Short-term Effects of 2% Atorvastatin Dentifrice as an Adjunct to Periodontal Therapy: A Randomized Double Blind Clinical Trial

David R. Rosenberg, MSc[*]; Catherine X. Andrade, DDS[†]; Alejandra P. Chaparro, MSc[†]; Carolina M. Inostroza, MSc[‡]; Valeria Ramirez, MPH[§]; Déborah Violant, PhD[‖]; José Nart, PhD[‖]

* Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Universidad de los Andes, Santiago, Chile.

† Department of Periodontology, Faculty of Dentistry, Universidad de los Andes, Santiago, Chile.

‡ Center of Biology and Oral Regeneration (CIBRO), Faculty of Dentistry, Universidad de los Andes, Santiago, Chile.

§ Epidemiology, Faculty of Dentistry, Universidad de los Andes, Santiago, Chile.

‖ Department of Periodontology, Universitat Internacional de Catalunya, Barcelona, Spain.

Background: The pleiotropic effects of statins such as immunomodulation and anti-inflammatory effects may also improve periodontal conditions. The aim of the present study is to assess the effectiveness of a dentifrice medicated with 2% atorvastatin in improving clinical periodontal parameters as a complement to nonsurgical periodontal treatment (NSPT).

Methods: A randomized, double blind clinical trial was performed with 2 parallel groups (atorvastatin group: NSPT plus medicated 2% atorvastatin dentifrice; placebo group: NSPT plus placebo dentifrice). The effectiveness of these treatments was assessed using periodontal measurements obtained at baseline and one month later. The measurements were probing depth (PD), clinical attachment level (CAL), bleeding on probing (BOP), gingival index (GI) and periodontal inflamed surface area (PISA). Multiple linear regression models were used to compare outcome variables after adjusting for gender, diabetes and tobacco use.

Results: A total of 36 individuals participated in this study (atorvastatin group, 18; placebo group, 18). Both groups showed improvements in periodontal parameters. The atorvastatin group showed a significant decrease of 297.63 mm^2 in PISA (95% CI: 76.04 - 519.23; p value = 0.01), greater than the reduction observed in the placebo group. There was also a significantly greater reduction in mean PD, percentage of sites with PD ≥ 5 mm, mean CAL, percentage of sites with CAL ≥ 5 mm, BOP and GI in the atorvastatin group compared to placebo group.

Conclusion: NSPT plus 2% atorvastatin medicated dentifrice was more effective in improving clinical periodontal parameters than NSPT plus a placebo dentifrice.

KEY WORDS:

Atorvastatin, Dentifrices, Chronic periodontitis, Clinical trial (s)

The common approach used in the treatment of periodontal disease, based primarily on the control of the etiologic agent (bacterial biofilm), has not been sufficient to reduce the high prevalence of periodontal disease.[1] The emerging understanding regarding the role of host immune response in periodontal tissue destruction and the specific inflammatory mechanism involved[2–4] have encouraged researchers to explore new strategies in the management of periodontal disease. The presence of microbes associated with the progressive forms of periodontal disease in individuals with no evidence of disease progression suggests that the disease is a product of the immune response and inflammatory processes and not a result of the

mere presence of the bacteria. Consequently, in susceptible individuals, the dysregulation of inflammatory and immune pathways leads to chronic inflammation, tissue destruction and disease.[4]

Recently, improvements have been reported in the status of periodontal disease associated with the use of statins.[5, 6] Statins are effective lipid-lowering agents with additional effects that are beneficial in treating periodontal disease such as anti-inflammatory properties, stimulation of bone formation and immunomodulatory actions.[7–9] Various animal studies have demonstrated that statins decrease pro-inflammatory cytokines and mediators associated with bone loss.[10, 11] Araujo et al. showed that rats with experimental periodontitis (EP) plus 10 mg/kg atorvastatin (a member of the statins) exhibited reverse bone loss caused by EP, decreasing pro-inflammatory cytokines such as IL-1β and TNF-α and reducing the markers of bone destruction such as metalloproteinase (MMP-2 and MMP-9) and the receptor activator of nuclear factor kappa B ligand (RANKL).[10] Dalcico et al. observed similar results in rats with experimental periodontitis.[11] Treatment with oral simvastatin reduced the expression of inducible nitric oxide synthase (iNOS), MMP-1, MMP-8 and RANKL and increased bone morphogenetic protein-2 (BMP-2) and osteoprotegerin levels (inductors of bone formation) in the periodontal tissue.[11]

Recently, clinical trials have shown improvement in periodontal clinical parameters in medically healthy patients with the exception of having chronic periodontitis using 1.2% atorvastatin or 1.2% simvastatin (1.2 mg/0.1 ml) as a biodegradable controlled-release gel adjunct to scaling and root planing (SRP) in treatment of chronic periodontitis, observing greater improvement with the use of atorvastatin.[5, 6]

Despite the aforementioned evidence regarding the benefits of statins in periodontal disease, there remains a lack of information regarding the best vehicle, most appropriate doses, and confirmation of the true effects of statins in periodontal disease.

Considering that dentifrice is a complement widely used in oral hygiene techniques, dentifrice could be an effective medium with which to release statins, especially atorvastatin, which has demonstrated a greater topical effect.

The aim of the present investigation was to assess the effectiveness of a dentifrice medicated with 2% atorvastatin to improve clinical periodontal parameters in adult patients after nonsurgical periodontal treatment.

MATERIALS AND METHODS

Study Design and Patients

The study design incorporated a clinical trial with two parallel groups (1:1). Each group comprised 19 patients. The investigation was performed at the Department of Periodontology, Universidad de los Andes. Patients were enrolled in the study between June 2013 and August 2013 and were recruited from the Health Care Center, Universidad de los Andes (San Bernardo, Santiago, Chile). The University Ethics Committee approved the study protocol in accordance with the Revised Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013). Each patient agreed to participate in the study, providing his or her written informed consent. The study protocol has been reviewed and published on the public ClinicalTrials.gov website and has been assigned the identifier NCT01929135.

The patients accepted for the study met the following inclusion criteria: age between 30 and 60 years old, at least 14 teeth (excluding third molars), and chronic periodontitis according to the Page and Eke classification.[12] Diabetics only were included in the study when considered to be controlled, which was confirmed by laboratory tests and the corresponding inter-consultation to the treating physician.

The exclusion criteria were as follows: inability to comply with the study protocol; receiving antibiotic therapy or non-steroidal anti-inflammatory drugs during the previous two months or using calcium channel blockers, phenytoin, cyclosporine, or any associated drug that might affect gingival tissue; periodontal treatment during the previous 12 months; autoimmune disorders (self-reported); uncontrolled or poorly controlled diabetes; undergoing systemic statin treatment; requiring antibiotic prophylaxis before periodontal treatment; or requiring non-steroidal anti-inflammatory drugs for postoperative pain management after periodontal treatment.

It was estimated that a total of 38 patients would be required for the detection of a difference between groups using a two-tailed α of 0.05 and a power of 0.90 for a comparison of two means if there was an absolute decrease of 1.2 mm in the clinical attachment level (CAL). Two parallel groups were formed (1:1): one group of 19 patients that received NSPT plus medicated 2% atorvastatin dentifrice, and a second group of 19 patients that received NSPT plus non-medicated dentifrice as a placebo.

NSPT consisted of two sessions of scaling and root planing of all the teeth until the root surface was considered to be smooth and clean. Patients in both groups had non-previous specific oral hygiene techniques. Therapy was accompanied by instructions for oral hygiene, using the Bass technique, providing the patients with soft toothbrushes and the appropriate dentifrice. Patients were also instructed on the use of dental floss. Oral hygiene technique including flossing was evaluated at each clinic session, confirming it to be done properly. Twice-daily brushing was indicated with 0.5 mL of dentifrice for 2 minutes, followed by the expectoration of excess dentifrice for 10 to 15 seconds, without rinsing or consuming liquids or solid foods for at least 30 minutes.

After treatment, both groups of patients were contacted via telephone every week by a secretary to record any reactions to the dentifrice and to remind the patients of their next evaluations.

Formulation of Medicated and Placebo Dentifrices

The dentifrices used in this study were manufactured in the laboratory of a known Chilean pharmacy[¶] and obtained by prescription. The dentifrice was either medicated with 2% atorvastatin (2 mg of atorvastatin x 0.1 mL of fluoride dentifrice) or was not medicated (placebo: fluoride dentifrice without atorvastatin).

The dentifrices were dosed in 5 mL syringes with each 0.5 mL measurement indicated to facilitate dispensing of the product and to ensure proper use. Each patient received 6 syringes, sufficient for one month of treatment.

Bias Control

To control sources of bias, an individual from the Administrative Department of the Universidad de los Andes (Daniela Carreño, Health Care Center, Universidad de los Andes) conducted random allocation of the medicated or placebo dentifrices, using a computer-generated random

table, prior to the periodontal clinical evaluation. The researchers (C.A. and Carolina Lopez, the Department of Periodontology, Faculty of Dentistry, Universidad de los Andes) were neither involved in the randomization process nor were they aware of the assigned groups in any of the outcome evaluations. Both the patients and the clinicians were blinded to the assignments until the end of the study. The atorvastatin dentifrice and the placebo dentifrice were identical in terms of taste, color, and consistency and were dispensed in the same manner.

Intra-examiner Calibration

Before beginning the study, intra-examiner calibration was achieved by twice making a record of the PD, CAL and BOP in five patients, with a 24-hour interval between first and second records. All teeth, excluding third molars, were measured by periodontal probing at 6 sites (mesiobuccal, mediobuccal, distobuccal, mesiolingual/palatal, mediolingual/palatal and distolingual/palatal). PD was defined as the distance from the gingival margin to the base of the clinical pocket for each site; CAL was measured as the distance between the base of the clinical pocket and the cement-enamel junction (CEJ) and BOP was considered to be positive if bleeding was present on

probing or at five seconds later. Calibration was accepted if the measurements at baseline and after 24 hours were within 1 mm at the 95% level (correlation coefficients between duplicate measurements; r = 0.95), indicating that there was no systematic bias in the measurements.

Periodontal Evaluation

Measurements were obtained at baseline and 1 month later (post-therapy).

The enrolled patients were examined by two calibrated examiners (C.A and C.L) using a basic examination instrument kit and a University of North Carolina no. 15 color-coded periodontal probe. The parameters evaluated were the following: periodontal inflamed surface area (PISA), mean probing depth (PD), percentage (%) of sites with PD 0–2 mm, percentage of sites with PD 3–4 mm, percentage of sites with PD ≥ 5 mm, mean CAL, percentage of sites with CAL 0–2 mm, percentage of sites with CAL 3–4 mm, percentage of sites with CAL ≥ 5 mm, bleeding on probing (BOP), gingival index (GI), [14] and percentage of clean surfaces of teeth (oral hygienic index, OHI).[15]

PISA was calculated via a Microsoft Excel spreadsheet# using data from CAL, gingival recession and BOP, as proposed by Nesse et al.[13]

PD was defined as the distance from the gingival margin to the base of the clinical pocket for each site. The mean for a full mouth was then calculated and registered simultaneously with the percentage of sites with PD 0–2 mm, 3–4 mm and ≥ 5 mm. In a similar manner, CAL was measured as the distance between the base of the clinical pocket and the cement-enamel junction (CEJ). The mean was calculated for the complete mouth, and the percentages of sites with CAL 0–2 mm, 3–4 mm and ≥5mm were also recorded. In addition, we recorded the percentage of sites with bleeding on probing (BOP). GI was recorded to assess the severity of gingival inflammation

as described by Löe,[14] and the oral hygiene index (OHI) was evaluated as described by O'Leary et al.[15]

Primary and Secondary Outcome Variables

The primary outcome was a change in the PISA. The secondary outcomes included PD, percentage of sites with PD 0–2 mm, percentage of sites with PD 3–4 mm, percentage of sites with PD ≥ 5 mm, CAL, percentage of sites with CAL 0–2 mm, percentage of sites with CAL 3–4 mm, percentage of sites with CAL ≥ 5 mm, BOP, GI, and OHI.

Statistical Analyses

Continuous variables were described by measurements of central tendency and dispersion. Dichotomous variables were tabulated and described by absolute frequencies and percentages according to each group. The delta of the outcome variables was calculated as the difference between measurements before and after intervention. Multiple linear regression models were used to compare the deltas of the outcome variables after adjusting for gender, diabetes and tobacco use. A p value of < 0.05 was considered statistically significant. The analysis was performed with Stata software (version 12; StataCorp, Lakeway Drive, College Station, TX, USA).

The CONSORT flowchart (Figure 1) shows the number of patients included in this study and the number for whom follow-up was not possible.[16]

A total of 36 individuals completed clinical evaluations at baseline and after one month of therapy. 2 individuals failed to report at follow-up due to health reasons and domestic problems. The mean ages and standard deviations (SDs) of the atorvastatin and placebo groups were 45.7 (SD: 9.1) and 45.4 (SD: 9.1) years old, respectively.

In the placebo group, seven women (63.64%) and six men (85.71%) had severe periodontal disease, while in the atorvastatin group, the disease was seen in ten women (71.43%) and four men (100%).

The two groups were not equivalent in their proportions according to gender, diabetes and tobacco use; thus, the outcome variables were adjusted for these variables.

The baseline variables of the study patients for each group are exhibited in Table 1.

RESULTS

Clinical Evaluation

None of the patients showed any adverse reactions to either of the dentifrice formulations (medicated with 2% atorvastatin or a non-medicated placebo).

Evaluation Outcome Variables

Figure 2 shows the baseline measurements and post-treatment (1 month later) measurements for both placebo and atorvastatin groups.

Table 2 presents the results of multiple linear regressions, with differences between the placebo and atorvastatin groups for delta variables adjusted for gender, diabetes, and tobacco use (at baseline and at 1 month follow-up).

The following variables: PISA, mean of PD, percentage of site with PD ≥ 5mm, mean of CAL, percentage of site with CAL ≥ 5mm, BOP and GI showed statistically significant differences. The decrease was greater in the atorvastatin group compared to the placebo group.

DISCUSSION

In the present study, the use of a statin (2% atorvastatin)-medicated dentifrice as a complement to non-surgical periodontal treatment of patients with chronic periodontitis resulted in improved clinical periodontal parameters compared with a placebo group. Improvements were statistically significant for PISA, the mean of PD, the percentage of sites with PD ≥ 5 mm, the mean of CAL, the percentage of sites with CAL ≥ 5 mm, BOP, and GI. Both of the groups showed an improved oral hygiene index; however, no statistically significant difference was identified, indicating that both groups maintained comparable levels of oral hygiene throughout the study.

These results are consistent with those of other studies that revealed improvements in periodontal status in patients taking statin medications. However, it is important to note that none of the other studies reported the effects of statins via dentifrice application, and for this reason, direct comparison between our study and other studies is not possible.[5,6]

Previous reports have shown that systemic statin treatment has protective effects against periodontal diseases.[17, 18] Cunha-Cruz et al. showed that regular statin use (at least one statin prescription during each of three consecutive years) was associated with a non-significant 37% reduction in tooth-loss rate (RR = 0.63; 95% CI = 0.32 to 1.25) in the ensuing fourth year.[17] In addition, Lindy et al. reported that patients with periodontitis who were taking statins had 37% fewer pathological periodontal pockets than patients who were not taking statins (p value = 0.00043), and the periodontal inflammatory burden index (PIBI) was 40% smaller (95% CI = 19.5 – 66.7) in patients taking statins than in those who were not (p value = 0.00069).[18]

In our study, the effects of statins were evaluated by assessing the PISA, for which we found a statistically significant decrease of 297.63 mm^2 in the atorvastatin group compared with the placebo group. PISA quantifies the amount of inflamed periodontal tissue (represented by the surface area of inflamed periodontal epithelium, measured in square millimeters), suggesting that this index quantifies the inflammatory burden posed by periodontitis.[13] This particular parameter of periodontal status has been associated with pathologies such as diabetes in which a dose-response relation with glycemic control (HbA1c level) has been observed, and an increase in PISA of 333 mm^2 was observed to be associated with a 1.0 percentage point increase in HbA1c, independent of any influences from other factors.[19] These data revealed PISA to be a relevant indicator of the magnitude of the inflammatory status of periodontal tissue. However, this method does not enable the cause of gingival recession to be established, though it is important to consider that in the present study, gingival recession was related to the presence of periodontal pockets and clinical attachment loss.

The major reductions in PISA, mean PD, BOP and GI in the atorvastatin group, may clinically reflect the anti-inflammatory effects of the statin because of, as mentioned in several studies, changes in inflammatory mediator levels.[20] Albert et al. evaluated the effects of pravastatin on C-reactive protein (CRP) and observed a decrease of 0.02 mg/dL (interquartile range = -0.10 to 0.02), which corresponded to a 14.2% reduction compared with baseline levels ($p < 0.001$). Compared with the placebo group, pravastatin was associated with a 16.9% reduction in median CRP levels (p value < 0.001).[21] In addition, patients with

hypercholesterolemia treated with pravastatin and simvastatin showed reductions in levels of TNF-α[22,23] and IL-1β.[23] Research in animal models has supported a direct anti-inflammatory effect of statins. Hernandez et al. showed a reduction in NF-kB binding activity in peripheral mononuclear cells and decreases in macrophage infiltration, interleukin-8 and metalloproteinase-3 in association with the administration of simvastatin 5 mg/kg/day in rabbits.[24] Moreover, Paumelle et al. showed statins as having acute anti-inflammatory properties through the peroxisome proliferator–activated receptor α (PPAR α), which inhibits the protein kinase C (PKC) signaling pathway, thereby regulating inflammatory-response genes.[25] Additionally, the atorvastatin group showed statistically significant differences in percentages of sites with PD ≥ 5 mm and CAL≥ 5 mm, indicating a pronounced change in the extension and severity of periodontal pockets compared with the placebo group.

With regard to the topical use of statins in periodontal disease, Pradeep et al. investigated the effectiveness of simvastatin in biodegradable controlled-release gel form in addition to scaling and root planing (SRP) in patients with chronic periodontitis.[5] This system showed that after 6 months, there were significant improvements in the modified sulcus-bleeding index (2.32; SD = 0.80), in PD (4.26 mm; SD = 1.5) and in CAL (4.36 mm; SD = 1.9) with 1.2% simvastatin compared with a placebo.[5] These authors also observed a decrease in intrabony defects assessed by radiology.[5] Similar results have been obtained in susceptible patients such as tobacco smokers and diabetics with chronic periodontitis after SRP plus the administration of 1.2% simvastatin gel directly into pockets.[26,27]

The atorvastatin used in our study is a lipophilic statin that appears to be more effective than other statins such as simvastatin, pravastatin, lovastatin and fluvastatin in reducing LDL and total cholesterol.[28] Recently Pradeep et al. showed the effectiveness of 1.2% atorvastatin in biodegradable controlled-release gel as adjunct to SRP in patients with chronic periodontitis.[6] 1.2% atorvastatin showed a slight improvement at 6 month compared to results obtained in previous study using 1.2% simvastatin. The periodontal bone defect filling was 34.05% with use of atorvastatin and 32.54% with simvastatin, the decrease in PD was 3.40 mm (SD = 0.56) with atorvastatin and of 1.20 mm (SD = 1.24) with simvastatin, and decrease in CAL was 4.20 mm (SD = 0.60) and 1.63 mm (SD = 1.99) with atorvastatin and simvastatin, respectively.[5,6] These findings may indicate that atorvastatin application could possibly have greater anti-inflammatory effects.

In the present study, a total of 4 patients had diabetes, 1 in the placebo group and 3 in the atorvastatin group. Diabetes is considered a risk and modifier factor for periodontitis, especially when it is poorly or not controlled.[29] On the other hand, periodontal disease, can also affect diabetes and its complications.[29]

In our study, only well-controlled diabetic patients were included, which was confirmed by laboratory tests and the corresponding inter-consultation to the treating physician.

Considering the high prevalence of diabetes in the population, and the potential benefits of periodontal therapy to diabetic's general health, we did not exclude these patients from the study.

A previous study evaluated the effect of irrigation of periodontal pockets with a 1.2% simvastatin gel compared to placebo gel, in addition to scaling and root planning in patients with type-2 diabetes. They observed that the group receiving simvastatin gel presented a greater reduction in probing depth, attachment gain, and improved bone filling.[27] This background,

points out the potential use of topic statins as complement of conventional periodontal treatment of high risk patients.

Another group of patients that have increased susceptibility to periodontal disease, are smokers. In our study, 11 smokers were included in the placebo group, and 5 in the atorvastatin group. Smoking is considered the main modifier risk factor for periodontitis.[30] Some of the mechanisms involved, are oxidative stress and immune disfunction.[30] Clinically, smokers have elevated bone resorption, and periodontal conventional therapy does not give good and predictable long term results.[30] Considering this background, and the potential benefits reported for statins at both immuno-inflammatory as well as bone metabolism level, it is reasonable and highly likely that this type of patients be particularly benefited of the use of statin applied topically as complement of NSPT.

Considering both conditions as potential confounding factor, in this study, statistical adjustment was performed when results were analyzed.

Consequently, well-controlled randomized double blind clinical trials should be performed to establish the potential use and effectiveness of this complementary therapeutic approach in patients with increased susceptibility.

We recognize that one limitation of our design lies in having only one control evaluation (at 1 month). However, we consider this follow-up period to be key, as it is within the recommended time for reevaluation of non-surgical periodontal therapy, [31] allowing us to evaluate the effects of atorvastatin-medicated dentifrice as a complement to the NSPT prior to making a decision with respect to further surgical maneuvers and thus avoiding costly treatments. Further studies that investigate the long-term effects of this therapeutic approach are very relevant.

Topical application of statins could have the added benefit of decreasing some adverse effects such as those that occur with antibiotics or antiseptics.[32] Myopathy and hepatotoxicity are two of the adverse effects of statins reported in the literature, [33] both of which may be prevented by using a local delivery system, thereby decreasing the concentration of drugs in the bloodstream and, simultaneously, maintaining tighter control over the drug than is possible with systemic drug use. The delivery system (statin-medicated dentifrice) proposed by our study could have an enormous effect because it is feasible that it might be used successfully by a large proportion of the population, with the advantages of low cost and easy application. This delivery system might also be used not only as a complement to therapy but also for prevention and maintenance. The benefits obtained from this delivery system could become particularly important when treating high-risk periodontal patients such as tobacco smokers, diabetic patients and other susceptible patients with altered immunological responses.

CONCLUSION

We observed that the use of a dentifrice medicated with 2% atorvastatin as a complement to non-surgical periodontal treatment was more effective in improving clinical periodontal parameters in patients with chronic periodontitis compared with the use of a placebo dentifrice in conjunction with identical periodontal therapy. Although longer-term, multicenter, randomized, controlled clinical trials are required to confirm these observations, our finding suggests a possible new direction for the management of periodontal disease.

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Corresponding Author: Dr. David Rosenberg, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Universidad de los Andes, Santiago, Chile; Monseñor Álvaro del Portillo12455, Las Condes - Santiago, Chile; Telephone: +56 9 75171583; Fax number: +56 2 24322017; E-mail address: drosenberg@uandes.cl. (E-mail address may be published)

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Figure 1.

Flow-chart of patients enrolled in the clinical trial.

Figure 2.

Box plots of baseline and post-treatment measurements for placebo and atorvastatin groups.

Table 1.

Baseline variables of patients by group (placebo and atorvastatin)

Variable	Placebo	Atorvastatin
	n = 18	n = 18
Male	7 (38.9%)	4 (22.2%)
Diabetes	1 (5.6%)	3 (16.7%)
Tobacco use	11 (61.1%)	5 (27.8%)
Moderate periodontitis	5 (27.8%)	4 (22.2%)
Severe periodontitis	13 (72.2%)	14 (77.8%)
PISA (mm^2)	735.72 (360.28)	1076.99 (564.91)
Mean of probing depth (mm)	2.54 (1.03)	3.72 (0.75)
Probing depth 0–2 mm (% of sites)	51.79 (29.23)	27.67 (15.69)
Probing depth 3–4 mm (% of sites)	31.69 (20.98)	32.94 (13.5)
Probing depth ≥ 5 mm (% of sites)	13.75 (18.48)	32.55 (21.38)
Mean of clinical attachment level (mm)	2.45 (0.91)	4.01 (2.46)
Clinical attachment level 0–2 mm (% of sites)	60.12 (29.93)	34.23 (43.76)
Clinical attachment level 3–4 mm (% of sites)	31.36 (18.77)	26.98 (10.43)
Clinical attachment level ≥ 5 mm (% of sites)	4.45 (8.24)	36.96 (40.32)
Bleeding on probing (% of sites)	50.73 (28.64)	83.64 (20.94)
Mean of recession	-0.02 (1.24)	0.03 (1.58)
Gingival index	1.83 (0.39)	1.69 (0.48)
Oral hygiene index (%)	1.08 (23.26)	0 (0)

Data are shown as numbers (%) or medians (interquartile ranges).

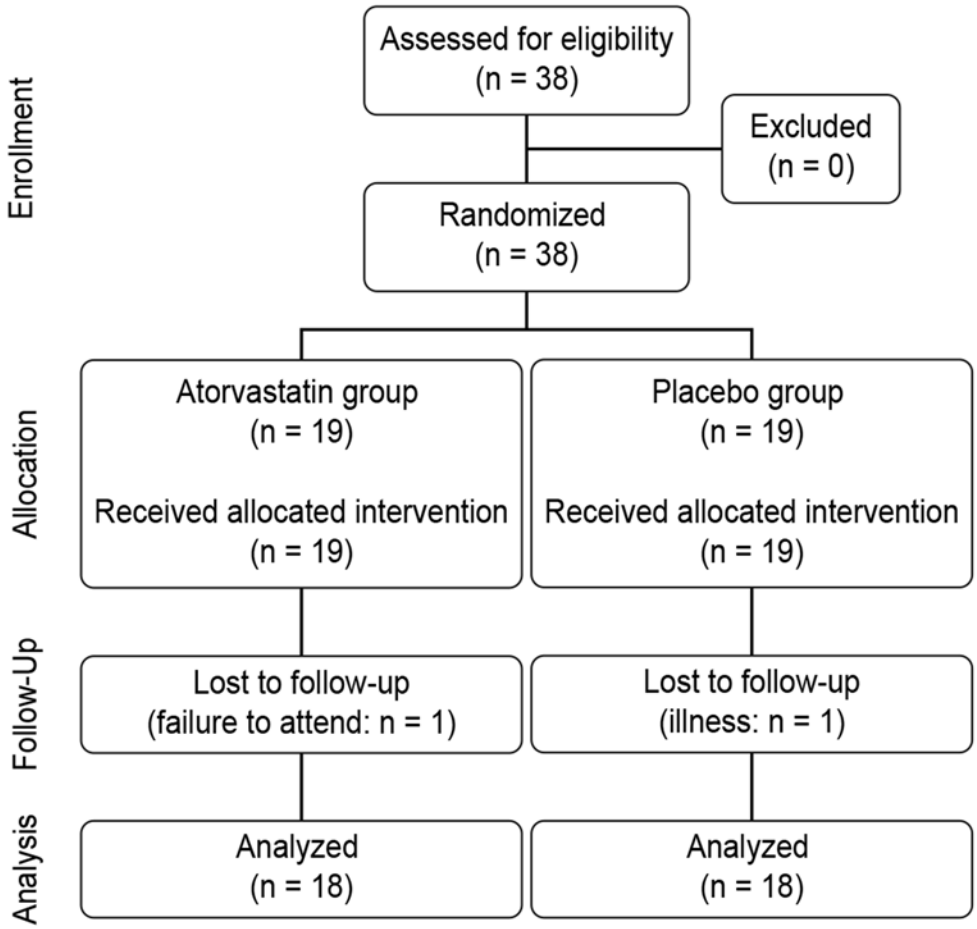
Table 2.

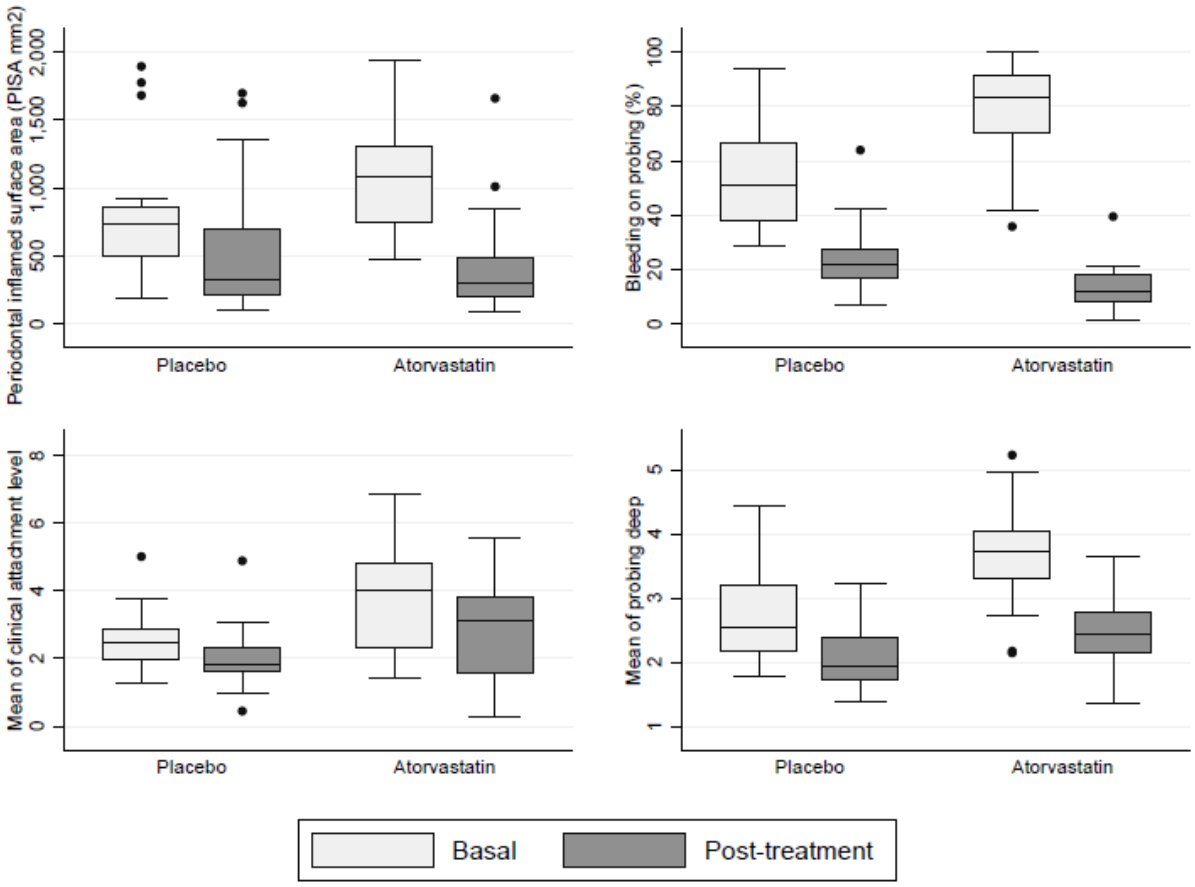
Adjusted difference between placebo and atorvastatin groups for delta variables (at baseline and 1 month follow-up)

Delta variable	Constant	Coefficient	p-value	Confidence interval (95%)
PISA mm^2	296.19	297.63	0.01*	76.04 - 519.23
Mean of probing depth (mm)	0.86	0.45	0.02*	0.08 - 0.83
Probing depth 0–2 mm (% of sites)	-28.07	-4.61	0.336	-14.23 - 5.01
Probing depth 3–4 mm (% of sites)	15.19	-6.21	0.315	-18.63 - 6.2
Probing depth ≥ 5 mm (% of sites)	10.10	13.43	0.002*	5.52 - 21.34
Mean of clinical attachment level (mm)	0.42	0.47	0.001*	0.22 - 0.72
Clinical attachment level 0–2 mm (% of sites)	-11.47	-3.61	0.308	-10.7 - 3.49
Clinical attachment level 3–4 mm (% of sites)	10.93	-3.02	0.423	-10.61 - 4.57
Clinical attachment level ≥ 5 mm (% of sites)	0.89	7.11	0.013*	1.61 - 12.61
Bleeding on probing (% of sites)	34.12	32.66	<0.0001*	19.7 - 45.63
Mean of recession	0.43	-0.01	0.947	-0.3 - 0.28
Gingival index	0.69	0.41	0.034*	0.03 - 0.79
Oral hygiene index	-44.29	1.31	0.908	-21.66 - 24.28

Adjusted for gender, tobacco use and diabetes (multiple linear regression)

*Statistically significant p value < 0.05


Enrollment
Assessed for eligibility
(n = 38)
Excluded
(n = 0)
Randomized
(n = 38)
Allocation
Atorvastatin group
(n = 19)
Received allocated intervention
(n = 19)
Placebo group
(n = 19)
Received allocated intervention
(n = 19)
Follow-Up
Lost to follow-up
(failure to attend: n = 1)
Lost to follow-up
(illness: n = 1)
Analysis
Analyzed
(n = 18)
Analyzed
(n = 18)


Periodontal inflamed surface area (PISA mm2)
0
500
1,000
1,500
2,000
Placebo
Atorvastatin
Bleeding on probing (%)
0
20
40
60
80
100
Placebo
Atorvastatin
Mean of clinical attachment level
0
2
4
6
8
Placebo
Atorvastatin
Mean of probing deep
1
2
3
4
5
Placebo
Atorvastatin
Basal
Post-treatment