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Adjunctive Therapy of Periodontal Disease with Minocycline Microspheres in Dental School Settings: A Retrospective Chart Review.

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Abstract

Background: The chronic periodontitis is a highly prevalent disease that affects over 60% of people older than 65 and 10-15% is a prevalence of severe form. The Scaling and root planing procedure (SRP) is a gold standard of periodontal treatment which effectiveness was proven through numerous longitudinal studies. The nature of this treatment is to mechanically disrupt bacterial biofilm, remove subgingival calculus, and infected cement layer from the affected root surface to create favorable conditions for repair and regeneration. Different adjunctive therapies are utilized to further improve outcomes with a range of 0.2-0.6 mm of CAL improvement (compared to SRP alone). Local delivery minocycline microspheres were extensively investigated and showed a statistically significant difference in a mean reduction of PD compared to SRP alone. The objective of the present study is to assess the efficacy of adjunctive therapy with minocycline microspheres in dental school settings measured in mean probing depth reduction.

Material and methods. 1660 patients were included in the present study. 540 patients for the test group and 1130 patients for the control group were identified through an automated search. Clinical and demographic data were extracted and analyzed. Mean PD reduction and BOP reduction was calculated for test and control groups as well as for subgroups based on the criteria of health history (smoking, diabetes, cardiovascular disease, arthritis), disease severity (initial probing depth, ADA case type). Percentages of sites reached the threshold of PD reduction of 1 and 2 mm were calculated for subgroups stratified by the initial PD and compared in test and control groups.

Results: For the Arestin group, mean short-term PD reduction was 1.14 mm, and long-term PD reduction was 1.18 mm. BOP reduction for the test group was 10.6% in the short-term follow-up and

- 4.24% for a long-term period.

Results: Control group showed a PD reduction of 1.2 mm for the short-term period and 1.5 mm for the long-term. BOP reduction was 12.95% for the short-term period and 8.19% for the long-term follow up, which was significantly higher than in the test group. Although the long-term PD reduction was significantly greater in the Control group, the difference in short-term PD reduction was not significant. There were no statistically significant differences in the percentage of sites reached PD ≤ 4 mm between test and control groups.

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Artem Shurduk

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ABSTRACT

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Background: The chronic periodontitis is a highly prevalent disease that affects over 60% of people older than 65 and 10-15% is a prevalence of severe form. The Scaling and root planning procedure (SRP) is a gold standard of periodontal treatment which effectiveness was proven through numerous longitudinal studies. The nature of this treatment is to mechanically disrupt bacterial biofilm, remove subgingival calculus and infected cement layer from the affected root surface to create favorable condition for repair and regeneration. Different adjunctive therapies are utilized to further improve outcomes with range 0.2-0.6 mm of CAL improvement (compared to SRP alone). Local delivery minocycline microspheres were extensively investigated and showed statistically significant difference in mean reduction of PD compared to SRP alone. The objective of present study is to assess efficacy of adjunctive therapy with minocycline microspheres in dental school settings measured in mean probing depth reduction.

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LIST OF ABBREVIATION

1. SRP – scaling and root planing.
2. PD – Probing depth.
3. BOP – Bleeding on probing.
4. REC – recession.
5. KT- Keratinized tissue.
6. CAL – Clinical attachment level.
7. SUP – suppuration.
8. CI – confidence interval.
9. SE – Standard error.
10. EMR – Electronic medical records.
11. MH – minocycline.
12. BMI – Body mass index.
13. CVD – Cardio-vascular disease.
14. PDM – Penn Dental Medicine.
15. PHI-Protected health information.

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CHAPTER 1. INTRODUCTION

1 Background and Study Rationale

The present study is a retrospective chart review. The study was reviewed and approved by the IRB and was conducted in accordance with all applicable University of Pennsylvania human subjects research requirements as well as applicable federal regulations.

1.1 Study Introduction

The chronic periodontitis is a highly prevalent disease that affects over 60% of people over the age of 65 and 10-15% is a prevalence of severe form (Chapple et al., 2013). The Scaling and root planning procedure (SRP) is a gold standard of periodontal treatment which effectiveness was proven through numerous longitudinal studies (Lindhe et al., 1984), (Pihlstrom et al., 1983). The nature of this treatment is to mechanically disrupt bacterial biofilm, remove subgingival calculus and infected cement layer from the affected root surface to create favorable condition for repair and regeneration. Different adjunctive therapies are utilized to further improve outcomes with range 0.2-0.6 mm of CAL improvement (compared to SRP alone) (Smiley et al., 2015). Local delivery minocycline microspheres were investigated in the multi-center RCT and revealed statistically significant difference in mean reduction of PD compared to SRP alone and SRP + placebo group (Williams et al., 2001). The rationale of present study is to assess efficacy of

adjunctive therapy of local application of minocycline spheres for periodontal sites with residual deep PD after initial therapy.

The study is based on data obtained during routine clinical examination and treatment of patients with the periodontal disease performed by predoctoral providers in dental school settings. The dental school settings provide more representative model for the efficacy of Arestin application in actual clinical practice because procedure is performed by the diverse group of practitioners rather than limited number of examiners.

1.2 Background and Relevant Literature and Data

The first comprehensive review paper on the adjunctive use of local delivery minocycline was published in 1998 by Vandekerckhove et al. The minocycline is a semi-synthetic antibiotic of the tetracycline group that showed promising results as an adjunct in treatment of periodontitis. Local delivery formulation relies on the sustained release properties of a carrier and allows for low-dose application. (Vanderkerckhove et al., 1998).

Different formulations were tested for optimal result. For example, films with 30% concentration of minocycline were prepared from either ethanol of chloroform solution, were tested in-vivo and in-vitro. Minocycline films showed sustained release and pilot clinical experiment showed reduction of motile microorganisms in periodontal pockets in 48 hours. (Elkayam et al., 1988)

Commercially available ointment formulation with 2% minocycline HCl was also tested and showed statistically significant added benefits in terms CAL gain and PD reduction compared with SRP. A parallel study on 13 patients with baseline PD ≥5 mm was published in 1996 and

showed average 0.3 mm of probing depth reduction when ointment was used as an adjunct compared to SRP. (Radvar et al., 1996). A larger study involving 52 participants with more severe periodontal disease (baseline PD ≥7 mm) and designed as a and showed average PD reduction of 3.1 mm in the test group (SRP + ointment) versus 2.1 mm PD reduction in the control group (SRP + vehicle). The 1 mm difference in PD reduction reaches level of clinical significance. Interestingly enough, minocycline ointment was applied 4 times in course of 4 weeks and results were measured in 12 weeks (van Steenberghe et al., 1993).

Formulation containing minocycline microspheres dispersed in the poly (glycolide-lactide) polymer, which is biodegradable matrix providing slow and sustainable release, was developed in Lederle Laboratories (NY, USA). Gel with micro-encapsulated minocycline was provided in disposable plastic syringes containing 4 mg of mixture which is equivalent 1 mg of minocycline. Microbiologic efficacy of this formulation was investigated in the study published in 1992 and revealed microbiological plaque composition that was more favorable for maintaining periodontal health. Specifically, the trial involved 30 participants with severe periodontal disease (at least 2 sites with PD ≥7 mm in one quadrant) who were randomized into test group (SRP with adjunctive use of minocycline microspheres) and control group (SPR with placebo powder). The plaque samples were collected at the baseline, 1 month, 3 months and 6 months and evaluated using dark-field microscopy to assess presence of spirochetes and motile rods. The cultivation flora technique was used to evaluate plaque composition and reveal presence of periodontal pathogens. The presence of yeasts was tested using selective agar media. As a result, the test group showed significantly lower percentage of spirochetes at 1 and 3 months and it also showed lower proportion of motile rods at 3 months compared with the test group. The study showed

lower percentage of Bacteroides spp. and P. intermedia at 1, 3 months, and lower proportion of E.corrodens at 3 months. Overall, microbiological response in the test group was more amenable for periodontal health. (Okuda et al., 1992)

Clinical efficacy of formulation was investigated by Braswell in 1992 in a parallel study with 47 participants and revealed 0.4 mm greater clinical attachment gain in the group with SRP plus minocycline group versus SRP alone. In contrary, a later study published in 1994 results of SRP group showed greater CAL gain on the SRP group. The difference did not reach the level of statistical significance. The study was designed as a split-mouth trial with 51 participants that were randomized into 4 groups: minocycline, minocycline plus SRP, SRP alone and no treatment. Researchers assessed both clinical and microbiological parameters. The only clinical parameter that showed statistical significance was PD reduction in the MH+SRP group in 1 month. (Jones et al., 1994)

A large multi-center study was published in 2001 by Williams as a part Phase 3 clinical trial (OPI-103A and 103B). This trial recruited 748 participants with moderate-to-advanced chronic periodontitis who were randomized into 3 groups: SRP + Placebo, SRP + MH spheres, and SRP alone as a control. As the primary outcome, investigators measured PD reduction with secondary outcome parameters (clinical response, OR (odds ratio) to reduce PD to the level ≥5mm which did not require further surgical therapy). The SRP + Arestin group reported a statistical significance when compared with both the SRP and SRP + placebo groups. The mean PD reduction for the SRP + MH group was 1.32mm, whereas the SRP + vehicle it was reported as 1.00 mm, and the SRP control group as 1.08 mm. The study additionally showed a greater

efficacy of treatment in the smokers and the greater OR for PD reduction to the level of ≥5 mm for groups with the baseline PD 5-7mm. (Williams et al., 2001)

The results of trials 103A and 103B were further investigated by Paquette in 2003. This group mainly focused on the Arestin efficacy in smokers and followed the design of Williams study. Data from 271 smoking patients was analyzed from the same groups: SRP + placebo, SRP + minocycline and SRP alone as a control group. The difference in PD reduction was statistically significant in 1, 6 and 9 months compared to the control group. The mean PD reduction in smokers from SRP + MH group was 1.19 mm from baseline and for SRP alone group it was 0.9 mm (D. Paquette et al., 2003). As the result, minocycline microspheres were FDA approved and routinely used in the clinical practice under brand name "Arestin" (Orapharma). (D. Paquette et al., 2003)

The secondary analysis of the Phase 3 trials was further continued by the Paquette in 2004 and mainly focused on the clinical response on the site-level. This study included 499 patients with moderate to advanced chronic periodontitis who were randomized into 2 treatment arms: SRP alone and SRP plus minocycline. Results showed that more sites treated with minocycline reached probing depth lesser than 4 mm at both 1 and 3 months. Smokers and all population showed similar results. The clinical response was more pronounced in the test group comparing with the SRP alone. (D. W. Paquette et al., 2004)

Added benefits for patients with poorly controlled diabetes were described in the study published by Skaleric et. al in 2004. This group included 20 patients with Type 1 Diabetes (HBA1C 7.5%)

and chronic periodontitis, as defined by the presence of at least 4 teeth with PD ≥ 5 mm, were enrolled in the study. All subjects received SRP at the baseline and patients in the test group received an application of the minocycline microspheres in all sites with PD ≥ 5 mm at base line and in 12 weeks. Clinical parameters that were evaluated included PD, CAL, PI, GI, and HBA1C. The test group showed significantly greater PD reduction and CAL gain, however, the difference in HBA1C levels was not statistically significant. (Skaleric et al., 2004)

The large post-marketing study of Arestin that was mainly focused on the efficacy of repeated minocycline application, was conducted in the private practice setting in 2004 by Lessem and Hanlon. A multi-center study with 895 participating dentists involved the treatment of 2805 patients who were allocated to two groups. All patients received SRP with adjunctive use of local delivery minocycline at the baseline. The first group containing 1095 patients was evaluated in 3 months and received the second round of local delivery minocycline which was reevaluated again in 6 months. The second group with 1710 patients received only one intervention and was assessed in 6 months. Results for the first group provided mean probing depth reduction at 1.94 mm in 6 months, which was significantly greater than probing depth reduction of 1.82 mm for the second group. Subgroups of patients with diabetes, smoking, and cardiovascular disease showed similar results. 62% of treated sites decreased to ≤5 mm after the first treatment and for 2 treatments, this number reached 67%. (Lessem & Hanlon, 2004)

The long-term effect of the adjunctive therapy with local delivery minocycline was investigated in a double-blind randomized control study that was published by Corelli et al. These researchers recruited 26 patients into the analysis (59 initially enrolled) where the test group received SRP

and minocycline at the baseline, 90, 180, 270, 360, and 720 days. The control group received SRP + vehicle at the same time-points. As the result, the test group showed greater PD reduction at the 270 and 360, although this result was not maintained at the 720 days. (Cortelli et al., 2006)

Microbiological evaluation of subgingival plaque after SRP and adjunctive use of minocycline showed a statistically significant differences in the reduction of red and orange complex when compared to samples of patients treated with the SRP alone. Clinically, the mean probing depth reduction for the test group (1.38 mm) was significantly greater compared with the control (1.01 mm). BOP reduction was also significantly higher in the Arestin group (25.2% vs 13.8% for SRP alone). (Goodson et al., 2007).

The difference in the microbiologic response in smokers was evaluated using the same patient population as the Goodson study form 2007. A Combination of SRP and minocycline microspheres showed a significant decrease of red complex bacteria and orange complex bacteria in smokers. In contrast, SRP alone did not reduce number of red complex bacteria in current smokers. (Grossi et al., 2007).

A study published by Hellstrom et al. in 2008 evaluated minocycline microspheres as an adjunct for the surgical therapy of Periodontal disease. Researches included 60 patients with at least 2 non-molar periodontal sites with probing depth $\geq$ 6 mm located in different quadrants. Participants were randomized in two groups where the control group (SO) received SRP at the baseline and surgery (Modified Widman Flap) at weeks 2 and 4. The test group (SMM) received SRP with minocycline placement at the baseline. At weeks 2 and 3 periodontal surgery

(Modified Widman flap) was performed on different quadrants supplemented with the placement of minocycline microspheres to all sites with PD ≥ mm including surgical sites each time. The application of the Arestin was also repeated at week 5. At the 25 week record, clinical parameters were reevaluated. The test group showed greater probing depth reduction in all treated sites (2.51 ± 0.1 mm) compared with the control group (2.05 ± 0.1 mm). It is worth noting that smokers from the test group exhibited significantly greater probing depth reduction (2.3 ± 0.09 mm) than smokers from the control group (2.05 ± 0.09 mm). (Hellström et al., 2008)

An association of clinical response for the adjunctive treatment with minocycline microspheres and antimicrobial activity was studied by the group of P. Bland in 2010. The clinical study was conducted on 127 subjects with moderate-to-advanced chronic periodontitis who were randomly assigned amongst two groups. The test group (62 patients) received SRP with the subgingival application of minocycline microspheres which was compared with SRP alone (Control group – 65 patients). Microbiological (DNA analysis) and clinical parameters were compared at the baseline and 30 day follow up. As the result, probing depth reduction significantly correlated with the decrease of red complex bacteria. The test showed significantly greater improvement of all clinical parameters compared to SRP alone. (Bland et al., 2010)

Comparison of clinical efficacy of adjunctive therapy of adjunctive use of local delivery minocycline with a local application of 25% metronidazole gel and SRP alone was published in 2013. This study involved 20 participants with 60 periodontal sites. Minocycline group showed significantly greater PD reduction (by 0.85% mm) when compared with SRP alone group, but

the difference in PD reduction between other groups did not reach the level of statistical significance. (Pandit et al., 2013)

The clinical effect of adjunctive therapy with minocycline during the maintenance phase was evaluated by Killien and his group in 2016. 60 patients were allocated into 2 groups and were followed for one year. All patients were in the maintenance phase of their treatment and after receiving routine maintenance with selective SRP of the inflated sites, patients from the test group also received the application of the minocycline microspheres. 9 patients were excluded because of different reasons over the course of this study. As the result, all groups improved clinical parameters without statistically significant differences between groups. The odds of having greater BOP reduction were greater in the minocycline groups and also test group in 6 months showed a decrease in levels of IL1 in the gingival crevicular fluid. (Killeen et al., 2016) The same trend was observed when patients were followed in 24 months. Radiographic examination showed stable crestal bone level, improvement in probing depth was maintained, but the difference between groups was not statistically significant. (Killeen et al., 2018)

The series of smaller clinical studies compared the efficacy of the local delivery minocycline with other modalities of adjunctive therapy without any reported significant difference between groups. A study that included 20 patients compared minocycline microspheres with the "Periochip", which is a local delivery formulation, containing 2.5 mg of chlorhexidine gluconate, with 3 months follow up. (Jhinger et al., 2015) Photodynamic therapy was also compared with adjunctive use of minocycline and SRP alone. 45 patients were enrolled and clinical parameters were followed up for 12 months. (Tabenski et al., 2017)

Overall, previous studies built extensive evidence supporting the implementation of minocycline as an adjunct to non-surgical therapy during both initial and maintenance phases of periodontal therapy. Arestin has been extensively used over the years, and a thorough analysis of the available data can be a valuable addition to the existing evidence.

CHAPTER 2. OBJECTIVES

2 Study Objectives

The purpose of this study is to evaluate the clinical effect of adjunctive therapy of chronic periodontitis with minocycline microspheres (Arestin) in the dental school setting.

2.1 *Primary Objective*

The primary objective of this study is to determine the efficacy of minocycline microspheres by measuring the mean PD reduction from the time of Arestin placement to the reevaluation and at the time of the most recent observation. PD reduction was measured by subtraction of PD at the reevaluation appointment from PD at the baseline (before MH application).

2.2 *Secondary Objective*

The secondary objectives of this study evaluated the clinical response which is defined as the percentage of sites that reached a threshold of PD reduction of 1 and 2 mm, BOP reduction after treatment which is the difference in the percentage of periodontal sites showing bleeding on probing before and after treatment, percentage of sites reached the PD ≤4 mm, stratified by initial probing depth, and calculation of the odds ratio for sites with different PD at the baseline to improve to the number ≤4 mm which is considered a threshold for surgical periodontal treatment. Also, the secondary objective included analysis of subgroups of patients based on health history (smoking, diabetes, cardiovascular disease, arthritis) and the severity of periodontal disease (case type).

3 Material and Methods

3.1 Material

3.1.1 Total Number of Subjects

The study is a retrospective case-control study that included a retrospective review of a total of 1660 subjects. Subjects for test and control groups were determined by the automated search using procedure codes in the EMR system. The sample size was a sample size of convenience which means that all available cases that matched inclusion criteria were included in the present study.

3.1.2 Inclusion Criteria

A total of 540 subjects were selected for the test group from the predoctoral clinic of Penn Dental Medicine from 2016-2020. The test group was selected as those diagnosed with chronic periodontitis and received periodontal treatment that included SRP with the adjunctive application of Minocycline microspheres. The control group (1120 subjects) consisted of patients from the same clinic who received 2 or more rounds of scaling and root planning on the same tooth (quadrant) within a 1-year interval from 2016 to 2020.

3.1.3 Exclusion Criteria

Patients who received adjunctive therapy with minocycline for peri-implant sites or any periodontal surgery were excluded. Subjects with incomplete follow-up data, such as missing

periodontal charting during reevaluation or long-term follow-up appointment, were also excluded. Furthermore, periodontal sites that were outside of the therapeutic range of PD 5-9 mm were excluded from the analysis.

3.1.4 Variables

Age, gender, race, smoking history (past, present), diabetes (type, controlled, uncontrolled), BMI, presence of CVD, and arthritis were extracted from the EMR system (Axium) and combined into Demographic variables of the present study. Clinical variables were ADA case type, the number of teeth treated with MH. PD, BOP, CAL for all treated sites at the baseline, during revaluation, after MH placement, and at the most recent examination. Time interval (days) from SRP (when it was done prior to minocycline application) to the MH placement, time from MH placement to the reevaluation, and time from the baseline to the point of the most recent observation (length of observation). Additionally, number of maintenance visits was calculated for each patient in both groups to verify similar maintenance compliance in both groups.

3.2 Methods

3.2.1 Data extraction

The automated search was performed on the EHR system and identified potential subjects for the test group (patients who received treatment with the local delivery minocycline) or control group

(patients who received repeated SRP for the same tooth/quadrant within a year). The dataset contained both demographic and clinical variables that were exported from EHR software (Axium) and imported into R-studio (version 1.2.5042). All included subjects were deidentified and assigned with unlinked numerical identification codes. (Figure 3)

3.2.2 Data management

The next step was to identify specific periodontal sites that received treatment. All sites with PD ≥ 5 mm at the baseline were assumed to receive periodontal treatment and were included for analysis. At this point, we applied filters for the exclusion of patients with missing observations at the follow-up appointments. We excluded patients who received any surgical treatment of periodontal disease and all periodontal sites with initial PD ≥ 9 mm were not analyzed. Probing depth and bleeding of probing of treated sites was tracked across different appointments and exported for predetermined timepoints.

For the control group, the first timepoint ("Initial" or T1) was periodontal charting that was performed on the same day or with the shortest interval prior to the first round of SRP. The second timepoint ("Short-term" or T2) coincided with the reevaluation appointment after the first SRP. The last timepoint for the Control group ("Long-term" or T3) was the most recent periodontal charting of the patient. (Figure 1).

The initial timepoint for the test group ("Minocycline placement" or T2) included PD and BOP from the periodontal charting performed on the same day or immediately prior to the date when local minocycline was applied. The data from the periodontal chart that immediately preceded

the initial “Minocycline placement” timepoint was also extracted and included in the first timepoint (“SRP” or T1). The periodontal charting from the reevaluation after minocycline placement was used as the source of data for the third timepoint (“Short-term” or T3). For the fourth timepoint (“Long-term” or T4), we analyzed the most recent periodontal chart available for the patient. (Figure 2) It’s worth mentioning that since the main goal of this study was to assess the clinical effect of Arestin, we did not exclude any subject who was missing data from the periodontal charting prior to the Minocycline application (T1), and also some patients received Arestin as the adjunct for their first round of SRP.

The clinical data were extracted for the treated sites into a new dataset and we calculated short-term and long-term probing depth reduction for each periodontal site. The percentage of sites exhibited positive bleeding on probing was also calculated for the initial timepoints and for follow up appointments.

Additionally, we extracted datasets for the following subgroups of patients: Smokers, Non-smokers, Diabetes, Cardiovascular disease, Arthritis, ADA periodontal case type 2, ADA periodontal case type 3.

3.2.3 Data analysis

Descriptive statistics (mean PD reduction) was used to evaluate primary outcomes. A two-sided Welch t-test with a 95% confidence interval was performed to compare results with the control group. The analysis of covariance (ANCOVA) was implemented with posthoc pairwise comparison and Bonferroni corrections to evaluate confounding factors. A proportion test was

performed to compare demographic variables in the test and control group and to compare percentages of sites with positive bleeding on probing.

Secondary outcomes included odds ratio to reduce PD <5 mm with 95% CI was calculated for subgroups with initial PD ≥5 mm, ≥6 mm, and ≥7mm.

4 Results

4.1 Demographics

The demographics and clinical picture were similar in all groups with some minor differences. The test group had a greater percentage of ASA 2 patients, patients with cardiovascular disease, and patients with ADA case type 2. The control group had a greater percentage of smoking patients. Demographic variables for the test and control group are summarized in Tables 1, 20, 46.

There were slightly more females than male subjects in the study (55.19% in the test group vs 51.96% in the control) and the biggest proportion was African American patients (38.15% in the test group and 41.2% in the control). The mean age of participants was 61.5 years for the test group and 62 for the control, age was ranging from 14 to 93 years. (Table 46)

Periodontal disease was assigned with case type 2 in 63.89% for the test group and 44.46% for the control. Patients who had ADA periodontal case type 3 comprised 24.63% and 30.45% for the test and control group respectively. Clinical profiles were very similar for the test and control groups with the greatest number of treated periodontal sites on first and second maxillary molars, followed by the mandibular molars. A total of 519 periodontal sites were analyzed in the test group and 11,130 sites were included in analysis for the control group. The vast majority of treated periodontal sites had an initial probing depth of 5 mm, followed by sites with an initial PD of 6 mm and significantly fewer sites with deeper probing depth. 26.4% of sites in the test

group showed positive bleeding on probing prior to the minocycline application, which was less than in the control group (37.73%). The sites that were treated were predominantly interproximal sites. Initial clinical presentation is summarized in Figures 5, 6, 7, 8, 15, 16, 17, 18.

The mean length of observation for "short-term result" was 112 and 150 days for the test and control group respectively. "Long-term" follow-up was performed in 247 days on average for the test group and 243 days for the control. When patients from the test group received SRP prior to the minocycline application, the average interval between the first SRP and MH placement was 45 days. During the 3 years of observation from 2016-2020, patients from the test group received 2.13 maintenance visits on average (range 0-12) which was not significantly different (p=0.47) than the number of maintenance visits that received by patients of the control group (2.19).

4.2 Clinical efficacy

Initial probing depth for the treated sites in the test group was 5.41 (± 0.03) mm. which decreased to 4.27 (±0.06) after application of the Minocycline microspheres for short-term follow up and mean probing depth for long-term follow up was 4.23 (±0.06) mm. (Figure 19, Table 21). The difference in mean probing depth was statistically significant between initial observation and short-term follow up. The difference between short-term follow-up and long-term follow-up did not reach the level of statistical significance in the test group.

Mean probing depth reduction in the test group for short-term follow-up was calculated as 1.14 (±0.06) mm and for long-term period it was 1.18 (±0.07) mm, which was not significantly

different from the short-term value (Figure 20, Table 22). BOP reduction for the short-term period was 10.6% and it decreased to - 4.24% upon long-term reevaluation.

For the control group, the mean probing depth for the treated sites was 5.61 (±0.01) mm at the initial examination and it decreased to 4.42 (±0.01) mm during short-term follow-up, which was significantly different from the baseline. For long-term follow-up, mean probing depth was 4.12 (±0.01) mm, which was significantly different from both initial and short-term values. (Figure 9, Table 2).

Mean short-term probing depth reduction was 1.20 (±0.01) mm, which became 1.50 (±0.01) mm at the long-term follow-up and there was a statistically significant difference between short and long-term mean PD reduction (p = 2.2e-16) (Figure 10, Table 3). The short-term BOP reduction was 12.95% and long-term PD reduction was 8.19% for the control group.

In comparing probing depth reduction between test and control groups, the short-term PD reduction did not reach statistical significance (1.14 and 1.2 mm respectively, Table 40). On the contrary, the long-term reduction was significantly higher in the control group (1.18 mm versus 1.50 mm with p = 1.63e-6, Table 41). The percentage of sites with positive BOP was compared using the proportion test and it was significantly higher in the control group at the baseline (37.73% compared with 26.40% for the test group with p-value = 2.31e-07) and at the short-term reevaluation (24.78% versus 15.8% for the test group with p-value = 9.64e-06). However, there was no significant difference in the percentage of sites with BOP between the test and control group in long-term follow-up. (30.64% and 29.54% respectively, Table 47).

4.2 Subgroups analyses

4.2.1 Initial probing depth

For the subgroup of periodontal sites with initial PD = 5 mm (368 sites in the test group and 6967 sites in the control), mean short-term PD reduction was 0.93 and 0.99 for the test and control group respectively and was not statistically significant between groups. A long-term PD reduction was significantly greater in the control group (1.19 mm compared to 0.92 for the test group, p-value = 0.0001).

Short-term PD reduction in the subgroup with initial PD = 6 mm (104 sites in the test group and 2356 sites in the control) was 1.37 and 1.31 on average for the test and control group, which was not statistically significant. Long-term PD reduction followed the same trend and it was calculated as 1.53 mm for the test group and 1.69 mm for the control group with no statistically significant difference.

The subgroup with initial PD = 7 mm (34 sites in the test group and 1047 sites in the control) showed mean short-term PD reduction 1.76 and 1.65 for test and control group respectively. Long-term PD reduction was 2.5 mm for the test and 2.16 mm for the control. Again, the difference between test and control groups within the subgroup was insignificant.

Mean short-term probing depth reduction for the subgroup with PD = 8 mm (12 sites in the test group and 518 sites in the control) at the initial presentation was 2.5 mm in the test group and

2.04 mm in the control group and the difference between groups did not reach the level of statistical significance. The same pattern can be observed in the long-term PD reduction, which was 2.08 in the test group and 2.72 in the control group (p-value = 0.3). Data obtained from subgroups stratified by initial PD was summarized in Tables 16, 17, 36, 37, and Figures 11, 12, 21, 22.

4.2.1 Smoking

The mean short-term probing depth reduction in the smoking population was 1.13 mm and 1.15 mm for test and control groups respectively without statistically significant difference between groups. Within the test groups, short-term PD reduction of smokers was not significantly different from both mean short-term PD reduction of non-smokers (1.08±0.07 mm) and all population (1.14±0.06 mm). For the control group, short-term PD reduction in smokers was significantly less than in non-smokers (1.15 mm compared to 1.23 mm respectively with p-value < 0.01), but when it was compared with all population (1.20 mm), there was no significant difference.

The mean long-term PD reduction in smokers was 0.87 mm for the test group and 1.51 mm for the control, and the difference was statistically significant (p<0.01). For the test group, the difference between smokers and non-smokers was significant (0.87 mm versus 1.29 mm respectively with p<0.01), but it was only marginal when smokers and all population were compared (0.87 versus 1.18 mm with p-value=0.02 before Bonferroni correction). In the control

group, the difference between subgroups did not reach the level of statistical significance. (Tables 9, 10, 29, 30)

In the control group, 19.13% of sites in the test group and 38.53% sites showed positive bleeding on probing in smokers at the baseline. These numbers decreased at the short-term reevaluation to 10.93% and 28.4% for test and control groups respectively. The measurements for positive bleeding upon probing rebounded up to 33.33% in the test group and 26.37% in the control. Therefore, short-term BOP reduction for smokers was 8.2% in the test group and 10.13% in the control. Long-term BOP reduction for the smokers in the test group was – 14.20%, but in the control, it slightly increased to 12.16%. (Table 47)

4.2.2 Diabetes

Short-term probing depth reduction in the subgroup of diabetic patients was 1.21±0.15 mm for the test group and 1.11±0.03 for the control, which was significantly less than PD reduction for all population in the control group ($p<0.01$), but not in the test group. Long-term PD reduction was calculated as 1.37±0.17 mm and 1.44±0,04 mm for the test and control group respectively. There was no statistically significant difference when the mean PD reduction of diabetes subgroup was compared to all population. Inter-group comparison in diabetic between test and control groups did not reveal any significant difference in both short-term and long-term PD reduction. (Tables 9, 11, 29, 31).

Positive bleeding on probing sign was found in 30.67% and 31.5% of sites within the subgroup of patients with diabetes in the test and control group respectively during the initial presentation. During the short-term reevaluation, 17.33% of sites in the test group and 26.86% of sites in the control had positive BOP. For the long-term reevaluation, BOP rebounded to 26.44% in the test group but showed slight improvement up to 25.73% in the control. The short-term BOP reduction was 13.34% for the test group and 4.64% for the control. The long-term BOP reduction in diabetic patients was recorded as 1.34% in the test group and 5.77% for the control. (Table 47)

4.2.3 Cardiovascular disease

The mean short-term PD reduction for patients who reported cardiovascular disease was 1.08±0.08 mm for the test group and 1.18±0.02 mm for the control without significant difference amongst all populations. The long-term probing depth reduction was 1.33±0.1 mm and 1.44±0.04 mm for test and control groups respectively. The difference with all populations was insignificant for the test group and it was marginally significant for the control group (p-value = 0.03 before Bonferroni correction). Comparing mean PD reduction between test and control groups for the subgroup of patients with the cardiovascular disease did not show any significant difference. (Tables 9, 12, 29, 32)

In the subgroup of patients with cardiovascular disease, 22.12% of sites in the test group had positive BOP before treatment, while for the control group this number was 37.44%. During the short-term reevaluation, BOP was found in 17.79% of sites in the test group and 24.5% of sites in the control. At the long-term reevaluation, 26.44% and 29.61% of sites in test and control

groups respectively exhibited positive bleeding on probing. Hence the short-term BOP reduction was 4.33% for the test group and 12.94% in the control group. The long-term reduction showed a rebound in both groups up to – 4.32% for the test and 7.83% for the control. (Table 47)

4.2.4 Arthritis

The subgroup of patients with arthritis showed a mean short-term PD reduction of 1.38±0.1 mm in the test group and 1.15±0.02 mm in the control group, with the marginally significant difference between groups (p=0.02 before Bonferroni correction). Comparing with all population, the PD reduction in the test group was also marginally different (p=0.03 before Bonferroni correction), but not in the control group. The long-term probing depth reduction was 1.26±0.02 mm for the test group and 1.38±0.02 for the control group. There was no significant difference found in both inter-group comparison and intra-group comparison for the long-term PD reduction in patients with Arthritis. (Tables 9, 13, 29, 33).

The arthritis subgroup showed 18.88% of sites with BOP in the test group before treatment, which was significantly less than 34.89% for the control. At the short-term reevaluation, 11.73% and 20.39% of sites expressed positive BOP, which rebounded in both groups to 24.49% for the test and to 34.92% for the control. BOP reduction was 7.15% and 14.5% for test and control groups respectively during the short-term re-evaluation. During the long-term follow-up, the test group showed -5.61% of BOP reduction and control group showed -0.03%. (Table 47)

4.2.5 Case type

For the subgroup of patients with ADA periodontal case type 2, mean short-term probing depth reduction was calculated as 1.13±0.06 mm and 1.24±0.02 for test and control groups respectively and it was insignificantly different in both groups and when compared with all population.
The subgroup of patients with periodontal case type 3 showed mean short-term PD reduction of 1.20±0.14 mm for the test and 1.16±0.02 mm for the control. (Tables 9, 14, 29, 34)
A comparison of short-term PD reduction of Case type 2 and Case type 3 showed marginal statistical significance for the control group (1.24 versus 1.16 for Type 3 with p-value=0.01 before Bonferroni correction), but not for the test group (1.13 for Type 2 and 1.20 for Type 3).

The long-term PD reduction for periodontal case type 2 was 1.19±0.09 mm in the test group and 1.48±0.02 mm for the control group a with statistically significant difference between test and control groups ($p<0.01$). Both the test and control groups reported no significant difference with all population and case type 3. The mean long-term PD reduction for Type 3 was 1.2±0.14 mm for the test group and 1.48±0.02 mm for the control.

For case type 2, 25.29% of sites in the test group had positive BOP sign during the baseline examination, compared with 35.55% in the control group. The short-term reevaluation revealed BOP in 12.5% and 21.33% of sites for the test group and the control respectively. At the long-term follow up 27.33% of sites in the test group and 25% of sites in the control group had positive BOP. Thus, the short-term BOP reduction was 12.79% and 14.22% in test and control groups respectively. The long-term BOP reduction was -2.04% for the test group and 10.55% for the control.

For case type 3, 29.5% and 35.28% of sites had BOP before treatment in the test and control group respectively, which decreased to almost identical 23% in the test group and 23.3% in the control at the short-term reevaluation. Upon long-term follow-up, 35.5% of sites in the test group and 30.47% of sites in the control showed positive BOP. Short-term BOP reduction was 6.5% and 11.95% for test and control groups respectively, which rebounded to – 2.75% in the test group and 4.81% in the control group.

4.3 Clinical response

In the present study, clinical response was defined as the percentage of sites that had probing depth reduction greater or equal threshold of 1 and 2 mm. The clinical response was assessed on the site level for groups with different baseline probing depths. We analyzed groups with initial PD ≥ 5 mm, ≥ 6 mm, ≥ 7 mm. Proportions of sites with defined clinical responses were compared and p-values were calculated using the proportion test.

For the subgroup with initial PD ≥ 5 mm (11,130 sites in the control group and 519 sites in the test group), 70.71% of sites in the test group and 80.23% in the control group exhibited clinical response ≥ 1 mm (had a probing depth reduction of 1 mm or greater). The difference was statistically significant with p-value = 2.78e-08. Clinical response of ≥ 2 mm was found in 52.35% of sites in the control group and 42.96% of sites in the test group which was significantly less (p-value = 5.06e-05) (Tables 18, 19, 38, 39. Figures 13, 23, 24, 25)

The subgroup with initial PD ≥ 6 mm (4163 sites for the control group and 151 sites in the test group) showed a clinical response of ≥ 1 mm in 82.08% of sites in the control group and 77.48%

of sites in the test group. 65% of sites in the control group and 60.92% of sites in the test group reached the threshold of PD reduction of ≥ 2 mm. The difference between the test and control group was insignificant for clinical responses ≥ 1 and ≥ 2 mm.

In the subgroup with initial PD ≥ 7 mm, 83.83% and 80.85% of sites for control and test groups respectively showed clinical improvement regarding PD reduction of ≥ 1 mm. The threshold of ≥ 2 mm was reached by 70.95% of sites in the control group and 70.21% of sited in the test group. The difference between test and control also did not reach the level of clinical significance in the subgroup with initial PD ≥ 7 mm.

4.4 Odds ratio

The probing depth less or equal to 4 mm is the important indicator of disease control. We calculated the percentage of sites that reached PD ≥ 4 mm for each subgroup stratified by the initial probing depth. (Table 44, Figure 26). It was reported that 67.24% of sites with initial PD ≥ 5 mm in the control group and 63.96% of sites in the test group reached probing depth ≤ 4 mm. The subgroup with initial PD ≥ 6 mm showed 52.91% and 54.30% for the control and test respectively. Only 43.11% of sites with initial PD ≥ 7 mm in the control group reached PD ≤ 4 mm, compared with 48.90% of sites in the test group, although this difference was not statistically significant.

Calculating the odds ratio for periodontal sites to reach probing depth of 4 mm or less when treated by the adjunctive therapy with minocycline microspheres compared to the repeated scaling and root planing, we did not find any statistical significance. For the subgroup with initial

PD ≥ 5mm odds ratio (OR) was 1.15, for the subgroup with PD ≥ 6 mm OR = 0.85, and OR = 0.79 for the subgroup with initial PD ≥ 7 mm.

5. Discussion

The results of this study showed greater long-term probing depth reduction of 1.50 mm in the group of patients who received repeated instrumentation within a year, compared with 1.18 mm of mean probing depth reduction in the Arestin group. Although, being statistically significant (p-value 1.63e-06), 0.32 mm of difference in probing depth reduction may not have great clinical significance.

The clinical results in regards to BOP reduction were also superior in the control group showing 8.19% less periodontal sites with positive bleeding on probing, however, test group showed 4.24% more sites with BOP than during the initial presentation.

The dynamics of probing depth throughout follow up appointments revealed different patterns in test and control groups. For the Arestin group, the greatest amount of PD reduction was observed on the short-term reevaluation appointment and this result was maintained without any significant change during long-term follow-up. Conversely, for the control group, the initial improvement on the short-term reevaluation was followed by some additional PD reduction that can be noted on the long-term follow-up. The same trend was maintained in all subgroups (Smokers, Non-Smokers, Diabetes, CVD, Arthritis).

Analyzing periodontal sites with the different initial probing depth we can see a generally greater change of probing depth in deeper sites. When comparing long-term probing depth reduction in test and control group, a significant difference was found only in sites with initial PD = 5 mm (0.91 mm for test the group and 1.19 mm for the control with p-value = 0.0001).

Subgroups that were filtered according to health history showed more uniform changes in clinical parameters with the difference that reached level of statistical significance only in short-term PD reduction between smokers and non-smokers groups. Within the control group, almost all subgroups had a significantly different clinical responses, which may have been related to the bigger sample size. Comparing different subgroups of test and control group, statistically significant difference was found in long-term PD reduction in smokers (0.87 mm for the test group and 1.51 mm for the control group with p-value < 0.01) and periodontal case type 2 (1.20 mm and 1.48 mm for test and control groups respectively).

It is important to notice that analyzing bleeding on probing for the baseline control group recorded more sites with positive BOP (37.73%) compared with the test group (26.3%). The same pattern was observed at the short-term reevaluation where the test group had 15.8% sites with BOP and for the control group, this number was 24.78%. However, during long-term follow-up, the difference between groups was insignificant (30.64% of sites in the test group and 29.54% of sites in the control group with p-value = 0.63).

In the test group, bleeding on probing showed a 10.6% of decrease at the short-term reevaluation, but during long-term follow up there were more sites with BOP than at the baseline (- 4.24% of BOP reduction). The same trend was observed in all subgroups separated by health history, being more pronounced in smokers (8.2% of short-term BOP reduction and -14.2% of long-term BOP reduction) and it was less distinct in non-smokers (Short-term BOP reduction 14.56% and Long-

term BOP reduction 1.83%) and Diabetes (13.34% of Short-term BOP reduction and 1.34% of Long-term BOP reduction).

The control group showed 12.95% of BOP reduction at the short-term reevaluation, which slightly rebounded up to 8.19% of long-term BOP reduction. This same pattern emerged through all subgroups, except smokers and diabetic patients where BOP slightly improved at the long-term follow-up compared with the short-term observation. For smokers in the control group, short-term BOP reduction was 10.13% and long-term BOP reduction was 12.16%. For diabetes, BOP reduction was less than in the general population, but it increased from 4.64% at the short-term examination to 5.77% at the long-term follow-up. Characteristics of BOP are summarized in the Table 47.

Generally, significantly more periodontal sites improved to ≥ 1 and ≥ 2 in the control group than in the test group. For clinical response ≥1 mm it was 80.23% sites versus 70.71% sites for control and test groups respectively. Clinical response ≥ 2 mm was 52.35% of sites in the control group and 42.96% of sites in the test group. When we compared subgroups stratified by initial probing depth, the difference between subgroups with PD ≤ 6 mm and PD ≤ 7 mm was insignificant. Also, the percentage of sites that reached PD ≤ 4 mm which is considered as the clinical sign of disease control, there was no significant difference between groups.

It is important to mention that the retrospective nature of our study restricts our ability to design the ideal control because rather than enrolling patients and randomizing them into groups

balanced by age, health history, and clinical presentation, we are reviewing clinical data related to different treatment modalities.

Our test group included patients who received adjunctive therapy with minocycline microspheres and non-surgical treatment of periodontal disease had some degree of heterogeneity. This is because Arestin is used at the initial stage of periodontal treatment as well as at the reevaluation and maintenance stages. The common indication for use of local delivery minocycline as the adjunctive therapy is the non-responding sites after initial periodontal therapy or progressing periodontal sites. Although some researchers exclude progressing sites from analysis (Smiley et al., 2015), our objective was to obtain evidence about the efficacy of adjunctive therapy as closely mimic implementation from real practice as possible.

The fact that many patients from the Arestin group previously received initial periodontal therapy led us to the decision to match the test group with the clinical data from patients who received repeated scaling and root planing. However, we know from the classic study published by the Loma Linda group in 1984 that there's no significant improvement in clinical parameters after the first round of SRP (Badersten et al., 1984), patients who were included in our study had periodontal therapy mainly on their molar teeth that is different from a patient clinical profile in the classic study.

Although we attempted to match the test and control group, there were some differences in a clinical presentation at the baseline. For example, the test group had more patients with cardiovascular disease (42.22% vs 27.77%), more patients with periodontal case type 2 (63.89%

vs 44.46%). The control group had significantly more smokers (34.48% compared to 29.44%) and clinically, there was a higher percentage of sites with BOP (37.73% vs 26.4%). Additionally, the test group received adjunctive therapy with Arestin on isolated periodontal sites compared with SRP in the control group that extended up to a whole quadrant in many patients.

It was also decided to keep the sample size of convenience when all available subjects are analyzed that led to unequal sample size in the test and control groups. The rationale was that the sample size of the control group provides more statistical power for the analysis of clinical response between different subgroups. Despite the differences, on the site level distribution of sites by the initial probing depth was similar in test and control groups.

It may be beneficial to provide a comparison with the clinical efficacy of the single instrumentation which can be done in future studies.

TABLES

Number of patients	1120
Female	582
Male	538
AVG age	62
Min age	14
Max age	93
Race - Black	462
Race - Hawaiian	75
Race - White	167
Race - Asian	59
Race - Other	45
Race - Unreported	310
ASAI	194
ASAIIA	323
ASAIIB	253
ASAIII	163
Smoker "Yes"	385
Smoker "No"	693
Smoker Unreported	32
Diabetes	181
HbA1c reported	54
HBA1C>7	49
CVD	311
Arthritis	324
ADA Type II	498
ADA Type III	341
ADA Type IV	2
ADA unreported	280
N of BMI reported	7

Table 1. Demographics of the Control Group.

	Initial	Short-term	Long-term
Mean PD	**5.62**	**4.42**	**4.12**
SD	0.98	1.47	1.53
VAR	0.96	2.15	2.35
SE	0.01	0.01	0.01

Table 2. Dynamics of probing depth for the Control Group.

	Short-term	Long-term
Mean PD red	**1.20**	**1.50**
Sd	1.36	1.54
Var	1.85	2.36
SE	0.01	0.01

Table 3. Probing depth reduction for the Control Group

Mean	1.19785373
Standard Error	0.01290851
Median	1
Mode	1
Standard Deviation	1.35932157
Sample Variance	1.84775513
Kurtosis	1.37671756
Skewness	0.01778748
Range	15
Minimum	-7
Maximum	8

Table 4. Descriptive statistics of mean short-term probing depth reduction in the Control Group.

Mean	1.50175597
Standard Error	0.01458985
Median	2
Mode	2
Standard Deviation	1.53748245
Sample Variance	2.36385228
Kurtosis	2.23449627
Skewness	-0.3865136
Range	16
Minimum	-9
Maximum	7

Table 5. Descriptive statistics of mean long-term probing depth reduction in the Control Group.

```
        Welch Two Sample t-test

data:  PdShort and PdLong
t = -15.6, df = 21871, p-value < 2.2e-16
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -0.3420856 -0.2657189
sample estimates:
mean of x mean of y
 1.197854  1.501756
```

Table 6. Results of t-test comparing mean short-term and long-term probing depth reduction in the Control Group.

```
Anova Table (Type III tests)

Response: CGclinicalS$PDredLongTerm
                           Sum Sq    Df   F value    Pr(>F)
(Intercept)                  23.9     1   11.0704 0.0008803 ***
PatientAge                    8.9     1    4.1352 0.0420256 *
`ASA Type`                   39.7     6    3.0695 0.0052983 **
`Pocket during procedure`  2953.3     1 1370.0925 < 2.2e-16 ***
Smoker                       31.9     2    7.3918 0.0006196 ***
Diabetes                      4.6     2    1.0616 0.3459244
CVD                           9.8     1    4.5333 0.0332658 *
Arthritis                    77.6     1   35.9864 2.055e-09 ***
`Perio Case Type`           119.3     2   27.6769 1.029e-12 ***
Residuals                 21969.6 10192
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

Table 8. Results of the ANOVA test for the Long-term probing depth reduction in the Control Group

```
Anova Table (Type III tests)

Response: CGclinicalS$PDredShortTerm
                           Sum Sq    Df  F value    Pr(>F)
(Intercept)                   0.0     1   0.0291  0.864496
PatientAge                   10.7     1   6.3305  0.011883 *
`ASA Type`                   47.1     6   4.6555 9.811e-05 ***
`Pocket during procedure`  1330.5     1 788.4177 < 2.2e-16 ***
Smoker                       38.0     2  11.2531 1.313e-05 ***
Diabetes                     13.0     2   3.8466  0.021383 *
CVD                           2.2     1   1.3303  0.248781
Arthritis                    16.2     1   9.5987  0.001952 **
`Perio Case Type`           170.8     2  50.6123 < 2.2e-16 ***
Residuals                 17150.9 10163
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

Table 7. Results of the ANOVA test for the Short-term PD reduction in the Control Group.

	Short-Term PD reduction	Long-term PD reduction
All population	1.20 (±0.01)	1.50 (±0.01)
Smokers	1.15 (±0.02)	1.51 (±0.02)
Non-Smokers	1.23 (±0.02)	1.52 (±0.02)
Diabetes	1.11 (±0.03)	1.44 (±0.04)
CVD	1.18 (±0.02)	1.44 (±0.02)
Arthritis	1.15 (±0.02)	1.38 (±0.02)

Table 9. Mean probing depth reduction for different subgroups within the Control Group.

P-value		Smokers		All population	
		Short	Long	Short	Long
Non-Smokers	Short	p<0.01		p>0.05	
	Long		p>0.05		p>0.05
All population	Short	p>0.05			p<0.01
	Long		p>0.05	p<0.01	

Table 10. Table of p-values for pairwise comparison of mean PD reduction for subgroups within the Control Group.

P-value		Diabetes		All population	
		Short	Long	Short	Long
Diabetes	Short		p<0.01	p<0.01	
	Long	p<0.05			p>0.05
All population	Short	p<0.01			p<0.01
	Long		p>0.05	p<0.01	

Table 11. Table of p-values for pairwise comparison of mean PD reduction for subgroups within the Control Group.

P-value		CVD		All population	
		Short	Long	Short	Long
CVD	Short		p<0.01	p>0.05	
	Long	p<0.01			p>0.05
All population	Short	p>0.05			p<0.01
	Long		p>0.05	p<0.01	

Table 12. Table of p-values for pairwise comparison of mean PD reduction for subgroups within the Control Group.

P-value		Arthritis		All population	
		Short	Long	Short	Long
Arthritis	Short		p<0.01	p>0.05	
	Long	p<0.01			p<0.01
All population	Short	p>0.05			p<0.01
	Long		p<0.01	p<0.01	

Table 13. Table of p-values for pairwise comparison of mean PD reduction for subgroups within the Control Group.

	Short-Term PD reduction	Long-term PD reduction
All population	1.20 (±0.01)	1.50 (±0.01)
ADA Case Type 2	1.24 (±0.02)	1.48 (±0.02)
ADA Case Type 3	1.16 (±0.02)	1.48 (±0.02)

Table 14. Mean probing depth reduction for periodontal case type subgroups within the Control Group

P-value		All population		Type 2		Type 3	
		Short	**Long**	**Short**	**Long**	**Short**	**Long**
All population	**Short**		p<0.01	p>0.05		p>0.05	
	Long	p<0.01			p>0.05		p>0.05
Type 2	**Short**	p>0.05			p<0.01	p>0.05	
	Long		p>0.05	p<0.01			p>0.05
Type 3	**Short**	p>0.05		p>0.05			p<0.01
	Long		p>0.05		p>0.05	p<0.01	

Table 15. Table of p-values for pairwise comparison of mean PD reduction for subgroups within the Control Group.

	5 mm	6 mm	7 mm	8 mm	9 mm
Mean PD red	**0.99**	**1.31**	**1.65**	**2.04**	**2.35**
SE	0.01	0.03	0.05	0.08	0.13
N	**6967**	**2356**	**1047**	**518**	**242**

Table 16. Mean short-term probing depth reduction for the control group stratified by the initial probing depth.

	5 mm	6 mm	7 mm	8 mm	9 mm
Mean PD red	**1.19**	**1.69**	**2.16**	**2.72**	**3.26**
SE	0.02	0.03	0.06	0.09	0.15
N	6967	2356	1047	518	242

Table 17. Mean long-term probing depth reduction for the control group stratified by the initial probing depth.

	≥ 5 mm	**≥ 6 mm**	**≥ 7 mm**
≥ 1mm	**80.23%**	**82.08%**	**83.23%**
≥ 2 mm	**52.35%**	**65.00%**	**70.95%**

Table 18. Clinical response of sites with initial probing depth in the Control Group

	≥ 5 mm	≥ 6 mm	≥ 7 mm
Mean PD red	**1.50**	**2.02**	**2.47**
SE	0.01	0.03	0.05
N	**11130**	**4163**	**1807**

Table 19. Mean long-term probing depth reduction for sites with different initial probing depth.

Number of patients	540
Female	298
Male	242
AVG age	61.5
Min age	17
Max age	93
Race - Black	206
Race - Hawaiian	72
Race - White	71
Race - Asian	24
Race - Other	15
Race - Unreported	150
ASAI	84
ASAIIA	269
ASAIIB	116
ASAIII	66

Smoker "Yes"	159
Smoker "No"	352
Smoker Unreported	64
Diabetes	91
HbA1c reported	58
HBA1C>7	18
CVD	228
Arthritis	178
ADA Type II	345
ADA Type III	133
ADA unreported	60
N of BMI reported	26
BMI average	28.48

Table 20. Demographics of the Test group.

	Initial	Short-term	Long-term
Mean PD	**5.41**	**4.27**	**4.23**
SD	0.73	1.30	1.44
VAR	0.53	1.70	2.07
SE	0.03	0.06	0.06

Table 21. Dynamics of probing depth during the treatment for the Test group.

	Short-term	Long-term
Mean PD red	**1.14**	**1.18**
Sd	1.28	1.49
Var	1.63	2.21
SE	0.06	0.07

Table 22. Probing depth reduction for the Test group.

Short-term PD reduction	
Mean	1.13513514
Standard Error	0.05602336
Median	1
Mode	1
Standard Deviation	1.2750701
Sample Variance	1.62580375
Kurtosis	1.64351786
Skewness	0.57133407
Range	10
Minimum	-3
Maximum	7

Table 23 and 24. Descriptive statistics for the short-term PD reduction for the Test group

Long-term PD reduction	
Mean	1.17760618
Standard Error	0.06529175
Median	1
Mode	1
Standard Deviation	1.4860149
Sample Variance	2.20824029
Kurtosis	0.52868132
Skewness	-0.2894718
Range	9
Minimum	-4
Maximum	5

Table 24. Descriptive statistics for long-term PD reduction for the Test group.

```
        Welch Two Sample t-test

data:  PdShortTG and PdLongTG
t = -0.49366, df = 1010.7, p-value = 0.6217
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -0.2112943  0.1263522
sample estimates:
mean of x mean of y
 1.135135  1.177606
```

Table 25. T-test to compare short-term and long-term probing depth reduction in the test group.

```
Anova Table (Type III tests)

Response: TGclinicalS$PDredShortTerm
                         Sum Sq  Df F value    Pr(>F)
(Intercept)                0.42   1  0.3269  0.567776
PatientAge                 1.44   1  1.1097  0.292686
`ASA Type`                23.57   5  3.6284  0.003135 **
`Pocket during procedure` 36.88   1 28.3819 1.556e-07 ***
Smoker                     1.22   2  0.4713  0.624479
Diabetes                   0.15   2  0.0571  0.944482
CVD                        0.06   1  0.0461  0.830097
Arthritis                  6.31   1  4.8558  0.028044 *
`Perio Case Type`          6.42   1  4.9420  0.026693 *
Residuals                602.89 464
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

Tables 26 and 27. Results of ANOVA test for short-term and long-term PD reduction in the Test group.

```
Anova Table (Type III tests)

Response: TGclinicalS$PDredLongTerm
                         Sum Sq  Df F value    Pr(>F)
(Intercept)                8.96   1  4.2629   0.03951 *
PatientAge                11.31   1  5.3816   0.02078 *
`ASA Type`                15.38   5  1.4640   0.20020
`Pocket during procedure` 68.70   1 32.6969 1.931e-08 ***
Smoker                     5.97   2  1.4196   0.24286
Diabetes                   5.11   2  1.2149   0.29769
CVD                        8.52   1  4.0539   0.04465 *
Arthritis                  0.01   1  0.0029   0.95714
`Perio Case Type`          3.96   1  1.8851   0.17042
Residuals                974.99 464
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

	Short-Term PD reduction	Long-term PD reduction
All population	1.14 (±0.06)	1.18 (±0.07)
Smokers	1.13 (±0.08)	0.87 (±0.11)
Non-Smokers	1.08 (±0.07)	1.29 (±0.09)
Diabetes	1.21 (±0.15)	1.37 (±0.17)
CVD	1.08 (±0.08)	1.33 (±0.1)
Arthritis	1.38 (±0.1)	1.26 (±0.02)

Table 28. Mean probing depth reduction for different subgroups within the Test Group.

P-value		**Smokers**		**All population**	
		Short	**Long**	**Short**	**Long**
Non-Smokers	**Short**	p>0.05		p>0.05	
	Long		p<0.01		p>0.05
All population	**Short**	p>0.05			p>0.05
	Long		p>0.05	p>0.05	

Table 29. Table of p-values for pairwise comparison of mean PD reduction for Smokers and Non-smokers subgroups within the Test Group.

P-value		**Diabetes**		**All population**	
		Short	**Long**	**Short**	**Long**
Diabetes	**Short**		p>0.05	p>0.05	
	Long	p>0.05			p>0.05
All population	**Short**	p>0.05			p>0.05
	Long		p>0.05	p>0.05	

Table 30. Table of p-values for pairwise comparison of mean PD reduction for Diabetes subgroup within the Test Group.

P-value		CVD		All population	
		Short	Long	Short	Long
CVD	Short		p>0.05	p>0.05	
	Long	p>0.05			p>0.05
All population	Short	p>0.05			p>0.05
	Long		p>0.05	p>0.05	

Table 31. Table of p-values for pairwise comparison of mean PD reduction for cardiovascular disease subgroup within the Test Group.

P-value		Arthritis		All population	
		Short	Long	Short	Long
Arthritis	Short		p>0.05	p>0.05	
	Long	p>0.05			p>0.05
All population	Short	p>0.05			p>0.05
	Long		p>0.05	p>0.05	

Table 32. Table of p-values for pairwise comparison of mean PD reduction for arthritis subgroup within the Test Group.

	Short-Term PD reduction	Long-term PD reduction
All population	1.14 (±0.06)	1.18 (±0.07)
ADA Case Type 2	1.13 (±0.06)	1.19 (±0.09)
ADA Case Type 3	1.20 (±0.14)	1.20 (±0.14)

Table 33. Mean probing depth reduction for subgroup based on case type within the Test Group.

P-value		All population		Type 2		Type 3	
		Short	Long	Short	Long	Short	Long
All population	Short		p>0.05	p>0.05		p>0.05	
	Long	p>0.05			p>0.05		p>0.05
Type 2	Short	p>0.05			p>0.05	p>0.05	
	Long		p>0.05	p>0.05			p>0.05
Type 3	Short	p>0.05		p>0.05			p>0.05
	Long		p>0.05		p>0.05	p>0.05	

Table 34. Table of p-values for pairwise comparison of mean PD reduction for arthritis subgroup within the Test Group.

P-value	TEST	Smokers		Diabetes		CVD		Arthritis		Case Type 2		Case Type 3	
CONTROL		Short	Long	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long
Smokers	Short	p>0.05											
	Long		p<0.01										
Diabetes	Short			p>0.05									
	Long				p>0.05								
CVD	Short					p>0.05							
	Long						p>0.05						
Arthritis	Short							p>0.05					
	Long								p>0.05				
Case Type 2	Short									p>0.05			
	Long										p<0.01		
Case Type 3	Short											p>0.05	
	Long												p>0.05

Table 35. Table of p-values for inter-group comparison.

	5 mm	6 mm	7 mm	8 mm	9 mm
Mean PD red	**0.95**	**1.38**	**1.76**	**2.5**	**5**
SE	0.06	0.13	0.31	0.7	
N	**368**	**104**	**34**	**12**	**1**

Table 36. Mean short-term probing depth reduction in the Test Group stratified by the initial PD.

	5 mm	6 mm	7 mm	8 mm	9 mm
Mean PD red	**0.92**	**1.53**	**2.5**	**2.1**	**5**
SE	0.07	0.15	0.31	0.6	
N	**368**	**104**	**34**	**14**	**1**

Table 37. Mean long-term probing depth reduction in the Test Group stratified by the initial PD.

	≥ 5 mm	≥ 6 mm	≥ 7 mm
≥ 1mm	**70.71%**	**77.48%**	**80.85%**
≥ 2 mm	**42.96%**	**60.92%**	**70.21%**

Table 38. Clinical response for sites with different initial PD in the Test group.

	≥ 5 mm	≥ 6 mm	≥ 7 mm
Mean PD red	**1.18**	**1.81**	**2.45**
SE	0.07	0.14	0.27
N	519	151	47

Table 39. Mean long-term PD reduction for sites with different initial PD in the Test group.

```
        Welch Two Sample t-test

data:  PdShort and PdShortTG
t = 1.0909, df = 573.28, p-value = 0.2758
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -0.05020064  0.17563782
sample estimates:
mean of x mean of y
 1.197854  1.135135
```

Table 40. Results of the t-test comparing short-term PD reduction for control and test groups.

```
        Welch Two Sample t-test

data:  PdLong and PdLongTG
t = 4.8451, df = 569.85, p-value = 1.633e-06
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 0.1927452 0.4555544
sample estimates:
mean of x mean of y
 1.501756  1.177606
```

Table 41. Results of the t-test comparing long-term PD reduction for control and test groups.

	≥ 5 mm	≥ 6 mm	≥ 7 mm
Control Group	**80.23%**	**82.08%**	**83.83%**
Test Group	**70.71%**	**77.48%**	**80.85%**

Table 42. Comparison of the clinical response ≥ 1 mm in test and control groups for subgroups with different initial PD.

	≥ 5 mm	≥ 6 mm	≥ 7 mm
Control Group	**52.35%**	**65.00%**	**70.95%**
Test Group	**42.96%**	**60.92%**	**70.21%**

Table 43. Comparison of the clinical response ≥ 2 mm in test and control groups for subgroups with different initial PD.

	≥ 5 mm	≥ 6 mm	≥ 7 mm
Control Group	**67.24%**	**52.91%**	**43.11%**
Test Group	**63.96%**	**54.30%**	**48.90%**

Table 44. Percentage of sites that reached PD ≤ 4 mm in test and control groups for subgroups with different initial PD.

	≥ 5 mm	≥ 6 mm	≥ 7 mm
Odds Ratio	**1.15**	**0.85**	**0.79**
CI 95%	**0.96 - 1.39**	**0.6 - 1.19**	**0.44 - 1.41**
P value	0.12	0.34	0.42

Table 45. Odds ratio for periodontal sites with different initial probing depth to reach PD ≤ 4 mm when treated with Arestin compared to repeated SRP.

	Test n=540	Control n=1120	Proportion test P-value
Avg age	61.5	62	
Male	44.81%	48.04%	0.24
Female	55.19%	51.96%	
ASA 1	15.56%	17.32%	0.4
ASA 2	71.3%	51.43%	2.2e-16
ASA 3	12.22%	14.55%	0.22
Smoking	29.44%	34.38%	0.05
Diabetes	16.85%	16.16%	0.78
CVD	42.22%	27.77%	5.35e-09
Arthritis	32.96%	29.93%	0.1
Case type 2	63.89%	44.46%	1.79e-13
Case type 3	24.63%	30.45%	0.76
BOP initial	26.4%	37.73%	

Table 46. Comparison of demographics in test and control groups.

Groups	Initial BOP	Short-term BOP	Long-term	Short-term reduction	Long-term reduction
All population					
TG	**26.45%**	**15.8%**	**30.64%**	**10.6%**	**- 4.24%**
CG	**37.73%**	**24.78%**	**29.54%**	**12.95%**	**8.19%**
P-value	**<0.0001**	**<0.0001**	0.63		
Smokers					
TG	**19.13%**	**10.93%**	**33.33%**	**8.2%**	**- 14.20%**
CG	**38.53%**	**28.4%**	**26.37%**	**10.13%**	**12.16%**
P-value	**<0.001**	**<0.001**	**0.05**		
Non-Smokers					
TG	**30.77%**	**16.12%**	**28.94%**	**14.56%**	**1.83%**
CG	**38.67%**	**23.23%**	**31.35%**	**15.44%**	**7.32%**
P-value	**0.01**	**<0.01**	0.44		
Diabetes					
TG	**30.67%**	**17.33%**	**29.33%**	**13.34%**	**1.34%**
CG	**31.5%**	**26.86%**	**25.73%**	**4.64%**	**5.77%**
P-value	**0.98**	**0.09**	0.6		
CVD					

TG	**22.12%**	**17.79%**	**26.44%**	**4.33%**	**- 4.32%**
CG	**37.44%**	**24.50%**	**29.61%**	**12.94%**	**7.83%**
p-value	**<0.0001**	**0.03**	0.37		
Arthritis					
TG	**18.88%**	**11.73%**	**24.49%**	**7.15%**	**-5.61**
CG	**34.89%**	**20.39%**	**34.92%**	**14.5%**	**-0.03**
p-value	**<0.0001**	**<0.01**	**<0.01**		
Type2					
TG	**25.29%**	**12.5%**	**27.33%**	**12.79%**	**-2.04%**
CG	**35.55%**	**21.33%**	**25.0%**	**14.22%**	**10.55%**
p-value	**<0.001**	**0.0001**	0.38		
Type 3					
TG	**29.5%**	**23.0%**	**35.25%**	**6.5%**	**-2.75%**
CG	**35.28%**	**23.33%**	**30.47%**	**11.95%**	**4.81%**
p-value	**0.19**	**1**	0.26		

Table 47. Comparison of BOP in all subgroups within test and control groups.

FIGURES

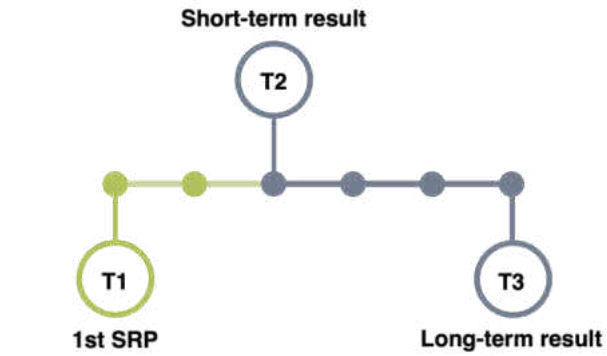

Figure 1. Timeline of treatment for the Control group.

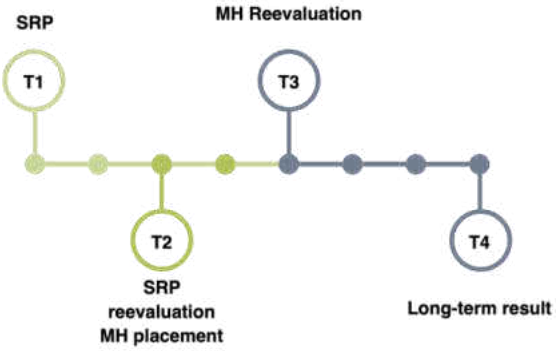

Figure 2. Timeline of treatment for the Test group.

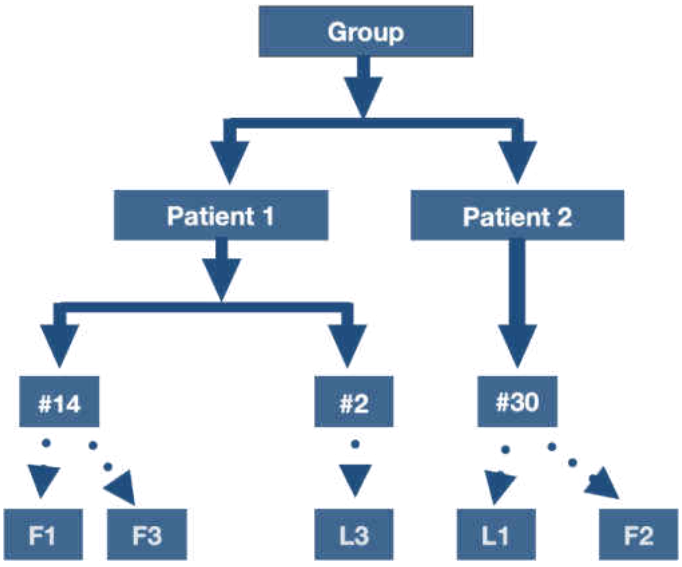

Figure 3. Structure of data.

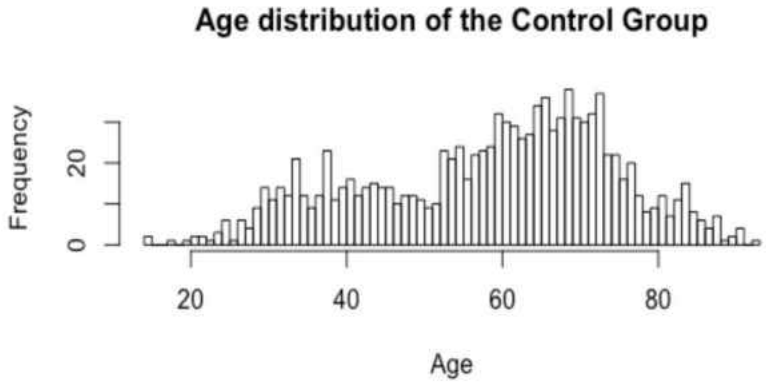

Figure 4. Histogram of age for the Control group.

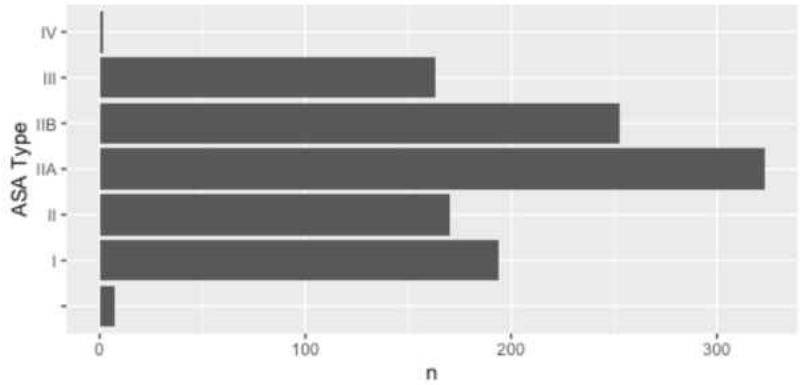

Figure 5. Distribution of patients by ASA type in the Control group.

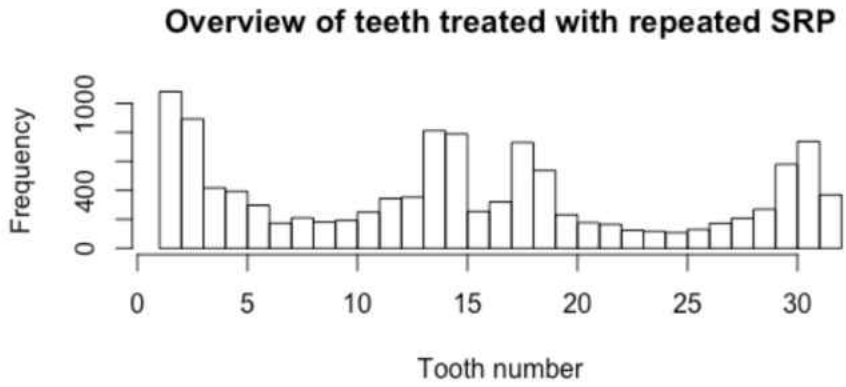

Figure 6. Histogram of teeth that received treatment in the Control group.

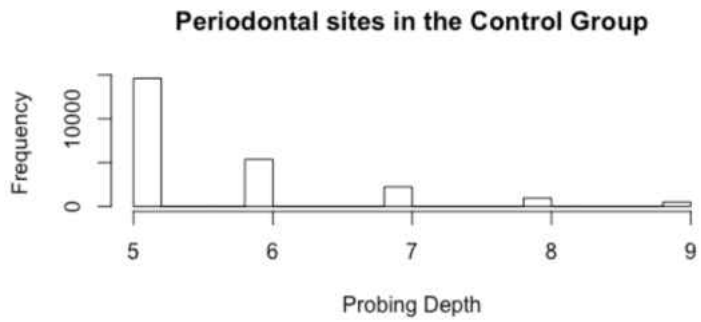

Figure 7. Histogram of treated periodontal sites by the initial probing depth in the Control group.

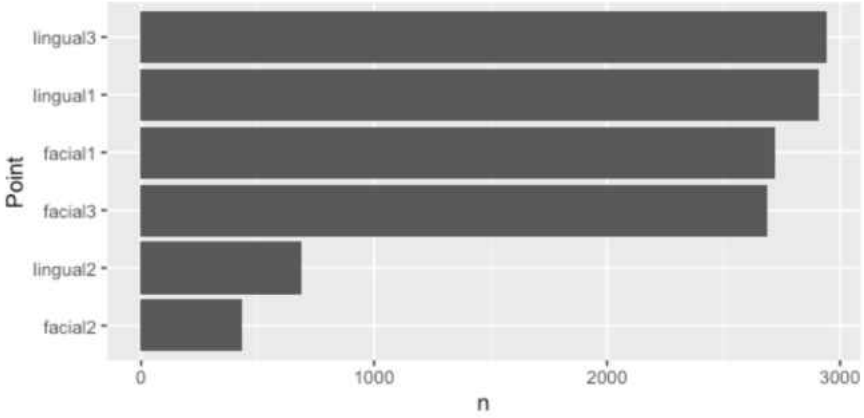

Figure 8. Chart of locations for treated sites in the Control group (1 and 3 indicate interproximal sites, 2 – mid-buccal and mid-lingual).

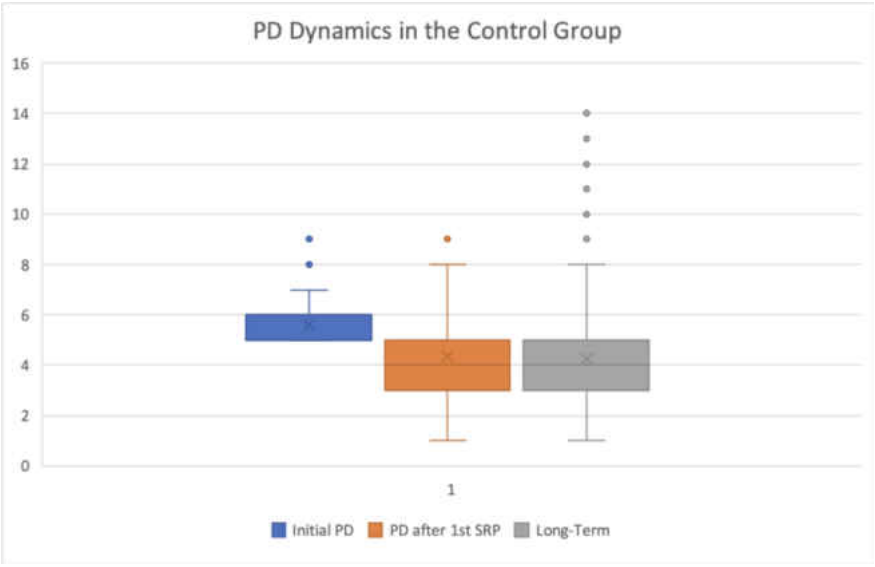

Figure 9. Box plot of PD dynamics in the Control group.

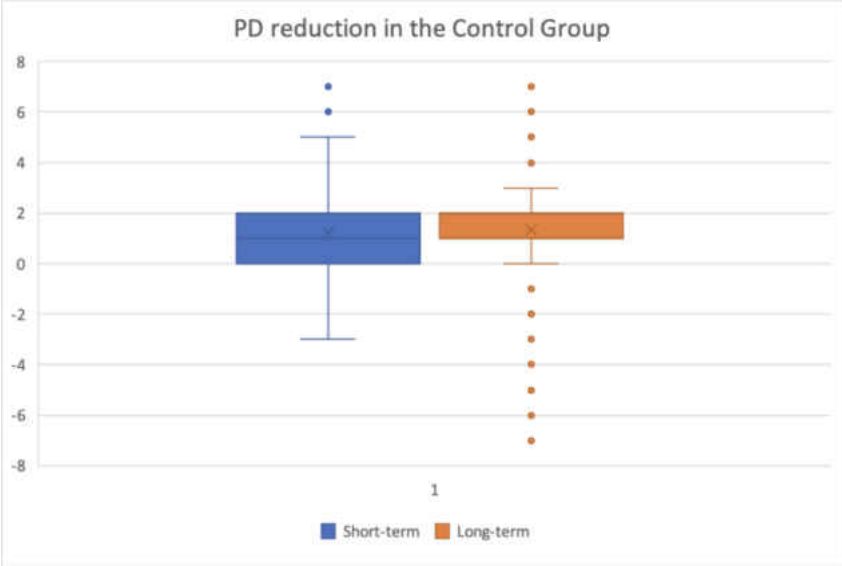

Figure 10. Boxplot for PD reduction for the Control group.

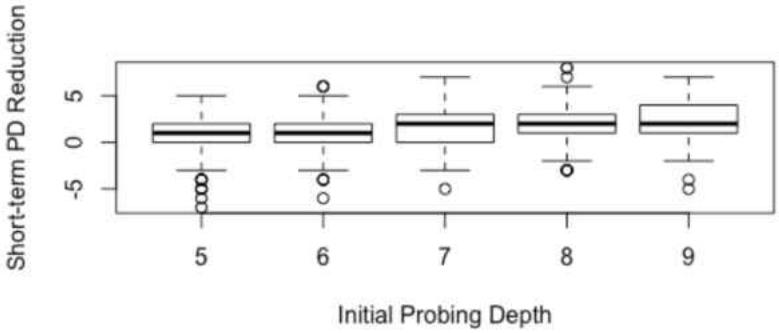

Figure 11. Boxplot for short-term PD reduction stratified by the initial PD in the Control group.

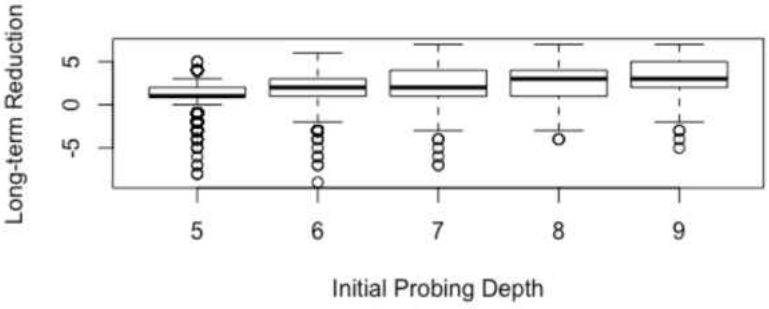

Figure 12. Boxplot for long-term PD reduction stratified by the initial PD in the Control group.

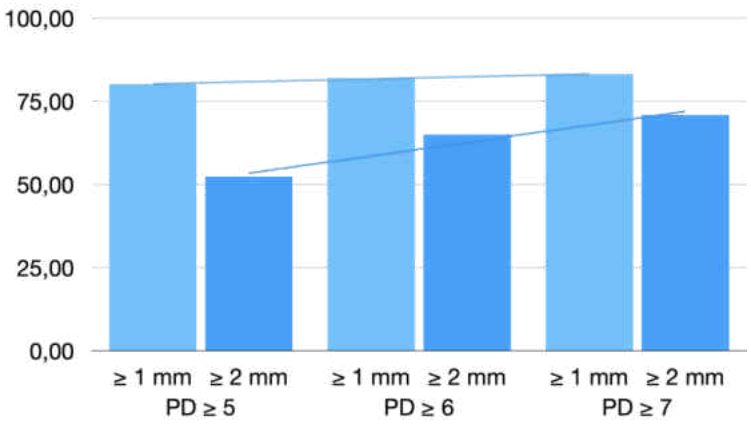

Figure 13. Clinical response for subgroups with different initial PD in the Control group.

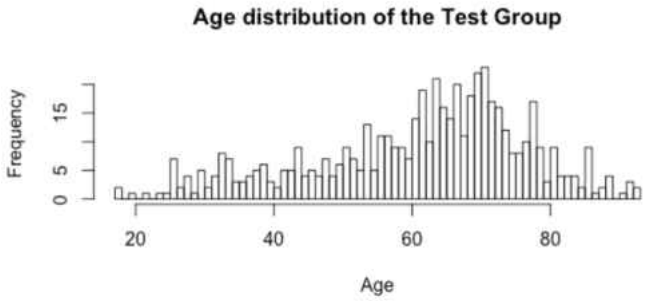

Figure 14. Histogram of age in the Test group.

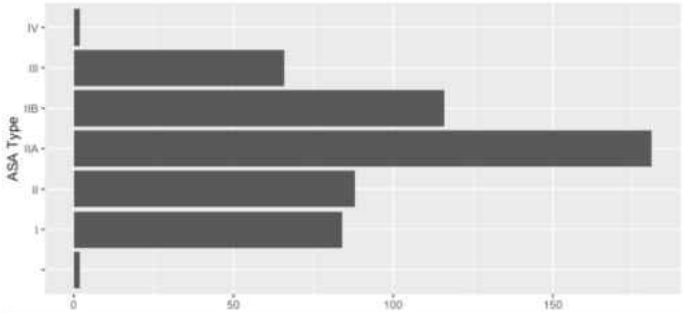

Figure 15. Distribution of Test group patients by the ASA type.

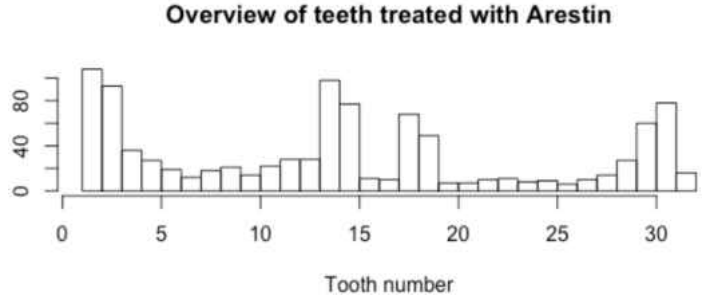

Figure 16. Histogram of treated teeth numbers in the Test group.

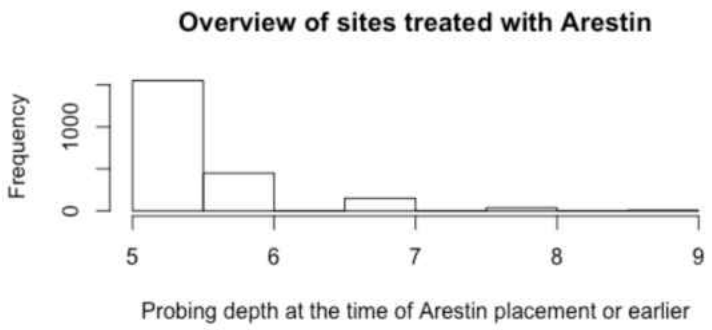

Figure 17. Histogram of initial probing depth for treated sites in the Test group.

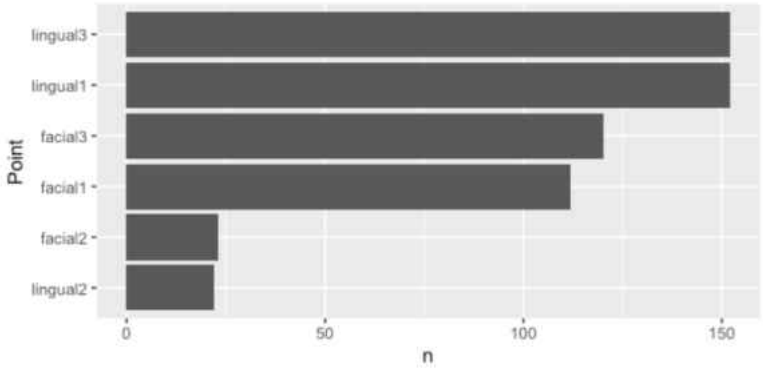

Figure 18. Chart showing location of treated sites in the Test group (1 and 3 indicate interproximal sites, 2 – mid-buccal and mid-lingual).

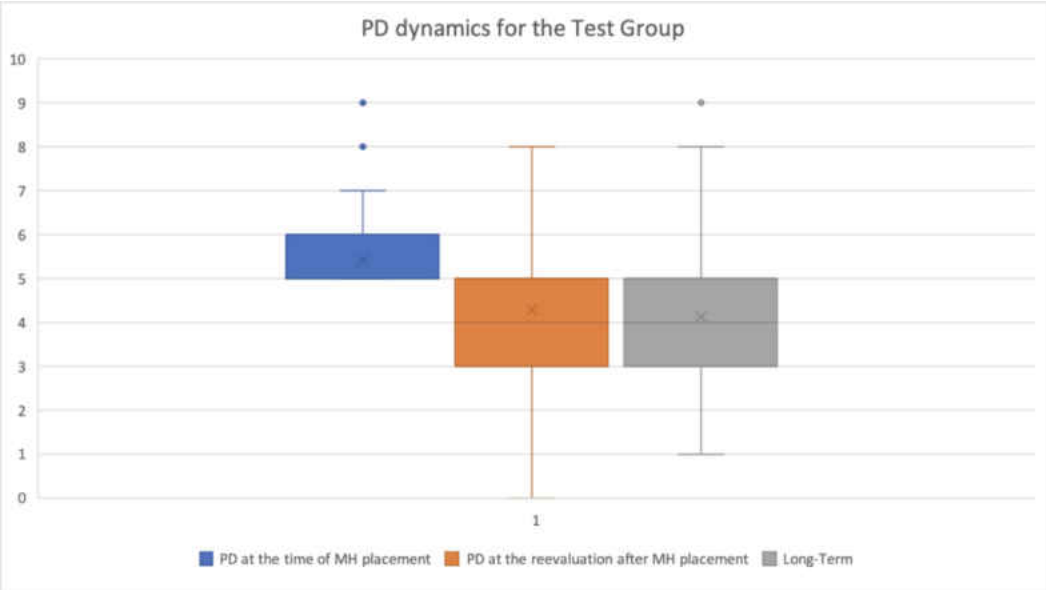

Figure 19. Boxplot for PD dynamics in the Test group.

Figure 20. Boxplot for PD reduction in the Test group.

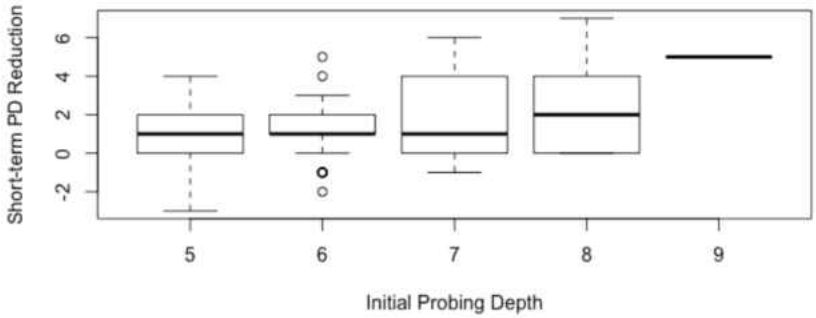

Figure 21. Boxplot of short-term PD reduction in the Test group stratified by the initial PD.

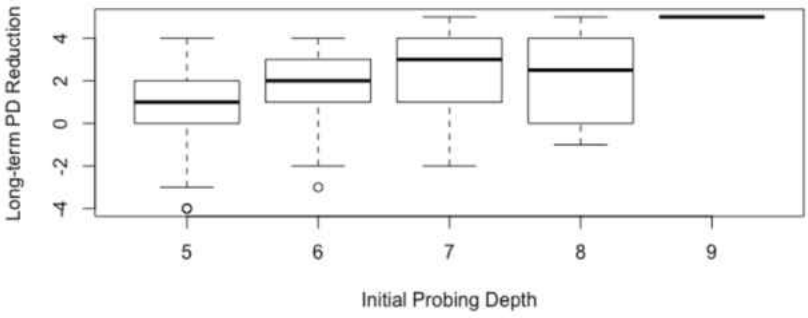

Figure 22. Boxplot of long-term PD reduction in the Test group stratified by the initial PD.

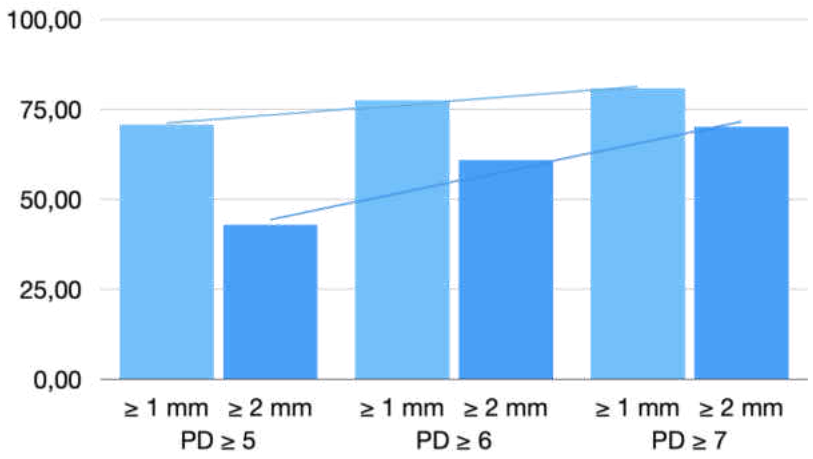

Figure 23. Clinical response for different subgroups based on initial PD in the Test group.

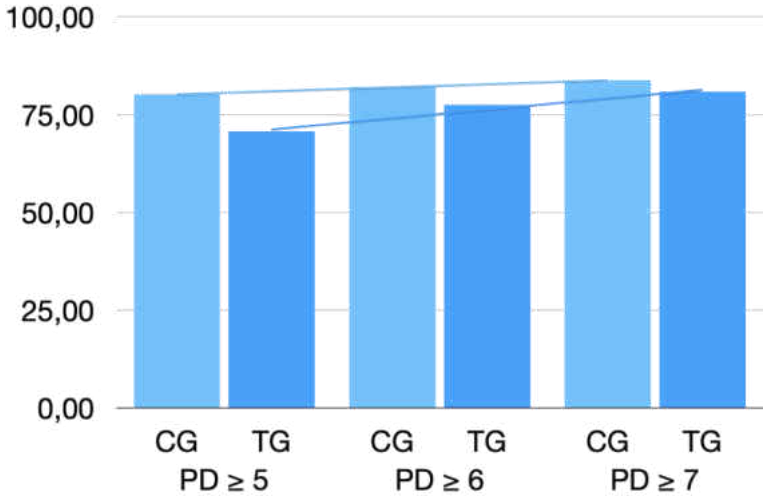

Figure 24. Comparison of clinical response ≥ 1 mm in test and control groups in subgroups with different initial PD (CG – Control group, TG – Test group).

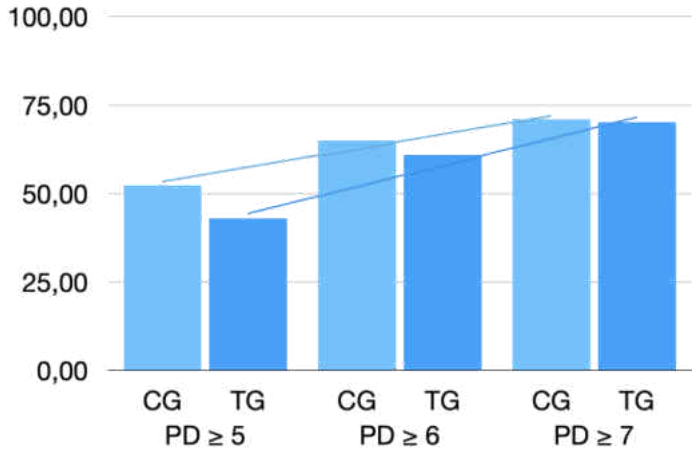

Figure 25. Comparison of clinical response ≥ 2 mm in test and control groups in subgroups with different initial PD (CG – Control group, TG – Test group).

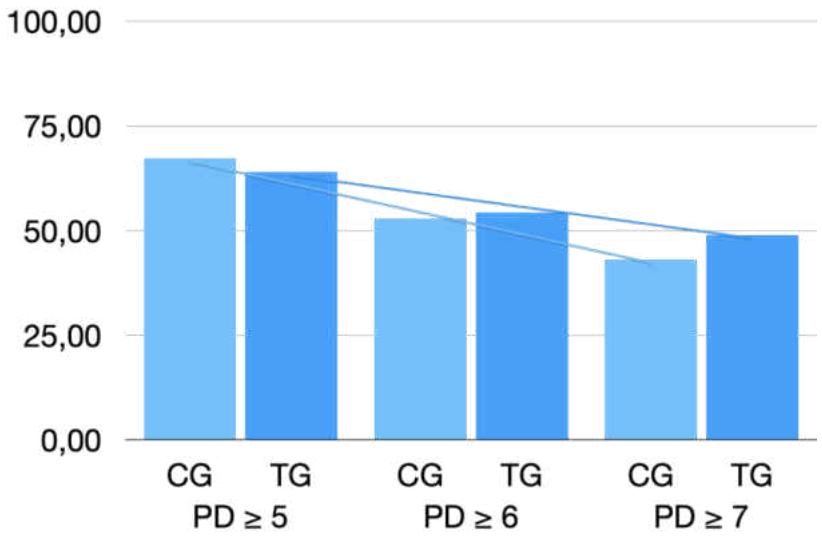

Figure 26. Comparison of percentage of sites reached PD ≤ 4 mm in test and control groups.

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