# Effects of Topical Use of Metronidazole in Causal Therapy in Patients Suffering from Chronic Periodontitis: A Case-Control Clinical Trial

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**Abstract:** *Purpose*: The purpose of this study is to evaluate the effects of topical metronidazole in addition to non-surgical causal therapy in patients suffering from chronic periodontitis.

*Materials and Methods*: The study involved a sample of 17 patients with chronic periodontitis. The sample was divided into 2 groups treated in two different centers: test and control. The test group underwent the application of topical metronidazole after scaling and root planing, while the control group received exclusively SRP.

*Results*: The difference in pre- and post-therapy PPD values in both groups were calculated: both mechanical therapy and mechanical therapy with the addition of topical metronidazole had a significant effect on the variation of PPD values. The best results were obtained in test group. The evaluation of mean FMBS variation from the baseline in the two groups showed a greater reduction in the test group.

*Conclusions*: The present study showed that the use of topical metronidazole in addition to the non-surgical causal therapy in patients with chronic periodontitis resulted in a better response to treatment than mechanical therapy only.

**Keywords:** Chronic periodontitis, Metronidazole, Scaling-Root Planing, Non-surgical causal therapy.

## 1. INTRODUCTION

Chronic periodontitis is an inflammatory disease of periodontal tissues characterized by loss of periodontal attachment [1].

The clinical aspects of chronic periodontitis also include: alterations of color, consistency and volume of the marginal gingiva, bleeding on probing of the marginal gingiva; reduced resistance to probing of marginal soft tissues (periodontal pockets and loss of attachment), recession of the gingival margin; loss of alveolar bone.

The inflammatory process of periodontal tissues can also lead augmented dental mobility, up to the loss of the involved teeth [1].

The most important etiological factor of periodontal diseases is the bacterial biofilm. If not correctly treated, this pathology can determine a progressive loss of connective tissue attachment and alveolar bone [2].

In chronic periodontitis the extent of periodontal tissue destruction is related to oral hygiene and plaque control, local predisposing factors, smoking, stress and systemic risk factors.

Chronic periodontitis is triggered and sustained by a wide range of bacterial species organized in biofilm above and subgingival. Biofilm composition varies according to subject and sites. Furthermore tissue destruction in chronic periodontitis does not affect all teeth in the same way; some teeth can be severely affected by destruction of periodontal tissues, while other teeth are almost free from loss of bone or attachment [1].

Multiple clinical and radiographic parameters are necessary to make the diagnosis of periodontitis. The diagnosis of periodontitis can be performed if one or more sites present inflammation, bleeding on probing (BOP), radiographic bone loss, and increased probing depth or clinical attachment loss.

The progression of periodontitis is variable and may show periods of rapid destruction. It can be associated with predisposing factors (related to the teeth or iatrogenic factors) and/or with systemic diseases (i.e. Diabetes mellitus, HIV infection). Morover it can be modified by cigarette smoking and emotional stress [3].

Since chronic periodontitis is triggered and sustained by microorganisms organized in biofilms living in supragingival and subgingival plaque, periodontal therapy involves the removal of the plaque through scaling and root planing (SRP) [1].

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Different antimicrobials like metronidazole, chlorhexidine, minocycline, doxycycline and tetracycline can be locally applied to complete non-surgical therapy. Using these drugs in periodontal pockets, periodontopathogenic microorganisms can be inhibited or eliminated and the inflammatory response of the tissues ay be modulated [4].

The use of local antimicrobials demostrated a considerable helpful result when correlated with SRP alone in previous systematic reviews. However a debate has been raised on the actual clinical efficacy of these antimicrobials [5-6].

A common used antimicrobial is metronidazole because of its efficacy against obligate anaerobic bacteria in inflamed subgingival pockets [7].

Metronidazole is a synthetic compound derivative of nitroimidazole interfering with bacterial DNA synthesis and causing cell death.

Metronidazole converts into a reactive reduced form affecting specifically anaerobic bacteria by inhibiting DNA synthesis [8].

The effects of metronidazole on the ability to modulate cytokine secretion were investigated by Rizzo *et al*. [9] by using a model of human periodontal ligament cells stimulated with a P.gingivalis lipopolysaccharide. The results showed that metronidazole can help reduce the influx of inflammatory cells by inhibiting the production of cytokines IL-1β, IL-6, IL-8, IL-12 and TNF-a. It can prevent destruction of periodontal tissue and resorption of alveolar bone, without cytotoxic effect on human periodontal ligament cells.

Furthermore metronidazole is prescribed to support conventional periodontal therapy in systemic or local administration because of its effectiveness against anaerobic bacteria and protozoa [10-11].

A topical presentation includes metronidazole in gel form, which is a bioabsorbable release device consisting of metronidazole benzoate in a matrix containing glyceryl mono-oleate and sesame oil [12].

In contact with the gingival crevicular fluid, the metronidazole gel forms inverted hexagonal liquid crystals [12]. This prevents the gel from easily therapeutic leaving the periodontal pocket, maintaining a level of drug in the subgingival area for a long period of time [13].

The studies of Riep *et al*. [14] and Leiknes *et al*. [13] showed that the local application of 25% metronidazole gel does not improve the outcome of therapy compared to SRP alone in sites with recurrent chronic inflammation in patients undergoing maintenance therapy after a period of 3 months, and also for a 6-month period in the study by Leiknes *et al*. [13]. Topical application of this antimicrobial has not exerted further effects on healing after periodontal surgery according to some authors [15].

However, in other studies, the comparison between adjunctive therapy with metronidazole and treatment with SRP alone showed a significant improvement [16-17].

The combination of SRP therapy + 25% metronidazole gel was better than conventional SRP treatment; these differences were maintained for 9 months as stated in Griffiths *et al*. study [16]. Moreover, the mean PPD reductions and clinical attachment level were 1.0 mm and 0.4 mm for the SRP group and 1.5 mm and 0.8 mm for SRP + 25% metronidazole gel group.

Al-Mubarak *et al*. [17] conducted a randomized clinical trial with 25% metronidazole gel in 14 patients with 3-month follow-up. This study showed that SRP therapy in addition to metronidazole had a statistically significant improvement (p <0, 03) in PPD with respect to all experimental groups. SRP alone and 25% metronidazole alone had a statistically significant improvement (p <0.05) in PPD compared to the control group. Nevertheless, the groups were not statistically and significantly different from each other.

The variability in the number of patients could be the cause of the differences between the studies. Indeed Needleman *et al*. [15] evaluated 38 patients, Leiknes *et al*. [13] considered 21 patients and Griffiths *et al*. [16] evaluated 92 patients of two different centers and followed patients for a longer period (9 months) [18].

A study by Kinane and Radvar [19] performed a six-month comparison of periodontal therapies using a 2% minocycline gel, 25% metronidazole gel and 25% tetracycline fibers associated with SRP in persistent periodontal pockets. The study showed that these local periodontal antimicrobial therapies were better than SRP alone; nevertheless the group treated with 25% tetracycline fibers had a greater reduction in probing depth after treatment. The average probing depth

reductions at 6 months were: scaling + tetracycline = 1.38 mm; scaling + metronidazole = 0.93 mm; scaling + minocycline = 1.10 mm; and scaling alone = 0.71 mm. A limitation of this study was the use of tetracycline fibers with non-resorbable support material, as these materials were obsolete and no longer used [18].

In order to provide a more significant improvement in periodontal clinical aspects some studies advice the use of local drug delivery systems in periodontal pockets as an adjunct to the deep periodontal pockets treatment, or in sites that do not favorably respond to scaling and root planning [18].

In order to define lesion type, periodontal diseases or specific cases, where local drug delivery systems would be more useful, we need additional randomized, controlled and long-term studies [18].

From the abovementioned studies it is clear that the results regarding the efficacy of metronidazole application in addition to mechanical therapy are currently not concordant due to the variability of the revaluation period between the various studies (from 3 to 12 months) and application regimen (causal therapy or maintenance therapy).

The purpose of this study is to evaluate the effects of topical metronidazole in addition to non-surgical causal therapy in patients with chronic periodontitis.

## 2. MATERIALS AND METHODS

Pre-existing informations from medical records of a number of patients who had previously been examined, treated and re-evaluated in two different centers were used.

### The Sample

The study involved a sample of 17 patients (59% females and 41% males) suffering from chronic periodontitis, with an age ranging between 35-62 years and an average age of 49.5 years.

Medical records of the patients were examined: 65% declared to be in good physical condition, 29% declared to be in excellent physical condition, while 6% reported to be in mediocre physical conditions.

Regarding data on risk factors for periodontal disease, 23.5% of patients suffered from hypertension, 5.8% had diabetes, while 11.7% said they were smoker.

The sample was divided into 2 groups: test and control. The test group underwent the application of topical metronidazole after scaling and root planing and was treated in a center, while the control group was subjected exclusively to SRP and was treated in another center that applies this protocol.

Patients from both groups underwent a preliminary examination, therapy and a re-evaluation.

### Phase I: Visit

During the first periodontal examination the compilation of periodontal record and the Full-Mouth Rx were performed.

All relevant parameters for periodontal diagnosis and planning were recorded in the periodontal charting: Full Mouth Plaque Score (FMPS); Full Mouth Bleeding Score (FMBS); Probing depth (PPD, Probing pocket depth) detected on 6 sites for each tooth.

### Phase II: Therapy

All patients underwent non-surgical causal therapy.

The patients underwent in a preliminary way to 1 or 2 sessions of supragingival instrumentation performed with ultrasonic instruments. Then they underwent 2 sessions of scaling and root planing, the first for the upper arch and the second for the lower arch at a distance of 1 week from the first one.

The test group, after subgingival instrumentation, underwent the application of topical metronidazole in gel. Three applications of metronidazole in gel were carried out: the first one at 1 month from the subgingival instrumentation, the second application 1 week after the first application and the third after 1 month from the second application. The gel used is a galenic formulation at 12.5% of metronidazole (Table **1**).

**Table 1: Metronidazole Based Gel Formulation**

| Formulation | 100g |
|---|---|
| metronidazole Ph. Eur. | 12,5g |
| citric acid monohydrate | 6,25g |
| hydroxyethyl | 0,5g |
| ethyl alcohol 90 ° | 18,051ml |
| $H_2O$ | 13,25ml |
| xylitol | 2,5g |

The metronidazole gel was applied with a chamfered needle syringe inside the gingival sulcus.

The control group, following the 2 sessions of subgingival instrumentation, doesn't underwent to the topical application of metronidazole in gel.

**Phase III: Revaluation**

The periodontal re-evaluation was carried out after a period of 3 months, since during this time period the maximum modification of the periodontal tissues is obtained in response to the therapy.

At the reassessment the periodontal charting was performed again.

**Statistical Analysis**

The following parameters have been considered for the statistical analysis: PPD (Probing Pocket Depth) and FMBS (Full Mouth Bleeding Score).

The statistical analysis was carried out on the individual dental sites considered as statistical units.

Regarding the PPD values, the statistical analysis was carried out using different statistical methods.

Normality test was carried out on the PPD values for: Pre and post treatment test group; Pre and post treatment control group; Difference of the PPD between test group and control group at T1.

3 statistical tests were performed for normal distribution. For all tests the null considered hypothesis was the following: H0 = the sample was taken from a population with normal distribution. If the p (normal) data is <0.05 than the normal distribution can be rejected.

Since the results of this analysis showed that the distribution was not normal, it was decided to continue the analysis with non-parametric tests.

The Wilcoxon matched pairs test was performed for the pre and post therapy PPD values of the test group and the control group.

The null hypothesis considered was the following: H0 = the median is the same in the two samples. All the p values shown are two-tailed. If the p value is small, it is possible to reject the idea that the difference is due to chance and it is possible to conclude that the median difference is significantly different from 0.

Subsequently, the Kruskal-Wallis test for PPD values was carried out in the two groups to test the following null hypothesis: H0 = different samples taken from populations with the same medians.

Regarding the Δt and FMBS values, the Normality test was performed for: Δt-test and t-control; ΔFMBS-test and ΔFMBS-control.

Also for these tests the following null hypothesis was considered: H0 = the sample was taken from a population with normal distribution. If the p (normal) data is <0.05 than the normal distribution can be rejected.

According to the results obtained (a normal population emerged) it was decided to perform with T-tests for: Δt between test group and control group; FMBS variation mean between T0 and T1 in both groups.

For these tests the following null hypothesis was considered: H0 = the sample averages are equal.

**RESULTS**

**Descriptive Statistics**

The test group was composed of 11 patients (55% males and 45% females) with an age ranging between 35-59 years and an average age of 45.4 years. The control group consists of 6 patients (83% females and 17% males) with an age ranging between 42-62 years and an average age of 50 years (Table **2**).

Patients in both groups were recalled and subjected to a periodical revaluation from 4 to 31 months approximately (112 to 926 days) compared to the first visit (Table **3**).

**Table 2: Anamnestic Data**

| Group | N° | Sex | | Age | | |
|---|---|---|---|---|---|---|
| | | M | F | min | average | max |
| Test | 11 | 55% | 45% | 35 | 45,4 | 59 |
| Control | 6 | 17% | 83% | 42 | 50 | 62 |

**Table 3: Δt Minimum-Average-Maximum**

| Group | N° | Δt (days) | | |
|---|---|---|---|---|
| | | min | average | max |
| Test | 11 | 378 | 587,09 | 926 |
| Control | 6 | 112 | 199,66 | 364 |

The test group statistics were performed on 1752 sites, while for the control group they amount to 864 (Table **4**).

Since 83.3% of the control group and 45.4% of the test group underwent at least one tooth extraction during the entire period of therapy, the sites that had been evaluated during the first visit and which were not detected during the revaluations were not considered for the statistical evaluation.

The analysis showed a maximum reduction of the PPD in the test group equal to 11mm, while in the control group this value amounts to 5mm.

In both groups there was a minimal reduction in the PPD value which results to be -4mm in the test group and -9mm in the control group, namely there was an increase in the PPD value equal to 4mm in the test group and 9mm in the group control.

Furthermore the analysis showed a mean PPD reduction value of 0.7 mm in the test group and 0.3 mm in the control group.

**Normality Test**

The Normality test for PPD evaluation was performed for: Pre and post treatment test group; Pre and post treatment control group; Difference of the PPD between test group and control group at T1. Therefore, 3 statistical tests were performed for normal distribution (Table **5**).

Since the p (normal) turns out to be <0.05, the analysis showed that the normal distribution can be

**Table 4: Descriptive Statistics**

| | test-pre | test-post | control-pre | control-post | PD reduction-test | PD reduction-post |
|---|---|---|---|---|---|---|
| N | 1752 | 1752 | 864 | 864 | 1752 | 865 |
| Min | 2 | 2 | 2 | 2 | -4 | -9 |
| Max | 14 | 11 | 10 | 14 | 11 | 5 |
| Sum | 6059 | 4827 | 2792 | 2492 | 1232 | 302 |
| Mean | 3,458333 | 2,755137 | 3,231481 | 2,884259 | 0,7031963 | 0,3491329 |
| Std.Error | 0,0387186 | 0,02525045 | 0,0449075 | 0,04772666 | 0,03295493 | 0,04859074 |
| Variance | 2,626475 | 1,11705 | 1,742414 | 1,968049 | 1m90272 | 2,042317 |
| Std. Dev. | 1,62064 | 1,056906 | 1,320005 | 1,402872 | 1,379391 | 1,429097 |
| Median | 3 | 2 | 3 | 2 | 0 | 0 |
| 25 prcntil | 2 | 2 | 2 | 2 | 0 | 0 |
| 75 prcntil | 4 | 3 | 4 | 3 | 1 | 1 |
| Skewness | 1,552067 | 1,735458 | 1,155907 | 2,831562 | 1,040941 | -0,8342991 |
| Kurtosis | 30,21819 | 34,06955 | 1,721656 | 12,58066 | 29,49687 | 4,525471 |
| Geom. Mean | 3,152481 | 2,597025 | 2,998146 | 2,660501 | 0 | 0 |
| Coeff. Var | 46,86189 | 38,36127 | 40,84831 | 48,63889 | 196,1602 | 409,3273 |

**Table 5: Normality Test for Pre and Post Therapy Test Group; Normality Test for Pre and Post Therapy Control Group; Difference of PPD between Test Group and Control Group at T1**

| | test-pre | test-post | control-pre | control-post | PD reduction-pre | PD reduction -post |
|---|---|---|---|---|---|---|
| N | 1752 | 1752 | 864 | 846 | 1752 | 865 |
| Shapiro-Wilk W | 0,8181 | 0,7273 | 0,8332 | 0,6577 | 0,8887 | 0,8954 |
| p(normal) | 1,18E-40 | 7,78E-47 | 4,33E-29 | 2,18E-38 | 9,07E-34 | 8,59E-24 |
| Anderson-Darling | 93,05 | 178,1 | 47,19 | 93,14 | 78,39 | 32,19 |
| p(normal) | 5,72E-161 | 0 | 3,06E-99 | 4,24E-161 | 6,37E-145 | 1,15E-71 |
| Jarque-Bera JB | 1638 | 2254 | 296,4 | 6776 | 1178 | 827,4 |
| p(normal) | 0 | 0 | 4,43E-65 | 0 | 1,54E-256 | 2,16E-180 |

**Table 6: Normality Test for Δt-Test and Δt-Control; Normality Test for ΔFMBS-Test and ΔFMBS-Control**

| | ΔT test | ΔT control | ΔBS test | ΔBS control |
|---|---|---|---|---|
| N | 11 | 6 | 11 | 6 |
| Shapiro-Wilk W | 0,8735 | 0,8734 | 0,9393 | 0,9529 |
| p(normal) | 8,61E-02 | 2,44E-01 | 5,13E-01 | 7,64E-01 |
| Anderson-Darling | 0,6181 | 0,4035 | 0,3135 | 0,2331 |
| p(normal) | 7,95E-02 | 0,2347 | 4,97E-01 | 0,6551 |
| Jarque-Bera JB | 1,378 | 0,8618 | 0,8342 | 0,4917 |
| p(normal) | 0,502 | 0,6499 | 0,659 | 0,7821 |

rejected. The normality test was performed for the study of: Δt-test and t-control; ΔFMBS-test and ΔFMBS-control (Table **6**).

According to the results obtained the null hypothesis previously stated cannot be refused, so the distribution considered is normal.

### Wilcoxon Matched Pairs Test

The Wilcoxon matched pairs test was used to test the significance of the variations in the same group between the pre- and post-therapy values related to the PPD. Therefore the test was performed both for the pre and post therapy PPD values of the test group and of the control group (Table **7**).

**Table 7: Wilcoxon Matched Pairs Test for PPD Pre and Post Therapy Test/Control Group**

| Wilcoxon test PPD pre/post therapy test group | |
|---|---|
| W: | 4,4488E05 |
| Normal appr. Z: | 19,698 |
| p(same median): | 2,2281E-86 |
| **Wilcoxon test PPD pre/post therapy control group** | |
| W: | 90620 |
| Normal appr. Z: | 7,9626 |
| p(same median): | 1,6849E-15 |

Since p values are <0.05 in both groups, it is possible to reject the previously defined hypothesis that the difference between pre- and post-therapy PPD values is due to eventuality.

### Nonparametric Kruskal-Wallis Test

Through this analysis (for non-normal distribution) the difference in the response to therapy was verified for the 2 types of treatments performed evaluating the PPD (Table **8**).

**Table 8: Nonparametric Kruskal-Wallis Test**

| Kruskal-Wallis test for equal medians | |
|---|---|
| H (chi^2): | 16,45 |
| Hc (tie corrected): | 18,01 |
| p(same) | 2,196E-05 |

Based on the results obtained (p <0.05) the null hypothesis defined above can be rejected because there is a significant difference between the medians of the samples. Therefore, there is a significant difference in the degree of therapy response for the 2 types of treatments in the test group and in the control group.

### T-Test

The T-test was performed on the following parameters: Δt between test group and control group; FMBS variation means between T0 and T1 in the two groups.

Evaluating the results obtained from the T-test on Δt between the test group and the control group, it is possible to reject the null hypothesis previously defined because p is <0.05. The means is 587.09 for the test group and equal to 199.67 for the control group, are significantly different from a statistical point of view.

Considering the results obtained from the T-test on FMBS variation means between T0 and T1 in the two groups, the null hypothesis previously declared can be rejected; the sample means (41.455 for the test group and 16.833 for the control group) are significantly different from a statistical point of view.

## 4. DISCUSSION

There is a general consensus that mechanical instrumentation must always precede antimicrobial therapy, since it is necessary to quantitatively reduce bacteria which otherwise can inhibit or degrade the

**Table 9: T-Test for Δt between Test Group and Control Group; T-Test on FMBS Variation Averages between t0 and t1 in the Two Groups**

| **Tests for equal means** | | | | | | |
|---|---|---|---|---|---|---|
| ΔT test | | ΔT control | | | | |
| N: | 11 | N: | 6 | | | |
| Mean: | 587,09 | Mean: | 199,67 | | | |
| 95% conf.: | (463,83 710,36) | 95% conf.: | (97,763 301,57) | | | |
| Variance: | 33666 | Variance: | 9429,1 | | | |
| Difference betwee means: | | 387,42 | | | | |
| 95% conf. Interval (parametric) | | (214,39 560,46) | | | | |
| 95% conf. Interval (bootstrap): | | (256,35 510,33) | | | | |
| t: | 4,7723 | p(same mean): | | 0,00024698 | Critical t value (p=0.05): | 2,1314 |
| Uneq. var. t: | 5,6925 | p(same mean): | | 4,27E-05 | | |
| ΔBS test | | ΔBS control | | | | |
| N: | 11 | N: | 6 | | | |
| Mean: | 41,455 | Mean: | 16,833 | | | |
| 95% conf.: | (35,114 47,795) | 95% conf.: | (-10,927 44,594) | | | |
| Variance: | 89,973 | Variance: | 699,77 | | | |
| | | | | | | |
| Difference betwee means: | | 24,621 | | | | |
| 95% conf. Interval (parametric) | | (6,1161 43,126) | | | | |
| 95% conf. Interval (bootstrap): | | (3,6364 43,439) | | | | |
| t: | 2,8359 | p(same mean): | | 0,012518 | Critical t value (p=0.05): | 2,1314 |
| Uneq. var. t: | 2,2046 | p(same mean): | | 0,071975 | | |

antimicrobial agent. However the advantage related to the specific elimination of target bacteria alone was used as an argument to spread the use of narrow-spectrum antibiotics in periodontal therapy [1].

The aim of this trial is to evaluate the effects of topical metronidazole added to non-surgical causal therapy in patients suffering from chronic periodontitis by examining the following periodontal parameters: PPD and FMBS.

Through the Wilcoxon matched pairs test the significance of PPD variations in the same group between the pre and post therapy values was established.

The difference in pre- and post-therapy PPD values within both groups represents the efficacy of therapy performed with or without the use of topical metronidazole. It can be deduced that both mechanical therapy and mechanical therapy with the addition of topical metronidazole had a significant effect on the variation of PPD values before and after therapy.

Through the study of the Nonparametric Kruskal-Wallis test, the difference in the response to therapy for the two types of treatment was verified by examining the PPD values in both groups. A significant difference was found between the median of the samples, which indicates a better response to the treatment with the addition of topical metronidazole to mechanical therapy compared to treatment with causal therapy alone.

In fact it was possible to measure a reduction in the maximum PPD value in both groups. Nevertheless it emerged that in the test group the maximum PPD reduction was greater (11mm) than in the control group (5mm). Thus in the test group it was possible to detect a more significant reduction in PPD than in the control group.

Furthermore, the minimum reduction in PPD was negative. However there was an increase in PPD greater in the control group (-9mm) than in the test group (-4mm). Accordingly in cases in which there was a worsening of PPD following therapy, an increase in

PPD was found greater in the control group than in the test group.

Evaluating the average of PPD reduction it emerged that this value is 0.7 mm in the test group and 0.3 mm in the control group. Thus an average reduction in PPD increased for the test group compared to the control group, demonstrating greater improvement in the test group.

The analysis of the T-test carried out on Δt between the test group and the control group showed that the averages of the two groups are statistically different. However this data appears to be negligible as the revaluations were carried out after a period of time exceeding 3 months, a period in which the recovery following non-surgical therapy is almost complete [1]. While a continuous but slower and more limited healing can continue in the 9 or more months following the treatment [14].

FMBS variation means between T0 and T1 in the two groups (41.455 for the test group and 16.833 for the control group), are significantly different. Thus, a greater reduction in the test group demonstrates a better response to the therapy of the test group.

## 5. CONCLUSIONS

Within the limits of this study, the use of topical metronidazole in addition to the non-surgical causal therapy in patients with chronic periodontitis determines a better response to treatment than mechanical therapy alone. A significant improvement was found in the topical metronidazole group compared to the control group by evaluating both the reduction in PPD and the ΔFMBS between the first periodontal examination and the reassessment performed after therapy.

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