronal extension of the interdental bone crest (CEJ-BC) to the nearest millimeter. These measurements were performed at the deepest interdental point of the defect (i.e., deepest point of the site defined by the interdental line angles of the affected tooth). The intrabony component of the defect (INTRA) was calculated as INTRA = (CEJ-BD)−(CEJ-BC). The duration of the surgical procedure was timed, and the number of teeth involved in the surgical procedure was recorded. Hardship of the surgical procedure, presence (dichotomous), and intensity (visual analog scale, expressed in millimeters on a 100 mm scale, VAS) of pain and discomfort were evaluated upon completion of the surgery using a questionnaire.41

**Postsurgical Instructions and Infection Control**

Postoperative pain and edema were controlled with tablets of either 600 mg ibuprofen or 500 mg acetaminophen. Antibiotic coverage consisting of 200 mg/day of doxycycline was prescribed in the first postoperative week. No oral hygiene procedures were allowed in the treated area. Patients were instructed to rinse 3 times daily with 0.12% chlorhexidine and to use modified oral hygiene procedures for the first 11 postoperative weeks. Smokers were asked to limit and possibly avoid smoking. Each patient’s experience with the surgical procedure and the first postoperative week was evaluated using dichotomous questions with daily activities during the first postoperative week were evaluated upon completion of the surgery using a questionnaire.41

**RESULTS**

**Randomization**

Patient and defect characteristics of the test and control groups resulting from the randomization process are described in Table 1. No significant differences were observed in terms of patient-associated variables.

**Patient Retention and Missing Data**

A total of 121 subjects were entered and randomized. Eight subjects withdrew informed consent before surgery; 113 subjects received treatment (56 test and 57 controls, Table 1). During the 1-year follow-up, 4 subjects (3 controls and 1 test) were lost to follow-up. Complete observations were available for 109 subjects (55 test and 54 controls). This represented 90% of entered patients and 97.3% of the projected accrual.

**Oral Hygiene**

Baseline FMPS and FMBS are displayed in Table 1. At 1 year, FMPS was 11.7 ± 7.9 for test and 10.3 ± 6.9 for control-treated patients (P = 0.152, t test); similarly, the FMBS was 8.6 ± 5 for test and 8.1 ± 6 for control subjects (P = 0.329, t test).

**Data Management and Statistical Analysis**

Data were entered in a microcomputer and proofed for entry errors. The percentage of CAL gain with reference to the baseline intrabony component of the defect (CAL%) was defined as CAL gain/INTRA. The resulting database was locked and loaded.††† All calculations and analyses were performed using special software.‡‡‡ Data are expressed as means ± standard deviations. Unbalances in the test and control groups arising from the randomization process were evaluated using the unpaired t test for continuous variables and the chi-square test for categorical variables. The significance of the treatment effects on the dependent variables CAL changes and PD changes was estimated by constructing generalized linear models using the GLM procedure. The clinical center and treatment-by-center interaction were incorporated as stratification factors.42,43 In case of a non-significant treatment-by-center interaction, the interaction term was removed from the analysis and the main effect model was applied.42 Final models were selected by elimination of non-significant factors. Model diagnostics included distribution of errors and analysis of residuals. For all analyses, the alpha error was set at 0.05.

**Maintenance Care (Week 11; Months 6 and 9)**

All patients were maintained in maintenance programs where they received full-mouth professional prophy-

laxis and calculus removal at week 11, and 6 and 9 months as previously described.13

**‡‡‡ SAS version 6.12, SAS Institute.**

**§§§ SAS Institute, Cary, NC.**

**** Gore-Tex suture material, W.L. Gore & Associates, Flagstaff, AZ.

##  Gore-Tex suture material, W.L. Gore & Associates, Flagstaff, AZ.

### Pal-out gel, Haye-Nee Dental AG, Boggio, Switzerland.
Table 1.
Patient and Defect Characteristics at Baseline (N = 113)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test</th>
<th>Control</th>
<th>Significance (t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N subjects</td>
<td>56</td>
<td>57</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 ± 9.9</td>
<td>46.6 ± 11.7</td>
<td>0.386</td>
</tr>
<tr>
<td>Gender (% females)</td>
<td>58.9</td>
<td>68.4</td>
<td>0.294*</td>
</tr>
<tr>
<td>Non-smokers (%)</td>
<td>73.21</td>
<td>69.64</td>
<td>0.676*</td>
</tr>
<tr>
<td>FMPS (%)</td>
<td>9.6 ± 6.2</td>
<td>10 ± 6.7</td>
<td>0.362</td>
</tr>
<tr>
<td>FMBS (%)</td>
<td>10.4 ± 5.8</td>
<td>9.7 ± 5.9</td>
<td>0.250</td>
</tr>
<tr>
<td>Mobility (PTU)</td>
<td>13.6 ± 9.4</td>
<td>14.5 ± 9</td>
<td>0.319</td>
</tr>
<tr>
<td>PD (mm)</td>
<td>8.2 ± 1.9</td>
<td>8.2 ± 1.8</td>
<td>0.484</td>
</tr>
<tr>
<td>REC (mm)</td>
<td>1.3 ± 1.3</td>
<td>1.4 ± 1.5</td>
<td>0.380</td>
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<tr>
<td>CAL (mm)</td>
<td>9.5 ± 2.1</td>
<td>9.5 ± 2.4</td>
<td>0.459</td>
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<tr>
<td>CEJ-BD (mm)</td>
<td>10.4 ± 2.2</td>
<td>10.2 ± 2.6</td>
<td>0.302</td>
</tr>
<tr>
<td>Intra (mm)</td>
<td>6.3 ± 1.7</td>
<td>6.3 ± 1.8</td>
<td>0.420</td>
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</table>

* Chi-square.

Table 2.
Surgical Parameters (N = 113)

<table>
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<tr>
<th>Variable</th>
<th>Test</th>
<th>Control</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periosteal incision</td>
<td>64%</td>
<td>29%</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Vertical releasing incision</td>
<td>36%</td>
<td>27%</td>
<td>0.308*</td>
</tr>
<tr>
<td>Interdental primary closure</td>
<td>98%</td>
<td>100%</td>
<td>0.3108*</td>
</tr>
<tr>
<td>N teeth involved</td>
<td>4.1 ± 2.5</td>
<td>3.6 ± 1.7</td>
<td>0.1†</td>
</tr>
<tr>
<td>Surgical time (minutes)</td>
<td>98.7 ± 45.7</td>
<td>74.9 ± 33.6</td>
<td>0.001†</td>
</tr>
<tr>
<td>Surgical time/tooth (minutes)</td>
<td>27.1 ± 13.4</td>
<td>22 ± 8.6</td>
<td>0.01†</td>
</tr>
</tbody>
</table>

* Chi-square.
† t test.

Evaluation of Surgical Procedures and Postoperative Period

Table 2 describes the surgical procedures performed in the test and control groups. Significantly more periosteal incisions were performed to achieve primary closure on top of GTR membranes (P = 0.0002, chi-square). Test surgery with membrane positioning required, on average, 24 minutes longer than for controls. This increase in surgical time was significant (P = 0.001), even after correction for the number of teeth involved (P = 0.01). During the procedure, 30.4% of test subjects reported feeling moderate pain (14 ± 14 VAS units, with 0 = no pain and 100 = unbearable pain), compared to 28.6% of control subjects who reported similar pain intensity (21 ± 15 VAS, P = 0.305). Subjects in the test group estimated the hardship of the procedure at 24 ± 25 VAS units, while control patients gave values of 22 ± 23 VAS units (easy to cope = 0 and difficult to cope = 100). The difference was not statistically significant (P = 0.67).

Figure 2 (A through C) displays the prevalence and extent of postoperative pain. No significant difference was observed in the prevalence of test and control subjects reporting postoperative pain (Fig. 2A). More than 50% of the subjects in both groups experienced no postoperative pain. Among the subjects reporting pain, pain intensity was described at values of 28.1 ± 20 VAS (test) and 26.4 ± 17.6 VAS (control) (0 = no pain and 100 = unbearable pain, Fig. 2B). Pain lasted an average of 14.1 ± 15.6 hours in test patients and 24.7 ± 39.1 hours in the controls (P = 0.103, t test, Fig. 2C). More than 50% (53.6%) of test subjects and 51.8% of control subjects reported postoperative discomfort other than pain.

Postoperative morbidity was limited to a minority of patients. Thirty-five percent (35.7%) of test patients and 32.1% of controls reported that the procedure interfered with daily activity for an average of 2.7 ± 2.3 days in the test group and 2.4 ± 1.3 days in the controls (P = 0.74). In both groups, the surgery interfered with work in 25% of cases, while interference with recreation was limited to 8.9% of tests and 7.1% of controls.

The most frequent postoperative complications are displayed in Figure 3 and Table 3. Postoperative edema was most prevalent at week 1, and more frequently associated with the test treatment (P = 0.01, chi-square). In the following weeks, the prevalence rapidly decreased. Suppuration of the surgical areas was never observed, while small hematoma were infrequently observed in both test and controls (7.3% and 5.4% of cases at 1 week in test and controls, respectively).

Interdental membrane exposure (test) and flap dehiscence (control) reached their highest prevalence between weeks 3 and 5 (Table 3). A total of 53.6% of membranes were exposed at week 3; detection of exposed membranes decreased in the subsequent weeks, possibly as the result of exfoliation of the exposed portion of the membrane. Subjects with exposed membranes at week 2 had significantly higher percentages of plaque (FMPS = 11.4 ± 6%) than subjects with unexposed membranes (FMPS = 8.6 ± 6.1%, P = 0.048, t test). Differences in CAL gains at 1 year, however, were not statistically significant (3.7 ± 1.8 mm in unexposed sites and 3.3 ± 2.6 mm in exposed sites, P = 0.246). In addition, interdental membrane exposure occurred in 50% of
cases where the defect was located on the distal side of the affected tooth and only in 30% of those cases with a mesial defect.

Clinical Outcomes
Table 4 displays the clinical outcomes at 1 year and the changes in clinical parameters between the baseline and 1-year appointment. In both groups, a significant treatment effect was observed. In the test group, the baseline CAL of 9.5 ± 2.1 mm improved to 5.9 ± 1.9 mm at 1 year (P < 0.0097); in the control group, baseline and 1-year CAL were 9.5 ± 2.4 mm and 6.9 ± 2.2 mm (P < 0.0097), respectively. The observed changes in CAL between baseline and 1 year were gains of 3.5 ± 2.1 mm for the GTR group and 2.6 ± 1.8 mm for the access flap group. The difference between test and control groups was statistically significant (P = 0.0117). The distribution of CAL changes is displayed in Table 5. Clinical attachment loss was observed in 1.82% of the sites treated with GTR and in none of those treated with SPPF alone; CAL gains ranging from 0 to 3 mm were observed in 47.3% of GTR-treated sites and in 66.7% of the access flap-treated sites. GTR therapy resulted in CAL gains ≥ 4 mm 50.9% of the time, while access flap achieved the same result in 33.3% of sites.

Probing depth reductions were 4.4 ± 2.4 mm for the test group and 3.6 ± 2.1 for the control group (Table 4). One year after therapy, residual PD was 3.8 ± 1.5
mm for the test group, and 4.7 ± 1.4 for controls (P = 0.0013, t test). The frequency distribution of residual PD 1 year after the test or control procedure is displayed in Table 6. The test procedure resulted in PD ≤4 mm in 94.5% of the cases.

Between baseline and 1 year, the gingival margin receded 0.9 ± 1 mm in the test group and 0.9 ± 1.3 mm in the controls. Table 7 displays the average gingival margin recession observed in the interdental area (REC) and on the buccal aspect of the defect-associated tooth (REC-A) and the buccal aspect of the adjacent tooth (REC-B). No significant differences were observed between test and controls.

The significance of the treatment effect was evaluated taking into account the potential sources of variability arising from the multi-center design and previously described covariates. The following variables were entered into the model: treatment, center, treatment-by-center interaction, smoking status, FMPS, FMBS, baseline tooth mobility, baseline PD and CAL, baseline CEJ-BD, and INTRA. The final model was selected by elimination of non-significant factors and is presented in Table 8. The model was statistically significant and explained 52% of the observed variability in CAL gain. The following variables were included in the final model: treatment effect, center (best versus worst), smoking status, baseline PD, baseline mobility, and baseline INTRA. The adjunctive effect of a bioabsorbable membrane was highly significant:

Table 4.
1-Year Outcomes (N = 109)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test</th>
<th>Control</th>
<th>Significance (t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility (PTU)</td>
<td>12.7 ± 8.7</td>
<td>12.9 ± 8.7</td>
<td>0.429</td>
</tr>
<tr>
<td>PD (mm)</td>
<td>3.8 ± 1.5</td>
<td>4.7 ± 1.4</td>
<td>0.0013</td>
</tr>
<tr>
<td>REC (mm)</td>
<td>2.1 ± 1.6</td>
<td>2.2 ± 1.7</td>
<td>0.404</td>
</tr>
<tr>
<td>CAL (mm)</td>
<td>5.9 ± 1.9</td>
<td>6.9 ± 2.2</td>
<td>0.0097</td>
</tr>
<tr>
<td>Changes in mobility</td>
<td>0.48 ± 5.2</td>
<td>1.34 ± 5.5</td>
<td>0.214</td>
</tr>
<tr>
<td>PD reduction (mm)</td>
<td>4.4 ± 2.4</td>
<td>3.6 ± 2.1</td>
<td>0.0237</td>
</tr>
<tr>
<td>Changes in REC (mm)</td>
<td>0.9 ± 1</td>
<td>0.9 ± 1.3</td>
<td>0.496</td>
</tr>
<tr>
<td>CAL gain (mm)</td>
<td>3.5 ± 2.1</td>
<td>2.6 ± 1.8</td>
<td>0.0117</td>
</tr>
<tr>
<td>CAL gain %</td>
<td>56.0 ± 32</td>
<td>42.0 ± 28</td>
<td>0.0071</td>
</tr>
</tbody>
</table>

Table 5.
Frequency Distribution of CAL Gain (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Changes in CAL (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Loss 0-1 2-3 4-5 ≥6</td>
</tr>
<tr>
<td>Test</td>
<td>1.82 16.36 30.91 29.09 21.82</td>
</tr>
<tr>
<td>Control</td>
<td>0 31.48 35.19 25.93 7.41</td>
</tr>
</tbody>
</table>

Table 6.
Frequency Distribution (%) of Residual Probing Depths (PD) at 1 Year

<table>
<thead>
<tr>
<th>Group</th>
<th>PD ≤3</th>
<th>3 &lt; PD ≤5</th>
<th>PD ≥6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>50.9</td>
<td>43.6</td>
<td>5.5</td>
</tr>
<tr>
<td>Control</td>
<td>13.0</td>
<td>68.5</td>
<td>18.5</td>
</tr>
</tbody>
</table>

Table 8.
Significance of Treatment Effect (GTR versus flap surgery) on CAL Gains at 1 Year (after correcting for center effects and significant confounding factors)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment effect</td>
<td>1 ± 0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Center effect†</td>
<td>-2.1 ± 0.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking status‡</td>
<td>-0.7 ± 0.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline PD (mm)</td>
<td>0.4 ± 0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Baseline mobility (PTU)</td>
<td>-0.03 ± 0.02</td>
<td>0.036</td>
</tr>
<tr>
<td>Baseline intrabony defect (mm)</td>
<td>0.1 ± 0.14</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*Model: CAL gain = β0 + α1 treatment effect + α2 center effect + α3 smoking + α4 probing depth + α5 baseline tooth mobility + α6 intrabony defect + ε
R² = 0.52—model significance, P < 0.0001.
† Center effect: variability in CAL gains among the 8 centers. The parameter estimates the spread in CAL gains between the center with the largest and smallest gains in clinical attachment.
‡ Smoking status: variability in CAL gains between smokers and non-smokers.
GTR treatment with bioabsorbable membranes resulted in CAL gains 1 mm greater than the access flap control \((P = 0.001)\). A significant center effect was also observed \((P = 0.01)\). The difference between the center that obtained the largest improvements in CAL and the center with the smallest improvements was 2.1 mm. Among the considered defect characteristics, initial probing depth was a highly significant covariate \((P = 0.01)\), as well as baseline tooth mobility \((P = 0.036)\), while baseline INTRA did not reach statistical significance in the model.

**DISCUSSION**

This parallel group, randomized, multi-center, controlled clinical trial was designed to compare the clinical outcomes, postoperative healing, and morbidity associated with 2 treatment modalities of intrabony defects. Both treatments consisted of flap elevation with a papilla preservation flap,\(^{30}\) defect debridement, and flap closure. In the test group, a bioabsorbable barrier membrane was positioned before closure of the flap. The 2 treatments resulted in significant improvements between baseline and 1 year in terms of CAL gains and PD depth reduction (Table 4). The test treatment, however, showed significantly greater CAL gains \((P = 0.0117)\) and PD reductions \((P = 0.0237)\) compared to controls. An added benefit of 1 mm associated with the membrane was observed after correction for other known covariates (Table 8). It is noteworthy to underline that these results were obtained comparing 2 well-balanced experimental populations (Table 1). In fact, no significant differences were observed between the control and test groups in any of the known patient and defect variables that potentially could affect the clinical outcomes.\(^{15-17}\)

The optimal balance was due to the efficacy of the randomization process, based on balanced permuted blocks and blocking to prognostic variables. The observed CAL gain of 3.5 ± 2.1 mm in the test group compares well with the existing literature. An average CAL gain of 3.6 ± 1.5 mm was observed in a meta-analysis of 592 intrabony defects treated with bioabsorbable barriers in 17 studies.\(^{14}\) On the contrary, the CAL gain of 2.6 ± 1.8 mm obtained in the control group was greater than any reported in the classic literature. In fact, CAL gains of 1.8 mm were calculated in a meta-analysis of 847 defects treated with access flap in 28 studies.\(^{44}\)

The limited, although clinically and statistically significant, difference of 1 mm between the test and control treatment in the present study could therefore be partly due to the optimal and “above expectations” performance of flap surgery. Similar results were observed in a previous multi-center study,\(^{13}\) conducted under similar experimental conditions. In both studies, the excellent results of flap surgery could be explained, at least in part, by the rigorous plaque control protocol and peculiar design of the access flap. The simplified papilla preservation flap allows full preservation of the interdental tissues and therefore primary closure of the interproximal space, possibly enhancing wound protection and stability.

In the present study, primary closure was obtained in 98% of sites treated with membranes and in 100% of sites treated with access flap. Primary closure was maintained during the healing period in 46.4% of test sites and 92.7% of controls. The impact of wound protection on clinical outcomes and the negative influence of mechanical trauma and bacterial contamination on the healing process have been widely discussed, especially in cases treated with barrier membranes.\(^{6,18,20,22-24,27-29}\) In the present study, a high percentage of exposed membranes was observed in some of the clinical centers, and it was frequently associated with reduced amounts of CAL gains (Table 9). However, the best outcomes were not always associated with high performance in terms of wound protection. Other factors, like smoking habits and patient compliance, could have played an important role in determining the different results in the different centers.

The issue of predictability of clinical outcomes has been addressed by observing the frequency distribution of CAL changes at 1 year (Table 5). It is important to stress that attachment loss was observed in 1.8% of the test sites and in none of the controls. Percentages of sites gaining significant amounts of attachment (≥4 mm), however, were much higher in sites treated with barrier membranes (50.9%) than in sites treated with access flap (33.3%). The reported outcomes are consistent with previous observations\(^{14}\) of 2.7% attachment loss and 62.5% CAL gain of ≥4 mm in 651 intrabony defects treated with GTR in 17 studies.

The significance of the treatment effect was evaluated with a multivariate analysis (Table 8) taking into account the potential sources of variability such as the treatment modalities, the multi-center design of the study, and the patient and defect characteristics. The final model explained 52% of the observed variability. The performance of each clinical center had a very strong effect on the final outcome. The spread observed among the centers was 2.1 mm. This variability is clinically relevant and could be dependent on differences in the enrolled patients in terms of social background, type of periodontal disease, response to therapy, persistence of specific pathogens, along with differences in technical ability, clinical organization, and experience of the different clinicians. This level of variability was also observed in a previous multi-center study\(^{13}\) and confirms the relevance of patients and clinician-associated factors in the outcomes of periodontal surgical therapy.

Among the many measured variables, smoking, baseline probing depth, and baseline tooth mobility were
significantly associated with reduced expected amounts of CAL gains. Other factors found to be relevant in previous investigations,15-17,19 such as FMPS, FMBS, and depth of the intrabony component of the defect, were not significant. The lack of significance of FMPS and FMBS on clinical outcomes in the present study can be attributed to the infection control protocol and rigid plaque control regimen enforced during the study. Baseline and 1-year FMBS and FMPS were about 10%,16 thereby reducing the range of values of these potential covariates. The lack of significance of the baseline intrabony component of the defect15,17 (INTRA) is probably due to the impact of probing depth in the statistical model: probing depth and INTRA are highly correlated.

Also of interest was the effect of baseline tooth mobility. In the multivariate model, it was found to be significantly associated with CAL gain: the greater the baseline mobility, the smaller the clinical attachment gain observed at 1 year. The effect of tooth mobility on periodontal therapy has been previously investigated in some animal and clinical studies. Two animal and 2 clinical studies reported no difference in the clinical outcomes comparing mobile and non-mobile teeth.45-48 On the contrary, Lindhe and Ericsson in a dog study49 and Fleszar et al. in a clinical trial50 concluded that non-mobile teeth showed a better outcome than mobile teeth after periodontal surgery. A comparison between the cited studies and the present study is difficult since the methods used to measure mobility and treatment modalities were different. In the present study, baseline tooth mobility was measured with an electronic instrument after resolution of periodontal inflammation and resulted, on average, in 14 PTU (Table 1). A total of 31 teeth presented with significantly elevated baseline mobility ranging from 14 to 38 PTU. The experimental teeth presented with severe clinical attachment loss, deep pockets, and deep intrabony defects (Table 1). Surgery and the postsurgical follow-up period were performed to optimize the healing response of each treated site, with a special emphasis on mechanical and biological protection, and control of bacterial contamination. Possibly, the stringent conditions under which this study was performed and the high mobility of some teeth allowed the detection of an effect of tooth mobility on the final outcome. The observation of an impact of tooth mobility on CAL gains has a very important clinical implication. Clinicians might want to consider reducing tooth mobility before undertaking periodontal regenerative surgery. A controlled intervention study, however, is necessary to determine whether reducing baseline mobility (e.g., with splinting) could enhance the outcomes of periodontal regenerative surgery.

A major goal of periodontal therapy is to reduce probing depth to limit the risk of local reinfection. Shallow pockets have a strong, negative predictive value for future disease progression, while deep pockets in treated patients are a risk indicator for periodontal disease progression.51 In the present study, GTR-treated sites resulted in 3.8 ± 1.5 mm PD at 1 year, which compares more favorably with the 4.7 ± 1.4 mm observed in the control group. From a clinical standpoint, it is even more significant that 50.9% of sites treated with barrier membranes showed a PD of 3 mm at 1 year and only 5.5% presented with pockets deeper than 5 mm (Table 6). In the flap-treated group, most sites (68.5%) resulted in PD of 4 to 5 mm, and 18.5% of sites had pockets deeper than 5 mm.

### Table 9. CAL Gains Observed at Different Clinical Centers

<table>
<thead>
<tr>
<th>Center</th>
<th>N</th>
<th>Smokers (%)</th>
<th>CAL Gain (mm)</th>
<th>CAL Gain (%)</th>
<th>N</th>
<th>Smokers (%)</th>
<th>CAL Gain (mm)</th>
<th>CAL Gain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>33.3</td>
<td>2 ± 2</td>
<td>32 ± 29</td>
<td>7</td>
<td>28.6</td>
<td>1.7 ± 2.7</td>
<td>33 ± 45</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>37.5</td>
<td>2.5 ± 2.1</td>
<td>47 ± 35</td>
<td>8</td>
<td>12.5</td>
<td>2.9 ± 1.9</td>
<td>48 ± 30</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>33.3</td>
<td>2.6 ± 1.1</td>
<td>45 ± 14</td>
<td>7</td>
<td>42.9</td>
<td>2.7 ± 1.4</td>
<td>52 ± 25</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>0</td>
<td>1.5 ± 0.7</td>
<td>25 ± 0</td>
<td>3</td>
<td>0</td>
<td>2.3 ± 1.2</td>
<td>47 ± 23</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>40</td>
<td>3.9 ± 2.1</td>
<td>55 ± 32</td>
<td>8</td>
<td>25</td>
<td>4.6 ± 1.5</td>
<td>75 ± 24</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>14.3</td>
<td>0.9 ± 0.7</td>
<td>13 ± 10</td>
<td>8</td>
<td>25</td>
<td>4.8 ± 2.1</td>
<td>64 ± 31</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>33.3</td>
<td>1.8 ± 1.7</td>
<td>30 ± 27</td>
<td>7</td>
<td>42.9</td>
<td>2.1 ± 1.1</td>
<td>34 ± 21</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>25</td>
<td>4 ± 0.8</td>
<td>62 ± 12</td>
<td>8</td>
<td>25</td>
<td>5.6 ± 1.2</td>
<td>83 ± 19</td>
</tr>
</tbody>
</table>

* Prevalence of membrane exposure at week 2.
Periodontal therapy and especially periodontal surgery are frequently associated with recession of the gingival margin, an adverse effect that concerns both patients and clinicians. Regenerative approaches, however, potentially could help to limit this unwanted side effect, by reducing probing depth via an increase in clinical attachment. The present study shows very limited amounts of recession in both the test and control group, not only at the interproximal experimental sites, but also at the buccal sites of the experimental teeth and at the buccal sites of the teeth next to the defect (Table 7). This is relevant, since the positioning of a barrier membrane and especially the peculiar “offset suture” used to coronally displace the buccal flap could enhance the risk for buccal recession in the GTR-treated sites. The careful flap management and suture technique used in this experimental population could explain the observed stability of the gingival margin in both test and control sites.

The need to coronally position the buccal flap to cover the barriers in the test sites required a significantly greater number of periosteal incisions than in the controls (64% and 29%, respectively, \( P = 0.0002, \) Table 2), while the number of vertical releasing incisions was similar. The greater mobility of the buccal flap required in the membrane-treated sites was usually achieved with periosteal incisions and mesio-distal extension of the flap.

On average, GTR surgery required an additional 24 minutes compared to access flap alone. The increase in surgical time was significant (\( P = 0.001 \)) and remained so even after correction for the number of teeth involved in the procedure (\( P = 0.01 \)). Obviously, the increased duration of the procedure is mostly due to membrane adaptation and positioning and to the coronal displacement of the flap.

In regards to postoperative complications, edema was more prevalent in both sites in the first week and more frequently associated with the test treatment (Fig. 3). It rapidly dropped at week 2 and 3, and was noted in some of the test subjects up to week 8. An occasional occurrence was hematoma, noted in 7.3% of test cases and 5.4% of controls at week 1. Suppuration was never observed.

There were no differences between test and control groups relating to postoperative pain (Fig. 2). Less than 50% of patients in both groups reported postoperative pain. Pain intensity was described as mild and limited to the first 24 hours after surgery. Patients did not report any other relevant complication.

In conclusion, the present study: 1) confirms the added benefits of guided tissue regeneration compared to access flap alone; 2) confirms the general efficacy of GTR in different clinical settings; 3) suggests a possible influence of baseline tooth mobility on the clinical outcomes; and 4) expands our knowledge in the area of clinical and patient outcomes with new data useful for developing treatment plans. These data indicate that GTR adds almost 30 minutes to the clinical procedure. Furthermore, prevalence of postoperative edema was increased in GTR-treated patients, while no significant differences were observed between groups in terms of postoperative pain, discomfort, and interference with daily activities.

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