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Effects of local and systemic Atorvastatin on inflammation and alveolar bone loss in experimental periodontitis in rats

Sara Masoumi,[a] Kamran Kouzeforush Abadi,[b] Shahin Setoudehmaram,[c] Nader Tanideh,[d] and Bahram Movahed[d]

[a]Department of Periodontology, International Branch, Shiraz University of Medical Sciences, Shiraz, Iran.
[b]International Branch, Shiraz University of Medical Sciences, Shiraz, Iran Medical Sciences, Shiraz, Iran.
[c]Orthodontic Research Centre, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran.
[d]Department of Pharmacology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.
Correspondence to Shahin Setoudehmaram (email: shahin2110@yahoo.com).
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Objectives The first cause of tooth loss in developed countries is periodontitis and mostly occurs in people over 40 years old. Atorvastatin is a statin drug class, which has a revolutionary impact on the treatment of high cholesterol and also stimulates bone morphogenic protein which has osteogenic potential. The aim of this study was to evaluate the effect of local and systemic Atorvastatin in the treatment of periodontitis.

Materials and Methods Forty eight Sprague Dawley rats were randomly divided into six groups of eight in each; experimental periodontitis was induced by ligature in five of them in each group daily (1) systemic Atorvastatin 12.5 mg/kg (2) systemic solvent (3) local Atorvastatin 0.25 mg/kg (4) local solvent (5) no drug was administered and group (6) left non-ligated, and rats were sacrificed on 11th day. Histopathological analysis on periodontal tissue; malondialdehyde (MDA) and superoxide dismutase (SOD) tests on serum were performed to investigate bone loss and inflammation. The statistical tests for MDA and SOD samples were one-way ANOVA with Duncan post-hoc whereas in histopathological samples nonparametric Kruskal–Wallis and Mann–Whitney tests were used.

Results Although local injection and oral administration of Atorvastatin significantly decreased alveolar bone loss and serum MDA levels, no significant difference in their effectiveness was observed. Serum SOD levels were not significantly changed in all administered groups. *P*-value < 0.05.

Conclusion In this study, both local injection and oral forms of Atorvastatin decreased inflammation and bone loss in periodontitis. However, no significant difference in their effectiveness was detected. However, local injection is superior to oral form due to effective lower dose.

Keywords atorvastatin, histopathology, periodontal disease, rat

Introduction

The first cause of tooth loss in developed countries is periodontitis and mostly occurs in people over 40 years old.[1] Periodontal disease is an inflammatory infection, which has been observed in the preserving tissues of teeth in sensitive individuals to this disease. The gingival disease affected by plaque (gingivitis) is reversible if it is limited to the gingiva and is different from the periodontal disease, which is chronic and aggressive. Chronic periodontitis is irreversible and if left untreated can result in tooth loss. According to the changing nature of the disease criteria, the prevalence of periodontitis is different in every study. The third international meeting of health and nutrition (NHANES III) has reported the prevalence of periodontitis in the moderate and severe situations is about 14% of the population older than 26 years in USA.[2]

Periodontitis is a multifactorial disease initiated by microbial plaque, but its spread and severity depend on the environmental factors, acquired diseases, and individual's genetic predisposition. Loosening of teeth, destruction of preserving tissue, and its loss is the most important factor of this disease.[3] The initial inflammatory response to the dental microbial plaque is leaded by polymorphonuclear neutronphils (PMN), which will detect the microorganisms of microbial plaque through their surface receptors. The activation of these receptors by the pathogen results in their phagocytosis and the secretion of pro-inflammatory cytokines such as IL-B, IL-6, IL12, and TNF-α, which cause periodontal tissue destruction. In the inflamed gingival, high levels of the tissue-degrading enzymes such as matrix metalloproteinases (MMPs) are found. MMPs cause the destruction of the extracellular matrix; including collagen, gelatin, and elastin, which will eventually result in periodontal tissue destruction and the loss of alveolar bone. When the inflammatory products reach the bone surface, bone destruction might start representing in this way the transition from gingivitis to periodontitis.[4]

Periodontitis with local inflammation that is made through the release of pro-inflammatory cytokines leads to increasing of systematic inflammation[5] and the accumulation of inflammatory mediators increase inflammatory activity in atherosclerotic plaque.[6,7]

Atorvastatin is a statin drug class that had a revolutionary impact on the treatment of high cholesterol through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA). The inhibitory impact of HMG-CoA reductase is usually attributed to their ability in the reduction of the synthesis of endogenous cells. Statins are responsible for a variety of biochemical changes including reduction of the cholesterol accumulation in macrophages, an increase of intracellular synthesis of NO, reduction of the inflammatory process and increase of the stability of atherosclerotic plaques.[8] Atorvastatin is also used to suppress metalloproteinase.[9,10] Statins reduce the production of mevalonate, geranyl pyrophosphate, and farnesyl pyrophosphate and the next production in a way to make cholesterol. Therefore, statins could prevent the inflammatory process by inhibiting the pathway of cholesterol and the interference with the performance of RAS family of proteins.[11] Statins are also the strong stimulants of protein forming bone morphology protein (BMP-2), which is the main inducer of the

potential bone formation. Simvastatin, Myostatin, and Atorvastatin induce the transcription of the BMP-2.[12]

Numerous laboratory animal species including non-human primates, dogs, rats, guinea pigs, Syrian hamsters, ferrets, and rice rats have been used in the pathophysiology study or preventive treatment tests for periodontitis control or its improvements.[13] In a study of Chang et al.,[14] Atorvastatin significantly reduced bone loss and the amount of IL-6 in serum and helped the formation of bone. In the study of Subramanian et al.,[5] the reduction of periodontitis and inflammation rate by Atorvastatin was stated as a finding. de Araújo Júnior et al.[8] mentioned the anti-inflammatory properties of oral Atorvastatin that is appeared by the reduction of cytokine expression and oxidative stress in the experimental periodontitis. Balli et al.[12] had an experiment on 100 rats in different periodontitis phases and found systemic and topical Atorvastatin effective in the first phase of periodontitis and suggested that it is useful in periodontal treatment as an implant substance.

In the cited studies, local effects of Atorvastatin on the inflammation and loss of alveolar bone in periodontitis has not been studied enough and no comparisons have been done from the different aspect of the effectiveness of local and systemic methods and there is also a need for expanded research to verify the effect of this essential drug.

The aim of this study is to evaluate the effect of local and systemic Atorvastatin in the treatment of periodontitis by measuring inflammation by malondialdehyde (MDA) and superoxide dismutase (SOD) tests from gingival samples and histopathology analysis of slices of alveolar bone of the rat's second molar teeth (experimental periodontitis induced by ligature).

Investigation Method

Animals

After statistical consultation, 46 rats from male Sprague Dawley race (to remove the effect of sex hormones) with the weight of 180–200 g and with the age of 8–12 weeks were used in this study.

Preparation of Solution

After the experiments, propylene glycol and phosphate buffer solution were chosen as solvents.

Periodontitis induction

After anesthesia through subcutaneous injection, animal ketamine hydrochloride 10% compound with a dose of 70 mg/kg and zylazine 2% with a dose of 10 mg/kg, ligature thread (3-0 ETHIBOND EXCEL polyester green-coated braided non-absorbable) was tied around the second molar teeth on the left side of maxillary and tied in the palatal area.

Grouping

The rats were randomly divided into six groups of eight in each and a control group without ligature thread was considered as a control to show the impact of experimental periodontitis.

First group

Oral Atorvastatin was administered by gavage method after the periodontitis induction for 10 days, 1 ml each day of oral solution and sacrificed on the 11th day.

Second Group

Like the first group, only the pharmaceutical solution was administered without pharmaceutical substance.

Third Group

After periodontitis induction for 10 days, 0.05 ml each day injection Atorvastatin was injected in buccal alveolar on the left side of maxillary second molar at the base of the teeth in a subperiosteal way by a 0.5 cc syringe and sacrificed on the 11th day.

Fourth Group

Like the previous group and only the injection solution without pharmaceutical substance was injected.

Fifth Group

After periodontitis induction for 10 days without any pharmaceutical substance. This group was sacrificed on the 11th day.

Sixth Group

This group was sacrificed with other groups without any kind of periodontitis induction and any pharmaceutical substance.

All animals were kept in the standard situation (12 h the day length and 12 hours the night length, at 22°C ambient temperature with access to food and water) in the groups.

All groups were transferred to the container of saturated ether for sacrificing and then they were sacrificed and beheaded and the soft tissue was separated from maxillary by scalpel and then put in 10% formalin with three times the volume of the sample for 3 days.

Superoxide Dismutase Test

Activity was measured by Misre and Fridorich process. This method is based on the autoxidation inhibition of adrenaline to adrenochrome SOD pH = 10.2. Adrenochrome absorbs light in 480 nm. Landa buffer solution 550 is prepared by 0.3 mol/l of $NaHCO_3NaCO$ with pH = 10.2 and 400 Landa of 0.075 EDTA and 750 Landa of 1.30 serum diluted sample. A control tube containing distilled water instead of the sample is also prepared. After a minute of adding 500 Landa of 1.8 nmol/l adrenaline, acid chloride solution (HCL) with pH = 2 is added to the control tube and test sample and the 280 nm absorption is read. Percentage of inhibition of adrenaline autoxidation against different standard SOD density was drawn. Using the above information and considering the amount of produced enzyme that perform 50% inhibition of adrenaline auto oxidation,[15] the result of SOD activity has been reported based on unit/mg protein or unit/ml.

Malondialdehyde Test

Malondialdehyde is an indirect index of lipid peroxidation and colorimetric is done based on the inactive TBARS acid. Approximately, 0.5 mm of serum is added to the 2 mm TBA reagent which includes 0.375% of TBA, 15% trichloroacetic acid and 0.25 mol of hydrochloric acid. The solution is boiled for 15 min and then cooled and centrifuged in 170 *g* for 15 min in 4°C.

Absorption of floating solution on the surface is measured in 523 nm and obtained in TBARS density by the calculation of TEP standard. The results are reported based on the nmol/mg of serum protein.[8]

Slide Preparation Steps

Declassifying

After taking samples out of formalin, maxilla is put in the 10% nitric acid for 72 h.

After removing the thread around the teeth, areas of premolar and molar teeth on the left were cut in the direction of back to front and parallel with the midsagittal axis. Each part is put in a dry capsule and in formalin for 12 h and then passed through autotechnicon machine containing the dishes of 70%, 80%, 96% and 100% formalin alcohol, xylene, and paraffin, respectively. After the above steps, molding is done with thin 5-micron slices of paraffin from the mid area of samples. To destroy, paraffin is put in the oven with 80°C for 45 min and then staining was done.

H&E Staining

To stain hematoxylin and eosin (H&E), samples were passed through three containers of xylelfor 3–10 min to remove the paraffin. In the next step, they were passed through ethylic alcohol 70%, 80%, and 96%, respectively, three times and each time for 1 min and put in hematoxylin after washing with water completely for 5 min and washed again to remove the extra stain. By adding 100 cc of 70% alcohol to 1 cc of 1% chloric acid, alcohol acid was obtained and it was entered to alcohol acid for 5 s, the samples then were entered to 2% ammonia water to fix the stain and then put in eosin for 1 min and after a complete wash they were taken to the container of 96 and 100% alcohol and three times to the xylelcontainer.

Histopathologic Study

Provided H&E slides were marked based on giving random numbers to the samples in each group and investigated by light microscope carefully and different magnifications in a blind way.

Investigation of Inflammation and Alveolar Bone Loss

The area between first and second molar teeth was studied with 40× magnification and parameters, such as infiltration of inflammatory cells; alveolar bone integrity and cementum were evaluated and graded as follows:

Score 0: Lack and little amount of infiltration of inflammatory cells, which are limited to the marginal gingiva and alveolar bone and cementum were preserved.

Score 1: Average infiltration of inflammatory cells (infiltration spreads through the gingiva), little loss of alveolar bone and cementum.

Score 2: Severe infiltration of inflammatory cells (outspread in the gingiva and PDL) and an average loss of alveolar bone and partial destruction of cementum.

Score 3: Severe infiltration of inflammatory cells, complete destruction of alveolar cells, and severe destruction of cementum.

Statistical Analysis

Statistical analysis was done for the analysis of the results of MDA and SOD tests by using one-way ANOVA with Duncan post-hoc test.

Statistical analysis was in a non-parametric way and with Kruskal–Wallis test to compare between groups and Mann–Whitney test was applied pairwise in different groups for grading of histopathological tests.

Kruskal–Wallis test was done with P-value < 0.05 care which indicates a significant statistical difference of grading variables of destruction (scores) and the number of the osteoclasts. This means that there is a difference among groups that this significant difference can be created by one difference of one group with all groups that was proved in Mann–Whitney test.

Results

SOD Test

In this test, the results were reported based on the serum amount of SOD with serum unit/mol unit. As it is observed, there is no significant difference among different groups, the maximum amount of SOD speed was reported in oral Atorvastatin (49.94), and the minimum amount was in an oral solvent (44.68) (Table 1).

MDA Test

In this test, the result is obtained based on the amount of MDA serum with nmol/mg unit. As it is observed, there is a significant difference (P-value ≤ 0.05) between the control group, injection Atorvastatin, oral Atorvastatin with other groups and the minimum amount was seen in the control group (1.22), and the maximum amount was in tied tread group (2.36) (Table2).

Histopathologic Evaluation

With Mann–Whitney test, there was a significant difference between the control group with the median of (0) and tied thread with the median of (3) (P-value = 0.000).

There was also a significant difference between injected Atorvastatin with the tied thread group (P = 0.001) and injected solvent (P-value = 0.004).

As it canbe seen in Table 3, the results of injected Atorvastatin were better than oral Atorvastatin, but there was no significant difference between these two groups (P-value = 0.228).

Table 1. **Mean amount of SOD (unit/ml) in the study groups**

Group	Mean	Std. deviation
Control	49.23	11.88
Tied thread	48.86	10.93
Oral atorvastatin	49.94	11.27
Oral solvent	44.68	12.42
Injected atorvastatin	43.79	11.31
Injected solvent	46.15	10.98

Table 2. **Mean amount of MDA (nmol/mg) in the study groups**

Group	Mean	Std. deviation
Control	1.22	0.49
Tied thread	2.37	0.71
Oral atorvastatin	1.45	0.52
Oral solvent	2.18	0.64
Injected atorvastatin	1.48	0.61
Injected solvent	2.10	0.77

Table 3. **Median distribution of histopathology score in the studied groups**

Group	Number	Median	Std. deviation
Control	8	0	0
Tied thread	7	3	0.57735
Oral atorvastatin	6	2	0.63246
Oral solvent	6	3	0.40825
Injected atorvastatin	8	1.5	0.53452
Injected solvent	7	3	0.48795

The maximum number of osteoclasts was counted in tied thread group and the minimum number was in the control group. The number of osteoclasts in Atorvastatin group was less than tied thread group.

The maximum amount of mixed inflammation was observed in tied thread group and the minimum amount was in injected Atorvastatin group. The maximum destruction of collagen was seen in the tied thread group and the minimum amount was in the control group.

The maximum amount of maxillary bone destruction in the studied groups was seen in the tied thread group and the minimum amount was in the control group and then oral Atorvastatin.

Discussion

The present study has shown that both systemic and topical Atorvastatin treatment had significant inhibitory effects on inflammatory changes and alveolar bone resorption following an experimental periodontic treatment in mice. It was also found that Atorvastatin is capable to inhibit inflammation and bone loss associated with collagen degradation.

An increase in oxidants and free radicals produced during inflammation is one of the mechanisms of tissue pathogenesis. It seems that increased serum levels of oxidants and decreased antioxidant enzymes promote inflammation and alveolar bone loss on cascade pathway by activation of proinflammatory cytokines, such as IL-6, IL-1, and TNF-α subsequently activated protease enzymes RANKL (osteoclast differentiation stimulator).

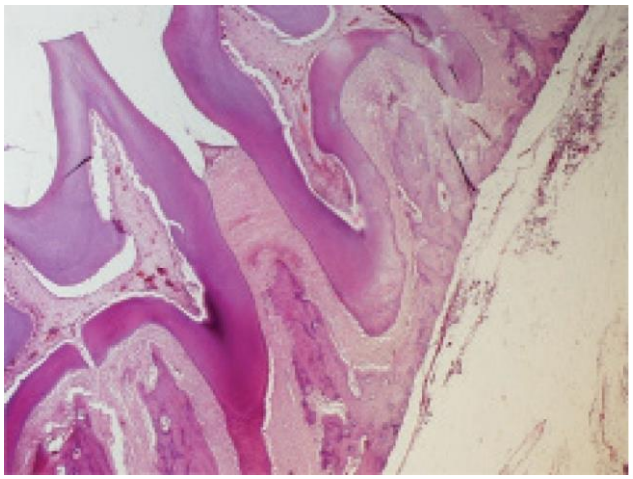

Fig 1. **Control group (H&E 40×) normal without periodontitis. Gingiva, cementum, bone, and collagen fibers are normal.**

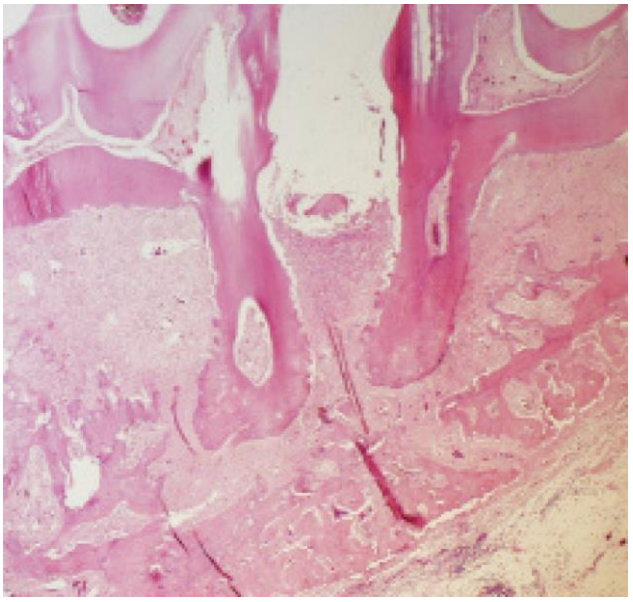

Fig 2. **Ligature threaded (H&E 40×) periodontitis group. Extensive loss of cementum and significant inflammatory cells infiltration.**

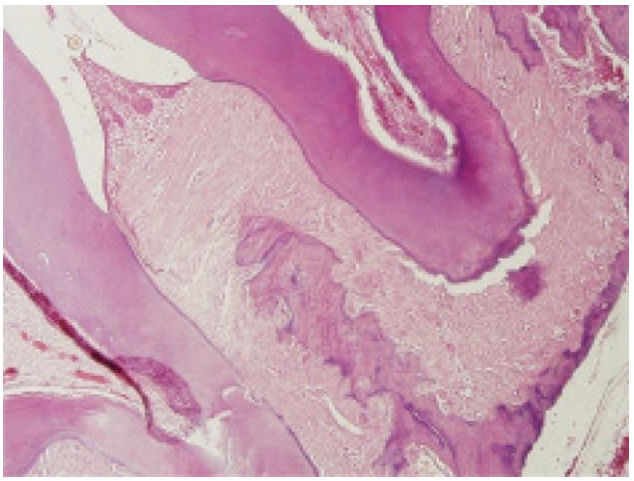

Fig 3. **Injected Atorvastatin group (score 1) (H&E 40×) little loss of alveolar bone and inflammation.**

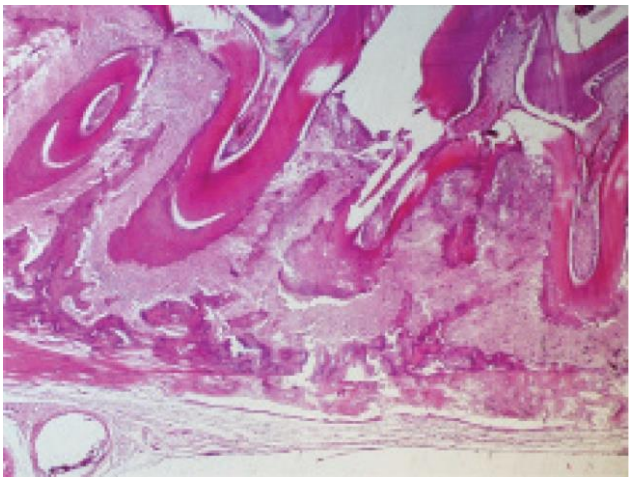

Fig 4. **Oral Atorvastatin group (score 2) (H&E 40×) severe infiltration of inflammatory cells in gingival, PDL and alveolar bone.**

Our result is consistent with other studies[15–17] demonstrated that the effectiveness of the oral administration of Atorvastatin to prevent the alveolar bone resorption and cartilage destruction in the experimental periodontitis.

Several authors have reported the successful use of Atorvastatin on periodontitis, by reducing tooth loss in patients with the chronic periodontitis,[15] exhibiting the fewer signs of inflammatory injury.[16]

In a study conducted by Bertl et al.[16] a significant clinical and radiographic improvements are obtained after local, but not systemic statin use as an adjunct to scaling root planning in deep pockets in patients with chronic periodontitis.

In another study, Sinjab et al.[17] found that adjunctive use of locally delivered statins to mechanical scaling and root planning is beneficial as it increases bone fill percentage. Improved inflammatory and bleeding control as well as probing depth reduction and clinical attachment level gain are possible following administration of these drugs in treating patients with chronic periodontitis.

In a study by de Araújo Júnior et al.[8] it has been reported that 10 mg/kg of Atorvastatin can reduce alveolar bone loss, proinflammatory cytokines, oxidative stress, and expression of extracellular matrix proteins, as well as RANK/RANKL while increases osteoprotegerin (OPG) in the periodontal disease in male Wistar albino rats.

In a study that was conducted by Chang et al.[14], he reported that Atorvastatin reduced the bone resorption parameters, including the Ca/Cr and P/Cr in 24 hours urine and the serum level of IL-6 can decrease the bone resorption and increase the bone formation. The results of this study have been consistent with the present study results.

In another study performed by Bali et al.[12] on 100 rats, it was for the first time that a study compared the effect of the local versus systemic Atorvastatin administration. They reported a positive effect of both administration paths on the periodontium by histomorphometry and immunohistochemistry tests.

The results of this study were in agreement with previous studies reporting the positive effects of Atorvastatin on periodontitis and have showed that Atorvastatin can prevent the alveolar bone loss at the macroscopic level in experimental periodontitis.[11,18]

Other studies showed a significant reduction of alveolar bone resorption and the collagen degradation in the experimental periodontitis after Atorvastatin administration.[21]

Based on the study conducted by Estanislau et al.[21] statins reduce bone resorption by inhibiting osteoclast forma tion. Bone formation is related to the increased gene expression of bone morphogenetic protein in osteoblasts.

Previous studies have shown that statins reduce the number of monocytes as precursors of Osteoclast.[22] Therefore, the reduction in the number of osteoclasts observed in the present study may be due to pleiotropic effects of statins on the osteoclast cells.

In our study after oral intake of Atorvastatin, the level of MDA decreased in rats in the experimental periodontitis model. It shows that lipid peroxidation has decreased. These results were confirmed by histological observation in which a reduction in the inflammation and destruction of the tissue was observed. Similar findings have been reported by de Araújo Júnior et al.[8]

Similar to previous studies, the level of mixed inflammation was lower in the Atorvastatin group. Some researchers believed that the oral intake of Atorvastatin could reduce the cytotoxicity and oxidative stress in experimental periodontitis.[12] Nassar et al.[11] compared the effect of topical and systematic Atorvastatin and reported the positive effects of both treatments on the periodontal tissue of the mouse using histomorphometry and immunohistochemistry tests. In the current study, both Atorvastatin treatments had decreased the inflammation and bone resorption but there were no significant differences between the topical injection and oral solution groups. Moreover, the dosage used in this study was determined based on the previous studies as well as the duration of treatment. The malondialdehyde test and histopathological study have shown that topical injection of Atorvastatin at 0.25 mg/kg dose was as effective as an oral solution at 12.5 mg/kg in reducing the inflammation and alveolar bone resorption in rats which had experimental periodontitis induced by ligature threads. The Atorvastatin dosage used in the topical treatment was 2% of that used in systemic treatment. Hence, considering the side effects of this drug in higher doses of the solution, the treatment with topical Atorvastatin may be the preferred method for this disease.

However, only in the recent study, the topical effects of Atorvastatin have been investigated. Furthermore, not enough comparative studies have been performed to investigate the difference in the effectiveness of the topical and systematic treatment. Therefore, additional experimental laboratory studies are needed on this field to find out the best treatment doses with the least side effects.

Conclusion

In this study, both local injection and oral forms of Atorvastatin decreased inflammation and bone loss in periodontitis. No significant difference in their effectiveness was detected. However, it seems that local injection is superior to oral form due to lower effective dose. n

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