Comparison of the clinical effects of subgingival application of metronidazole 25% gel and scaling in the treatment of adult periodontitis

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Objective: Control of subgingival plaque is of paramount importance in the treatment of periodontal diseases. The role of subgingival sustained-release antibiotic therapy needs elucidation. A single-blind clinical trial was carried out in 13 patients with adult periodontitis to compare the effects of subgingival application of metronidazole dental gel with those of subgingival scaling.

Method and materials: A split-mouth design was used so that each patient received all treatments simultaneously. Randomly selected quadrants were treated with application of 25% metronidazole gel, subgingival scaling, or a combination of scaling and gel application. The remaining quadrant in each patient was left untreated as a control.

Results: All three treatments were effective in significantly reducing Plaque Index, Gingival Index, and bleeding on probing over the 14-week observation period. No statistically significant differences were found between scaling alone and combined treatment. Scaling and combined treatment were better than metronidazole. Metronidazole produced transient effects, best noted during the first 4 weeks after treatment. No additive effect of metronidazole was noted in the combined treatment. At week 14, only combined treatment sites and scaled sites showed statistically greater probing depth reduction than control sites.

Conclusion: For the treatment of mild-to-moderate adult periodontitis, subgingival scaling alone is as effective as the combination of scaling and antibiotic therapy. (Quintessence Int 1998;27:41-48)

Key words: adult periodontitis, bleeding on probing, Gingival Index, metronidazole gel, Plaque Index, probing depth, subgingival antibiotic therapy, subgingival scaling

Clinical relevance

The computer image analysis technique is a potentially powerful evaluating tool for both laboratory and clinical investigations on the stain removal efficacy of dentifrices. All dentifrices tested could remove some mature stains, and one dentifrice targeted toward stain removal was more effective than the other.

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The cause-and-effect relationship between plaque microorganisms and periodontal disease is well documented. Plaque begins to re-form almost immediately after its removal; it must therefore be removed regularly to prevent and/or treat periodontal disease. Thus, periodontal therapy has included mechanical removal of supra- and subgingival plaque and calculus. Complete removal of irritants by mechanical means is difficult to obtain because of inaccessibility to periodontal instrumentation. Therefore, the search for supplementary antimicrobial substances to control the microflora has been extensive. Both systemic and topical administration of antibiotics have been clinically tested for the treatment of periodontitis. Topical application of metronidazole into gingival pockets has been found to be an effective adjunct to conventional treatment, with beneficial effects on clinical and microbiologic parameters. Baker et al have shown that the lowest concentration of metronidazole required to inhibit 50% of the strains (MIC50) is less than 1 μg/mL for relevant anaerobes such as Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, and Actinomyces viscosus.
bacterium nucleatum, and Wolinella recta. Stoltze determined that after a single subgingival application of 25% metronidazole gel (mean dose 2 to 5 mg per tooth), a concentration higher than 1 μg/mL was obtained in all samples at 4 and 8 hours, in 92% after 12 hours, in 50% after 24 hours, and in 8% after 36 hours.

Six-month efficacy studies have shown that two applications of 25% metronidazole dental gel (applied once a week for 2 weeks) is equivalent to subgingival scaling in its effect on probing depths and bleeding on probing in patients with adult periodontitis. The microbiologic parameters confirmed the change toward a plaque composition compatible with a healthy state. Subgingival scaling combined with the local application of an antimicrobial agent may be the treatment of choice.

Review of the literature

Systemically administered metronidazole is able to inhibit the development of plaque and gingivitis in animals or alter the composition of plaque and reduce infiltrated connective tissue and to stabilize the bacterial counts. In humans, it was found that in the absence of scaling and root planing, systemic metronidazole reduced the mean probing depths by 0.4 to 2.4 mm. Systemic metronidazole resulted in improvements that were sustained for 28 weeks; however, root planing resulted in greater clinical improvement than did metronidazole.

The effects of subgingival 40% metronidazole applied once weekly for 4 weeks and 0.2% chlorhexidine solution self-administered subgingivally once daily for 4 weeks after initial scaling and root planing were compared by Yeung et al. Highly significant improvement in periodontal health was noted over a 3-month period, and this result was maintained to the end of the study. There were no significant differences between the two treatment groups at any time except for sulcular bleeding index, which at week 7 and week 12 showed metronidazole to be more effective.

Klinge et al determined that probing depth (PD), bleeding on probing (BOP), and Gingival Index (GI) improved significantly in six beagle dogs with experimental periodontitis on the 25% metronidazole gel-treated side compared to the placebo-treated side. Klinge et al also studied the effects of 25% metronidazole gel in 61 patients in a multicenter study comparing four treatments: subgingival scaling, 25% metronidazole dental gel applied twice a week for 2 weeks, 15% dental gel applied once a week for 2 weeks, and 15% dental gel applied twice a week for 2 weeks. All four treatment methods were effective in reducing probing depths and bleeding on probing, and all three antibiotic regimens yielded results comparable to the results after subgingival scaling.

Ainamo et al compared 25% metronidazole dental gel with subgingival scaling for the treatment of adult periodontitis in 206 patients, of whom 199 completed the nine-center study. The gel was applied at 0 and 7 days in two randomly selected quadrants. Subgingival scaling was done on two sessions. The average PD and frequency of BOP were calculated over all sites, with an initial PD of ≥ 5 mm. Both treatments were effective in significantly reducing probing depth and bleeding on probing over a 6-month period. The mean PD was 5.9 mm for gel-treated quadrants and 5.8 mm before subgingival scaling. Probing depth was reduced in the two groups by 1.3 and 1.5 mm, respectively, after 24 weeks. Bleeding on probing was reduced by 32% after gel application and 39% after scaling. The difference between the treatments was statistically significant but was considered clinically unimportant. Radvar et al found greater improvement in clinical parameters in combined treatment groups than in groups treated with scaling and root planing alone; adjunctive treatment with tetracycline gave better results than combined treatment with 2% minocycline gel or 25% metronidazole gel.

The effect on periodontal healing of local application of 25% metronidazole gel after guided tissue regeneration procedures using expanded polytetrafluoroethylene membranes was reported by Sander et al. Six months after the removal of membranes, the median gain in probing attachment level as a percentage of the initial defect depth was 92% for test defects and 50% for control defects. Results indicate that local application of metronidazole gel has a beneficial effect on healing of periodontal vertical defects treated by guided tissue regeneration. Loesche et al reported a reduced need for periodontal surgery following phased application of metronidazole in patients with severe periodontitis.

The present study was carried out to test simultaneous application of Élyzol gel (Dumex) with subgingival scaling and see if differences exist in the responses of shallow and deeper periodontal pockets.

Method and materials

The study was carried out as an open, single-blind (operator-blind), randomized, controlled clinical trial comparing subgingival application of 25% metronidazole dental gel with and without subgingival scaling to subgingival scaling alone. A split-mouth design was used, whereby the patients received all treatments simultaneously, each treatment in one randomly selected quadrant of the dentition. The fourth quadrant served as control.
Patients were included in the study if they had at least one tooth in each quadrant with a probing depth of ≥ 5 mm but were excluded if they had used antibiotics in the last 3 months, had received periodontal treatment in the last 6 months, or had severe periodontal disease. All patients included gave informed consent after having received verbal and written information about the study. The research protocol was approved by the Research Center of the College of Dentistry, King Saud University.

**Treatment protocol**

Each quadrant was randomly selected to receive one of the following treatments:

1. Application of 25% metronidazole dental gel (Elyzol) only. The drug was supplied in standard 1.8-mL glass cartridges containing 250 mg of metronidazole. The gel was applied with a syringe with a blunt cannula and placed in the bottom of all sulci and pockets around the teeth in the quadrant on days 0 and 7. Excess gel was removed gently with cotton applicators; thus the exact amount received was not calculated.

2. Subgingival scaling. Subgingival scaling was performed in one session under local infiltration anesthesia (2% lidocaine with 1:80,000 epinephrine, 1.8 mL per quadrant). Moderate to heavy supragingival calculus was removed by ultrasonic scaling with Cavitron 2002 (Dentsply). Subgingival scaling and root planing was performed as needed with Hu-Friedy rigid Gracey Curettes.

3. Subgingival scaling and Elyzol gel application (combined treatment). When subgingival scaling was completed, Elyzol gel was applied as explained earlier, after complete hemostasis was obtained through gentle pressure with cotton gauze.

4. Untreated control quadrant. This quadrant received no treatment.

**Probing depth**

A total of 1,482 sites were registered (scaling, 378; Elyzol, 372; combined treatment, 360; and control sites, 372). The mean probing depth per quadrant (n = 13) is presented in Table 1. No statistically significant differences were found between the mean probing depths of the quadrants allocated to the different treatments at baseline. Other than the expected difference between the treatment methods and the control, no significant differences were observed between various treatments at different time intervals.

Further analysis, based on classification of the pockets as “shallower” when ≤ 4.4 mm or “deeper” when ≥ 4.5 mm, revealed some significant findings. After 4 weeks, shallower pockets were reduced by 19.7% with combined treatment, by 12.5% when scaled, and by 10.7% with Elyzol treatment (Table 2). There was a statistically significant difference in the reduction of the...
probing depth between Elyzol sites and the control sites after 4 weeks but not after 14 weeks. Scaling resulted in a significantly greater reduction in probing depth than did Elyzol treatment alone at week 14; however, no significant difference was found between Elyzol and combined treatment after either 4 or 14 weeks.

The deeper pockets showed greater probing depth reductions after 4 weeks (Table 3). Combined treatment resulted in 25.6% reduction, scaling in 20.8% reduction, and Elyzol treatment in 19.6% reduction. The quadrants did not show any significant differences in probing depth reduction after 4 weeks. After 14 weeks, however, scaled quadrants showed statistically significantly greater reduction in probing depth than did Elyzol-treated ones. Compared to the control, all treatments obtained significantly greater reduction in probing depth after 4 weeks, but after 14 weeks only combined treatment sites and scaled quadrants showed a statistically greater reduction in probing depth. The control quadrants also showed a mean reduction in probing depth of 14.1% after 14 weeks, which has to be taken into consideration (Table 4).

**Bleeding on probing**

The three treatment groups showed highly statistically significant reduction in BOP during the first 2 weeks. At week 14, all treatment sites and the control sites showed statistically significant reduction compared to the baseline data (Table 5). Elyzol produced significantly greater reduction in BOP than did the control up to week 14. The effect of combined treatment and scaling alone was significantly greater than that of Elyzol alone. There was no statistically significant diff...
ference between the effects of combined treatment and scaling alone on bleeding on probing.

Gingival Index

All three treatments and the control resulted in highly statistically significant reductions of GI during the first 2 weeks posttreatment. Interestingly, between weeks 4 and 6, Elyzol-treated quadrants showed a statistically significant increase in GI. At week 14, all sites, including the controls, showed highly statistically significant reductions compared to the baseline data (Table 6). Both combined treatment and scaling alone resulted in significantly higher reductions in Gingival Index than Elyzol treatment or no treatment.

Plaque Index

All treatment groups exhibited statistically significant reductions in PI after week 2 and up to 14 weeks posttreatment (Table 6). Both scaling alone and combined treatment resulted in significantly greater plaque reduction than did Elyzol treatment alone. There was no statistically significant difference in plaque reduction between Elyzol-treated quadrants and controls.

Discussion

The present trial was performed as a randomized intraindividual study using the split-mouth design and was based on 13 patients (12 at the 14-week observation) suffering from early to moderate periodontitis. There is the risk of overlapping contamination when an antibiotic is tested in the trial. Loesche et al. observed that metronidazole has a specific activity against gram-negative microorganisms and has no antiplaque property. Stolze and Stellfeld have shown that the systemic uptake of intraoral topical application of metronidazole is minimal. Both systemic and local metronidazole administration decrease PI and GI scores by changing the qualitative composition of microbiota in periodontal pockets. Such changes do not decrease the PI but may explain the improvement in GI.

The split-mouth design and randomized allocation of quadrants to the three treatments in the present trial resulted in similar baseline values with no distinct differences in any of the parameters. The use of the fourth quadrant as control within the same patient annulled the influence of dependent variables. All participants received professional oral hygiene instructions, beginning at day 0. Thus, the reduction in inflammation and
shrinkage of the gingival tissues attributable to controlled oral hygiene would equally effect all quadrants and was observed in all groups.

The length of the observation period in a trial depends on the procedure as well as the agent being tested. The present study compared an antibiotic (metronidazole) and the effect of scaling. Studies utilizing Elyzol have a 3- to 6-month observation period. Morisson et al estimated clinical healing after scaling and root planing after 4 weeks, while Badersten et al studied 15 patients with advanced periodontitis and reported that healing was not completed until after 4 to 5 months postsclaling. The differences in results may be attributed to differences in instrumentation, scaling, trauma, severity of the disease, systemic factors, etc.

The results of various treatments on probing depth were analyzed in two ways: (1) analyses of the pooled data based on the mean probing depth per treated quadrant and patient and (2) analyses of the effect on shallower and deeper pockets. Analysis of the effect on the probing depth as mean pooled data and on shallower pockets after 14 weeks showed reductions in probing depth for the three treatments varying from 0.15 to 0.46 mm and a reduction of 0.04 mm for the control. These changes are within the intraexaminer's ± 0.5 mm reproducibility range and are of questionable value.

The deeper pockets, after 4 weeks, showed probing depth reductions of 1.1 to 1.5 mm for the three treatments and 0.7 mm for the control—values that were all highly statistically significant and similar to those reported by Ainamo et al and Stetzel and Flores de Jacoby, who found a 1.3-mm reduction in probing depth after Elyzol treatment and a 1.5 mm reduction after scaling.

Combined treated and scaled quadrants show significantly greater probing depth reductions than did the control sites. No difference in probing depth reduction was observed between scaling and combined treatment after 4 weeks; thus, the effect of combined treatment seems mostly to be the result of scaling. After 14 weeks, the transient effect of Elyzol was further illuminated, because scaled quadrants showed significantly more probing depth reduction than did Elyzol-treated quadrants.

The striking difference observed in the probing depth reductions between deeper pockets and shallower pockets, and the mean PD, is not unexpected, because more shrinkage occurs in deeper pockets than in shallower pockets. The finding that scaling alone and combined treatment resulted in greater PD reduction than did Elyzol alone, is not in agreement with results reported by Klinge et al, Pedrazzoli et al, Ainamo et al, Stetzel and Flores de Jacoby, and Radvar et al. This difference may be explained by the present findings that Elyzol has a time-limited or transient effect. In the present study, no significant differences in PD were observed between sites subjected to scaling and combined treatment. This indicates that there was no added benefit from the use of Elyzol in the combined treatment of adult periodontitis. This is in contrast to results reported by Mubarik, who claims that "an additional effect on periodontal health can be obtained by a combined therapy," as a 2- to 3-mm reduction in probing depth and a 1- to 3-mm gain in the probing attachment level were

### Table 6

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Gingival Index (GI)</th>
<th>Plaque Index (PI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean ± SD</td>
<td>Week 4 Mean ± SD</td>
</tr>
<tr>
<td>Scaling GI</td>
<td>0.78 ± 0.05</td>
<td>0.23 ± 0.32</td>
</tr>
<tr>
<td>Scaling PI</td>
<td>1.23 ± 0.41</td>
<td>0.28 ± 0.25</td>
</tr>
<tr>
<td>Elyzol GI</td>
<td>0.94 ± 0.10</td>
<td>0.47 ± 0.30</td>
</tr>
<tr>
<td>Elyzol PI</td>
<td>1.37 ± 0.48</td>
<td>0.38 ± 0.32</td>
</tr>
<tr>
<td>Combined GI</td>
<td>0.95 ± 0.07</td>
<td>0.25 ± 0.31</td>
</tr>
<tr>
<td>Combined PI</td>
<td>1.52 ± 0.49</td>
<td>0.35 ± 0.23</td>
</tr>
<tr>
<td>Control GI</td>
<td>0.96 ± 0.06</td>
<td>0.71 ± 0.24</td>
</tr>
<tr>
<td>Control PI</td>
<td>1.36 ± 0.43</td>
<td>0.57 ± 0.27</td>
</tr>
</tbody>
</table>

*Significant (P < 0.05).
**Highly significant (P < 0.01).
***Very highly significant (P < 0.001).
obtained in a short time (3-month study) (Mubarik S, personal communication, 1995).

The present finding that scaling was statistically significantly more effective than Elyzol alone in reducing deeper pockets is in agreement with the results reported by Loe and colleagues,39 Joynston-Bech et al,41 and Walsh,42 who found similar trends when metronidazole was administered systemically.

The three active treatment methods showed similar trends in PI up to week 6. Thereafter, while scaling and combined treatment had a sustained effect, the Elyzol quadrant showed a sudden increase in PI, and at week 14 it became similar to the control quadrant. This indicates that the reduction in Plaque Index in Elyzol-treated quadrants is due mainly to improved oral hygiene and that the effect is transient. The transient effect of topically applied 25% Elyzol dental gel noted in the present study was also noted by Walsh et al.42 who noticed an increase in PI following the initial reduction, 1 month after systemic administration of 250 mg metronidazole.

The gingival index declined for all treatment groups and the control sites. Elyzol-treated quadrants, however, exhibited an increase in GI after 6 weeks, mirroring the increase in PI. Scaled and combination treatment quadrants did not show any difference in GI, but both showed significantly greater reduction in GI than did Elyzol-treated sites. The numerical difference was, however, no more than 0.3 mean units, which is of no clinical importance.

The BOP values, indicating the reduction of intracrevicular irritants, were highly significantly reduced for all three treatment quadrants and the control quadrants up to week 14. The reduction in BOP for the control sites is intriguing, because subgingival plaque and calculus were not removed. However, the results might be explained as an overlapping effect of Elyzol. The fact that scaling and combined treatment were superior to Elyzol treatment in reducing the BOP indicates that mechanical treatment was the effective part, while Elyzol was effective during the first 4 weeks. The present results are not in agreement with those of Pedazzoli et al.,40 who reported that Elyzol gel “tended to be better than scaling” in reducing the percentage of sites with bleeding, during a 24-week study period. The reason for these divergent results could be differences in scaling procedures and protocol or in Elyzol application and retention. Clearly, deeper pockets would actually receive a greater amount of the gel.

The multicenter study by Ainamo et al.44 reported that, statistically, scaling reduced BOP more than Elyzol did. This reduction was considered to be clinically unimportant. Mubarik (personal communication, 1995) found that, in the treatment of adult patients with moderate-to-severe periodontitis, the simultaneous use of scaling and Elyzol was more effective in reducing BOP and PD than either of the treatments alone, causing a gain in probing attachment level of 1 to 3 mm. He did not find any statistically significant difference between scaled and Elyzol-treated pockets, which is in contrast to the present findings. For now, the explanation is unknown, for example, differences in the material concerning probing depths, differences in registration, etc.

The depth of probe penetration depends on probing force, diameter of the probe tip, the inflammatory status of the tissues at the start of the study, and the placement of the probe, including its angulation.43,44 These factors may also explain differences in results. The use of a constant-force probe (25-g load using a Florida probe) enhances the value of the present results. One reason that the results for PD and BOP findings were different from those reported by Ainamo et al.,44 Klinge et al.,45 and Stettzel and Flores de Jacomy6 is that their samples had a higher mean PD (5.8 and 5.6 mm) than did the present patients (4.58 and 4.62 mm) for Elyzol-treated and scaled quadrants, respectively.

For the future, long-term controlled clinical trials should be undertaken to study the benefits of the potential immediate transient effect of Elyzol on acute periodontal diseases such as periodontal abscesses and in patients with persistent active pockets that are refractory.

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References


