Clinical Outcomes of Periodontal Regenerative Therapy Using rhFGF-2 with a Modified Minimally Invasive Surgical Technique for Intrabony Defects: Case Series with a 12-Month Follow-up

Kentaro Imamura, DDS, PhD
Eiichi Suzuki, DDS, PhD
Takahiro Takeuchi, DDS, PhD
Atsushi Saito, DDS, PhD

The Modified Minimally Invasive Surgical Technique (M-MIST) was designed to improve wound stability and reduce patient morbidity. This case series aimed to evaluate clinical outcomes of periodontal regenerative therapy using recombinant human fibroblast growth factor (rhFGF)-2 with M-MIST for the treatment of intrabony defects. Following initial periodontal therapy, nine intrabony defects in seven patients received rhFGF-2 therapy. Using M-MIST, a buccal incision was made to gain access to the defect without interdental and lingual incisions. After debridement, rhFGF-2 was applied to the defect. Periodontal parameters were evaluated at baseline and at 3, 6, and 12 months postoperatively. Composite Outcome Measure (COM) and patient-reported outcome measure (PROM, recorded using an oral health–related quality of life [QoL] instrument) were also used for evaluation. At 12 months postoperative, mean probing depth reduction was 4.2 ± 0.8 mm and clinical attachment gain was 4.7 ± 0.7 mm. The mean value for gingival recession was –0.3 ± 0.5 mm. According to COM, the outcomes of the treated sites were successful. An improvement in oral health–related QoL was noted at 12 months compared to after the initial periodontal therapy. This case series shows that rhFGF-2 therapy with M-MIST yields favorable clinical outcomes in the treatment of intrabony defects. Int J Periodontics Restorative Dent 2022;42:507–513. doi: 10.11607/prd.5572

Periodontal regeneration is defined as regeneration of the tooth-supporting tissues, including the cementum, periodontal ligament, and alveolar bone. It is a healing outcome that can occur when various systemic and local conditions are satisfied. One important local condition is soft tissue healing. To achieve this, minimally invasive surgeries were proposed with minimal flap reflections and gentle handling of periodontal tissues.1,2 Based on the papilla preservation technique and using very small incisions, the minimally invasive surgical technique (MIST) was advocated by Cortellini and Tonetti3,4 and Cortellini et al.5 Modified MIST (M-MIST) was later introduced with three major objectives in mind: (1) to minimize the tendency for interdental tissue to collapse, (2) to enhance the stability of wound and soft tissue healing, and (3) to reduce infection.6 Several biologic materials, such as recombinant human platelet-derived growth factor (rhPDGF)-BB7 and enamel matrix derivative (EMD),8,9 have been widely used for periodontal regeneration. An alternative biologic material is basic fibroblast growth factor (FGF-2). FGF-2 promotes proliferation of various cell types, angiogenesis, and wound healing.10–12 Preclinical studies from the present authors’ research group demonstrated the
effectiveness of FGF-2 on periodontal regeneration and root coverage.\textsuperscript{13,14} Based on these results, extensive clinical trials have been conducted in Japan, and the FGF-2 therapy was demonstrated to be safe and effective for periodontal regeneration.\textsuperscript{15,16} In 2016, a commercial formulation of 0.3\% recombinant human FGF-2 (rhFGF-2) received pharmaceutical approval for periodontal regenerative medicine in Japan. Using this commercial formulation, the present authors conducted a randomized controlled trial comparing the use of rhFGF-2 with deproteinized bovine bone mineral (DBBM) and rhFGF-2 alone in the treatment of intrabony defects.\textsuperscript{17} Both treatments yielded significant improvements in periodontal parameters at 6 months,\textsuperscript{17} and such outcomes were sustained at the 2-year follow-up.\textsuperscript{18}

Given the favorable outcomes of the rhFGF-2 therapy, it was believed that adding M-MIST would enhance the periodontal healing. The aim of this case series was to evaluate the clinical effects of the rhFGF-2 used with M-MIST in the treatment of intrabony defects.

\section*{Materials and Methods}

\subsection*{Patients}

Seven systemically healthy patients (two men, five women; age range: 30 to 68 years) were included in this case series. Written informed consent was obtained from all patients.

The inclusion criteria were as follows: diagnosis of aggressive or chronic periodontitis (stage III, grade B or C)\textsuperscript{19,20}; presence of a probing depth (PD) > 5 mm and an intrabony defect depth > 3 mm in the interproximal areas of teeth; and mean Plaque Control Record\textsuperscript{21} < 20\%. Exclusion criteria were as follows: an ongoing smoking habit; allergy to FGF-2; and systemic diseases. Written informed consent was obtained from the patients for inclusion in this case series.

\subsection*{Clinical Examination}

The following examinations were performed: PD, gingival recession (GR), and clinical attachment level (CAL) recorded at baseline (following initial periodontal therapy) and at 3, 6, and 12 months postoperative by calibrated surgeons (K.I., E.S., and T.T.). The ability to maintain primary wound closure during early healing (2 weeks postoperative) was assessed using the Early Wound Healing Index (EHI).\textsuperscript{22}

Composite Outcome Measure (COM)\textsuperscript{23} is based on the combined assessment of PD and CAL and is used to evaluate the outcomes of periodontal regenerative therapy. According to COM, a given treatment is judged as successful when a CAL gain ≥ 3 mm and PD closure (defined as postsurgery PD ≤ 4 mm) are achieved at 12 months postoperative.

The periapical radiographs were taken using customized film holders with the long cone paralleling technique, and radiographic bone fill (RBF) was calculated as a percentage, as described previously.\textsuperscript{24}

\subsection*{Surgical Interventions}

Initial periodontal therapy included oral hygiene instructions and scaling and root planing. All surgical procedures were performed by three periodontists (K.I., E.S., and T.T.) using surgical loupes at a magnification of ×8 or ×10 (SurgiTel). Following local anesthesia (2\% xylocaine with 1:80,000 adrenaline), bone sounding was performed. A buccal incision was placed using a microsurgical blade (No. 350, Feather) to gain access to the defect without lingual incisions. After removal of granulation tissues and root planing, 0.3\% rhFGF-2 (Regroth Dental Kit 600 µg, Kaken Pharmaceutical) was applied to the defect. The tension-free flap was immediately closed by 5-0 or 6-0 nylon sutures (Ethilon, Ethicon, Johnson & Johnson).

\subsection*{Patient-Reported Outcome Measures}

At baseline and 6 and 12 months postoperative, patients were asked to rate the perception of oral health using a Japanese version of an oral health–related quality of life (QoL) instrument, the OHRQL-J.\textsuperscript{25} The instrument comprised seven domains (pain, dry mouth, eating and chewing function, speech function, social function, psychological function, and health perceptions), with a total of 22 subscale items. Patients were asked to answer each item using a 5- or 3-point response scale. The total score from the 22 items produced overall OHRQL-J scores that ranged from 0 (the best impact...
possible) to 84 (the worst impact possible).

Statistical Analysis

Nine sites in seven patients were included in this case series. Therefore, the sites were regarded as the statistical unit. Data are expressed as mean ± SD. The changes in PD, GR, CAL, and RBF over time were evaluated by Friedman test with post hoc test. The level of significance was set at 5%.

Results

Patient demographics and defect characteristics are summarized in Table 1. The defect depth of the intrabony component ranged from 3.0 to 4.5 mm (mean: 3.7 ± 0.6 mm) and the width from 1.5 to 2.5 mm (mean: 2.1 ± 0.5 mm).

Representative treatment cases are shown in Figs 1 and 2. The average surgical time was 46.9 ± 5.7 minutes (range: 38 to 56 minutes). There were no notable adverse events. Incomplete flap closure was not observed. At 2 weeks postoperative, mean EHI was 1.9 ± 0.9 (Fig 3). Four surgical sites showed an EHI of 1 (no fibrin line in the incision area), two sites showed an EHI of 2 (fine fibrin line in the incision area), and three sites showed an EHI of 3 (fibrin clot in the incision area).

At 12 months postoperative, PD decreased to 2.2 ± 0.4 mm from a baseline value of 6.4 ± 1.0 mm (Fig 4) (mean reduction: 4.2 ± 0.8 mm). All surgical sites showed PD < 3 mm. CAL decreased to 3.6 ± 1.0 mm from baseline value of 8.2 ± 1.3 mm, with a mean CAL gain of 4.6 ± 0.7 mm. The mean value for GR was −0.3 ± 0.5 mm.

In all surgical sites, an increase in RBF was observed at 6 and 12 months postoperative (Fig 5): The mean RBF value was 38% at 6 months and 53% at 12 months.

At 12 months, all treated sites showed a CAL gain > 3 mm and PD ≤ 4 mm, which can be regarded as a successful treatment according to COM (Fig 6). In other words, the success rate by COM in the present study was 100%. The mean total OHRQL-J score at 12 months was 6.3 ± 3.2, showing a significant improvement from baseline in oral health–related QoL (Fig 7).

Discussion

The present case series shows that periodontal regenerative therapy using rhFGF-2 with M-MIST yielded a significant reduction in PD and gain in CAL from baseline in the treatment of intrabony defects. At 12 months postoperative, mean PD

Table 1 Baseline Patient Demographics, Clinical Parameters, and Defect Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient characteristics</th>
<th>Clinical parameters</th>
<th>Defect characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean ± SD 50.0 ± 13.8</td>
<td>PD, mm 6.4 ± 1.0</td>
<td>Intrabony component</td>
</tr>
<tr>
<td></td>
<td>Range 30–68</td>
<td>CAL, mm 8.2 ± 1.3</td>
<td>Depth, mm 3.7 ± 0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GR, mm 1.7 ± 0.8</td>
<td>Width, mm 2.1 ± 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sites with residual walls, n</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 walls 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 walls 1</td>
</tr>
</tbody>
</table>

PD = probing depth; CAL = clinical attachment level; GR = gingival recession. Data pertain to nine sites in seven patients. PD, CAL, GR, and intrabony component values are presented as mean ± SD. Baseline is defined as after the initial therapy.
Fig 1  Representative case 1. (a) Preoperative clinical view. At the mesial aspect of the mandibular right first premolar, PD was 6.0 mm and CAL was 7.0 mm. (b) Preoperative radiographic view. (c and d) During surgery, depth of the intrabony component was 4.0 mm. (e) After debridement, rhFGF-2 was applied in bone defect. (f) Clinical view at 12 months. PD was 2.0 mm, and CAL was 3.0 mm (CAL gain of 4.0 mm from baseline). The papilla fills the interproximal space. (g) The radiographic view at 12 months shows improvement in the previous defect area.

Fig 2  Representative case 2. (a) Preoperative clinical view. At the mesial aspect of the mandibular left first molar, PD was 7.0 mm and CAL was 7.0 mm. (b) Preoperative radiographic view. (c and d) During surgery, depth of intrabony component was 3.0 mm. After debridement, rhFGF-2 was applied in the bone defect. (e) The surgical site was sutured. (f) Clinical view at 12 months. PD was 2.0 mm, and CAL was 2.0 mm (CAL gain of 5.0 mm from baseline). (g) The radiographic view at 12 months shows bone fill at the defect area.
reduction was 4.2 mm and mean CAL gain was 4.6 mm. These values were greater than those reported in the previous studies of regenerative therapy using EMD with MIST (PD reduction: 3.6 mm; CAL gain: 3.6 mm)\textsuperscript{2} and EMD with M-MIST (CAL gain: 4.1 mm),\textsuperscript{26} although direct comparisons between different studies can be difficult. M-MIST elevates only a buccal flap, leaving the palatal/lingual and interdental tissues intact. It can be expected that early primary closure will be achieved, which contributes to minimizing bacterial infection during wound healing.\textsuperscript{22} FGF-2 accelerates wound healing through the increased rate of vascularization.\textsuperscript{27} The results of EHI suggested early wound healing following the treatment by rhFGF-2 with M-MIST.

In the present authors’ previous clinical studies, RBF values following rhFGF-2 treatment of three-wall defects were 29.4% and 52.1% at 6 and 24 months, respectively.\textsuperscript{17,18} These values were comparable to the present findings at 6 and 12 months (38% and 53%). Considering that the RBF in a previous study showed a progressive improvement from 6 to 24 months,\textsuperscript{18} it is expected that the bone levels in the present cases could increase further by 24 months.

The mean surgical time report herein (46.9 ± 5.7 minutes) was approximately 6 minutes shorter than that reported in an earlier study on M-MIST with EMD (54.2 ± 7.4 minutes).\textsuperscript{28} Aside from the potential difference in surgical skills among periodontists, one reason for this difference in surgical time may be the additional step (root conditioning)
required for treatment using EMD. The present technique could further benefit the patient by shortening the surgical time.

The total OHRQL-J score at 12 months was significantly reduced compared to baseline. Because this is a case series, it was not possible to draw definite conclusions regarding the relationship between surgical time and the oral health–related QoL. The investigation of patient-reported outcomes in relation to surgical time comparing different surgical techniques may provide salient information.

According to COM, the 12-month treatment outcomes can be interpreted as successful in all cases. It has been reported that periodontal regenerative therapies using various materials (EMD, rhPDGF-BB, DBBM, and β-tricalcium phosphate) with a single flap approach yielded successful outcomes in 46% to 78% of cases.23 The rhFGF-2 therapy with M-MIST might accelerate periodontal healing through optimized blood clot stability and gingival blood perfusion and provide a stable space.

There are limitations to this report. Due to the small number of subjects and the lack of a control group, the interpretation of the results must be done with care. It is also difficult to mention periodontal regeneration without histologic evaluation. Further human studies investigating histologic evidence are needed.

Conclusions

This case series demonstrates the potential effectiveness of rhFGF-2 with M-MIST in the regenerative therapy of intrabony defects. Further long-term and large-scale studies are needed to determine the true effects of this combined approach.

Acknowledgments

The authors thank the dental hygienists (Momoko Horie and Misono Hitomi) at Tokyo Dental College Suidobashi Hospital for their patient care. The authors declare no conflicts of interest.

References


