ORIGINAL ARTICLE https://doi.org/10.52206/jsmc.2025.15.2.1083 OPEN ACCESS

# Comparison of Oral Metronidazole and Simvastatin Gels in Treating Periodontitis: A Randomized Clinical Trial

Faiza Hasan,[1] Rahila Ikram,[2] Afshan Abbas,[3] Syed Munawar Alam,[1] Syeda Zain,[4] Hamzah Kamran,[5] Huzaiz Kamran[5]

*1. Fatima Jinnah Dental College, Karachi, Pakistan*
*2. Ziauddin University, Karachi, Pakistan*
*3. Sir Syed College of Medical Sciences for Girls, Karachi, Pakistan*
*4. United Medical and Dental College, Karachi, Pakistan*
*5. National University of Sciences and Technology, Pakistan*

## ABSTRACT

**Background:** Periodontitis is an inflammatory disease of connective tissue and alveolar bone. Simvastatin (SIMV) is an antihyperlipidemic drug whereas metronidazole (MET) is a commonly used drug to treat chronic periodontitis. SIMV and MET administered sub gingivally have been shown to have bone-stimulatory and anti-inflammatory effects in patients with chronic periodontitis.
**Objective:** To evaluate and compare the efficacy of 1% MET with 1% SIMV gel on clinical parameters and inflammatory biomarkers in patients with chronic periodontitis.
**Materials and Methods:** This randomized clinical trial included 30 patients which were divided into 3 groups by block randomization method. Control group received only scaling and root planning (SRP). Group 1 received 1% MET gel and group 2 received 1% SIMV gel as an adjunct to SRP. Periodontal pocket depth (PPD), clinical attachment level (CAL), tooth mobility (TM), bleeding (BOP), periodontal and gingival index (PI and GI), TNF-α, $PGE_2$, and nitric oxide (NO) levels were measured. ANOVA was used for comparing the outcomes variables between groups followed by Tuckey's test.
**Results:** Mean PPD was reduced from 3.25 mm to 1.36 mm by 1% SIMV gel and it reduced PPD to a significant level ($p<0.05$) as compared to 1% MET gel. Mean CAL was reduced from 3.48 mm to 1.67 mm by 1% SIMV gel and it reduced CAL to highly significant level ($p<0.001$) as compared to control. TM was reduced from 1.10 mm to 0.50 mm by 1% SIMV gel ($p<0.01$). BOP ($p<0.001$), GI ($p<0.001$) and TNF-α ($p<0.05$) levels were reduced by 1% SIMV gel ($p<0.001$) as compared to 1% MET gel.
**Conclusion:** Gel containing 1% SIMV is more efficacious in decreasing the clinical parameters and inflammatory biomarkers as compared to gel containing 1% MET in treating periodontitis.
**Keywords:** Chronic periodontitis, Metronidazole, Simvastatin.

This article may be cited as: Hasan F, Ikram R, Abbas A, Alam SM, Zain S, Kamran H, et al. Comparison of Oral Metronidazole and Simvastatin Gels in Treating Periodontitis: A Randomized Clinical Trial. *J Saidu Med Coll.* 2025;15(2):243-249. https://doi.org/10.52206/jsmc.2025.15.2.1083

## INTRODUCTION

The most common and less invasive treatment for periodontitis is scaling and root planning. If this disease is not intercepted it can lead to periodontal attachment loss and may result in tooth loss. The most significant local factor influencing the development and occurrence of periodontitis are plaque and calculus on the surface of root in the periodontal pocket and subgingival plaque. Therefore, the ultimate objective of nonsurgical root and pocket instrumentation is to make free the root from calculus and microbial deposits.[1]

Nonetheless, treated areas with SRP may recolonize with a microbiota and regain the pretreated state. The use of local drug delivery methods including gels, mouthwashes, chips, fibers, microparticles and nanoparticles have all been suggested as adjuvant therapy due to the limitations of SRP in the treatment of periodontitis.[2]

*Correspondence: Dr. Faiza Hasan*
*Professor,*
*Fatima Jinnah Dental College, Karachi, Pakistan*
*Email: drfaiza77@hotmail.com*

*Received: September 24th, 2024 - 1st Revision: October 10th 2024*
*2nd Revision: March 07th 2025 - 3rd Revision: March 17th 2025*
*Accepted: March 18th, 2025*

Metronidazole is commonly prescribed orally as an adjunct to SRP by the periodontologist for the treatment of gingivitis and periodontitis. It may not have been the right decision to use prophylactic antibiotics as an additional therapy for periodontitis in patients with normal general health conditions because of their potential side effects.[3]

Plenty of literature is available on the local delivery of metronidazole in treating periodontitis and they found it to be effective as an adjunct to SRP. Pavia et al. performed a meta-analysis to assess the impact of local MET along with SRP on PPD and CAL at follow-up intervals of 4, 8, 12, 24, and 36 weeks. All comparisons showed a substantial decrease in mean PPD.[4] Nandan et al. reported that the use of MET showed considerable improvement in both clinical and microbiological parameters adjunct to SRP in patients with periodontitis.[5]

SIMV inhibits the synthesis of cholesterol by lowering cholesterol levels. But in recent years, evidence shows that statins have a variety of vascular effects apart from decreasing cholesterol. It has been demonstrated that statins have significant anti-inflammatory and antioxidative effects. TNF-α, IL 6, IL 8 and MMP-9 can contribute to the tissue damage caused by chronic periodontitis and the statins causes the suppression of

these markers. Moreover, statins may promote the synthesis of VEGF and bone morphogenetic protein-2, which are responsible for bone formation. Therefore, it appears plausible that statins may offer protection against both chronic periodontal disease and cardiovascular disease.[6]

Yang et al. found that SIMV may diminish bone loss associated with inflammatory condition.[7] Bradley et al. used macromolecular SIMV prodrug in multiple doses of 1.5 mg locally and found decreases amount of inflammation and bone loss in experimentally induced periodontitis in rats.[8]

In periodontal therapy, SIMV is a new pharmacological drug that is used as a host modulatory agent.[9] Thus, this study was conducted to evaluate and compare the efficacy of 1% MET gel with 1% SIMV gel as a local drug delivery system adjunct to SRP in reducing the clinical parameters and inflammatory biomarkers in patients with chronic periodontitis.

## MATERIALS AND METHODS

The study design was approved by the International Center for Chemical and Biological Sciences' Independent Ethics Committee and Board of Advanced Studies and Research Committee, KU (IEC-029-HS-2017/Protocol/1.0). The research was conducted from 15th February 2022 to August 2022 at the University of Karachi, HEJ Research Institute of Chemistry and Department of Pharmacology. This study was not previously included into any database. Prior to the start of study procedures, written informed signed consent was obtained from each patient, followed by intra-oral and periodontal examination of the patient including their complete medical and dental history.

Sample size calculation was done on mean PD values between each study and control group retrieved from previous research,[16] using 95% confidence level and statistical power of 80% to detect a significant difference. The total calculated sample size was at least 10 in each group (control=10, study group 1=10 and study group 2=10). Throughout the trial, the examiner and participants were kept blinded, until the trial was completed (double-blinded study). In order to maintain a consistent sample size between groups throughout time, the randomization process was based on a block randomization technique with a set block size of three. Block randomization method was used to randomized subjects in each study group using Rand function on excel sheet.

Systemically healthy patients both male and female having at least 20 teeth present, age between 25 to 55 years were included in the study. Smokers, lactating mothers, patients who received any antibiotics or any other medications were excluded from the study. Patients who received any periodontal treatment for two years were also excluded.

Intra-examiner calibration was done 24 hours prior the initiation of the study. Five patients were examined twice and if the readings at baseline and after 24 hours were close to 1mm at the 95% confidence interval, the calibration was acceptable.

To prepare MET gel, 5 gm of MET was gradually added to propylene glycol to form a clear solution, through constant stirring using a magnetic stirring hot plate (IKA Works Inc.) at a temperature of 100-150°C. Warm water was used to dissolve the preservatives, which included 0.5 mg of EDTA, 0.75 mg of propylparaben sodium, and 1 gram of methylparaben sodium. Then the preservative-containing solution was added to the Carbopol 940 P gel. After that, 500 gram of MET 1% gel was created by adding the MET solution to Carbopol gel (containing the preservatives) at room temperature.[10]

To prepare SIMV gel, 20mg SIMV tablets (200 tablets) were dissolved in distilled water. Warm water was used to dissolve the preservatives, which included 0.5 mg of EDTA, 0.75 mg of propylparaben sodium, and 1 gram of methylparaben sodium. Then the preservative-containing solution was added to the Carbopol EDT 2020 gel. After that, 500 g of SIMV1% gel was created by adding the simvastatin solution with mild stirring using magnetic stirring hot plate (IKA Works Inc.) to Carbopol gel (containing the preservatives) at room temperature.[11]

The two formulations' pH, viscosity, spreadability, mucoadhesiveness, and syringeability were evaluated. Using the agar diffusion method, the lowest inhibitory concentration of 1% MET gel was determined. Additionally, a total microbiological count test was run to confirm the gels' quality.[12]

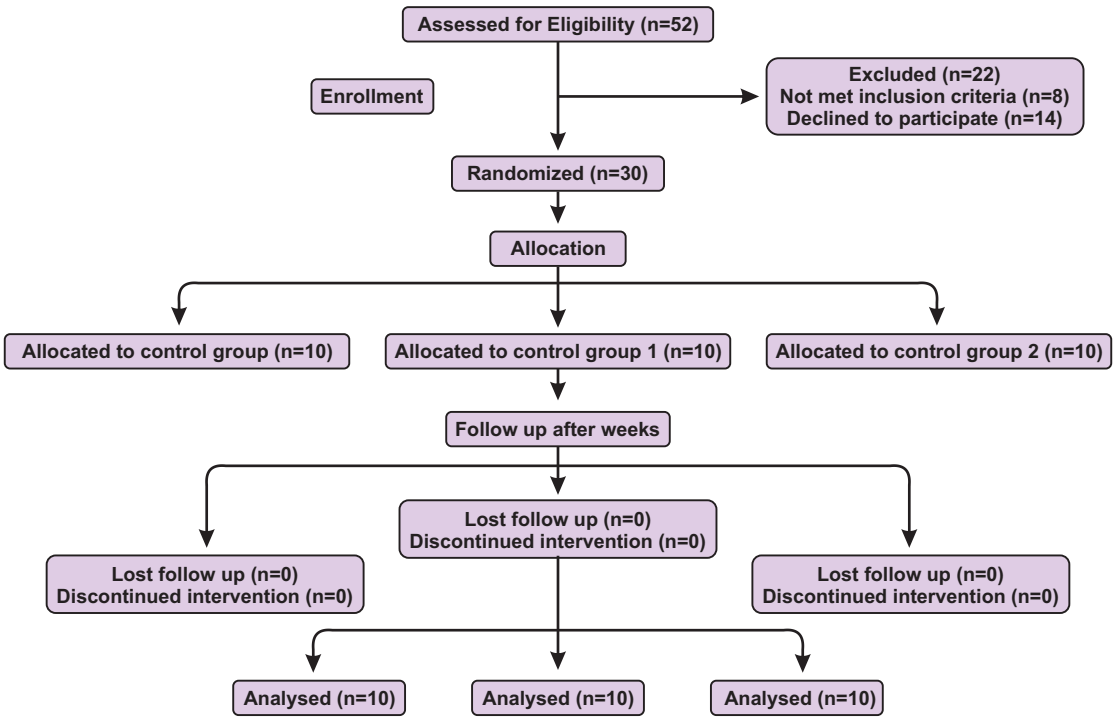
The Control group only received SRP. Study group 1 received SRP followed by the administration of 1% MET gel in to the periodontal pocket with a 25-gauge needle after 24 hours once a week for four weeks. Study group 2 received SRP followed by the administration of 1% SIMV gel in to the periodontal pocket with a 25-gauge needle after 24 hours once a week for four weeks.

Clinical parameters including PPD, CAL, TM, BOP, PI and GI, gingival index[13,14] was recorded at day 0 (baseline) and after 4 weeks of gel treatment.

The saliva samples were collected to measure the level of TNF-$^{\alpha}$[15], $PGE_2$ [16] and NO[17]at baseline and after four weeks of treatment. To prevent changes in antioxidants the samples were collected in between 11 to 12 noon. The patients were told to bend forward so that the unstimulated saliva flow into a sterile container and from each patient 3–5 milliliters of saliva was collected. Before being sent to the laboratory for centrifugation, saliva samples were stored at -20°C in refrigerator.

After that, the saliva samples were centrifuged for 10 minutes at a force of 12000 gm in order to eliminate cell debris. The clear supernatant fluid was pipetted and about 500 µl was stored in microtubes and stored at −80°C. The samples were thawed two hours before the measurement of biochemical variables, and was done by using an ELISA kit (Invitrogen California).

Data analysis was done using SPSS and the readings were plotted as Mean ± SD. To compare the clinical parameters and biochemical variables between study groups and control groups, ANOVA was used and post hoc Tuckey test was used for comparison of the outcome variables between the three groups.




**CONSORT Flow Chart**

## RESULTS

Mean PPD reduced from 3.25±0.35 mm to1.36±0.24 mm by 1% SIMV gel after 4 weeks ($p<0.01$). A comparison of PD values showed a significant decrease in both study groups as compared to control ($p<0.0001$). 1% SIMV gel showed slight reduction in PD as compared to 1% MET gel ($p<0.05$) (Figure 01). CAL decreased from 3.48±0.52 mm to 1.67±0.51mm in the SIMV study group 4 weeks after the intervention. A comparison of CAL values showed a significant decrease in 1% SIMV study group compared to control ($p<0.0001$). Within the study groups 1% MET gel showed significant reduction in the mean of CAL from 4.55±1.66 mm to 2.47±0.83 mm ($p<0.01$) after four weeks (Figure 02). Only 1% SIMV gel showed statistically significant reduction in TM within study groups after four weeks with mean value reduced from 1.10±0.19 to 0.50±0.10 ($p<0.01$) (Figure 03).

Comparison within in the study group showed statistically high significant reduction ($p<0.001$) in BOP in both study groups with change in mean values from 1.00±0.20 to 0.13±0.02 by 1% MET gel and 0.85±0.29 to 0.02±0.01 by 1% SIMV gel respectively. A comparison of mean of BOP showed a statistically high significant reduction in 1% SIMV gel group ($p<0.001$) as compared to control group (Figure 04). A statistically high significant reduction in PI ang GI was observed in both study groups ($p<0.001$) as compared to control group. Within the study groups 1% MET gel showed significant reduction ($p<0.01$) in GI with change in mean values from 2.51 ± 0.36 to 0.73±0.15. Among the groups 1% SIMV gel showed highly significant reduction ($p<0.001$) in GI as compared to 1% MET gel (Figure 05 and 06).

Among the groups 1% SIMV gel showed reduction in TNF-α level ($p<0.05$) as compared to 1% MET gel group with high reduction in mean value from 75.08±2.28 to 11.33±2.13. 1% MET gel showed slight reduction in TNF-α levels ($p<0.05$) as compared to control group. Significant changes were observed in $PGE_2$ level as compared to control ($p<0.05$) but no significant difference was observed among and within the groups. A highly significant reduction in NO level was observed in 1% MET group with change in mean value from 64.13±2.29 to 28.35±2.83, and 1% SIMV group with change in mean value from 65.29±2.24 to 18.8±2.48 ($p<0.001$) as compared to control group. No significant changes are observed in NO levels among and with the groups (Table 01).

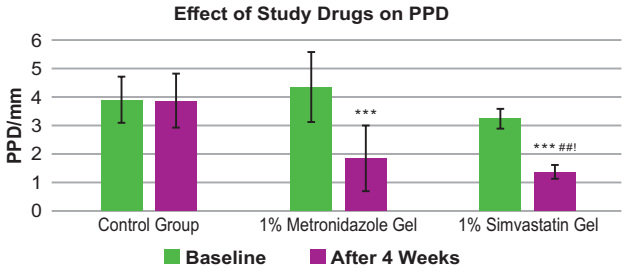



**Figure 01. n=30, Mean ± SD.*** p<0.001 when compared to the control group. ## p-value <0.01 when compared within a study group.! p<0.05 when compared among study groups.**

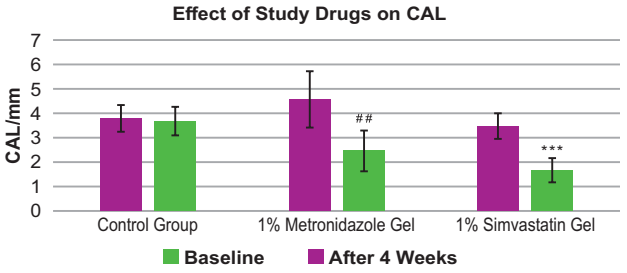



**Figure 02. n=30, Mean ± SD.*** p<0.001 when compared to the control group. ## p-value <0.01 when compared within a study groups.**

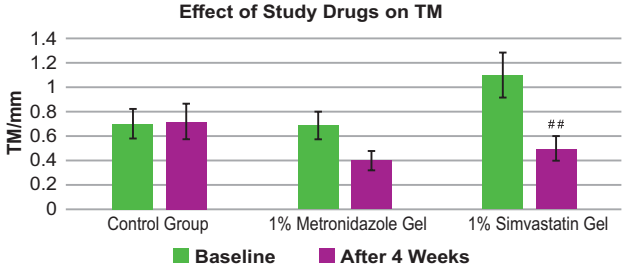



**Figure 03. n=30, Mean ± SD. ## p-value <0.01 when compared within a study groups.**

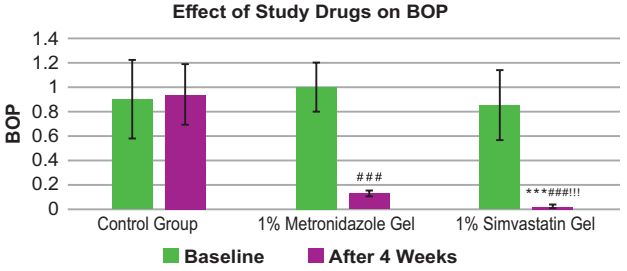



**Figure 04. n=30, Mean ± SD, score scale=0-1. *** p<0.001 when compared to the control group. ### p-value <0.001 when compared within a study groups. !!! p<0.001 when compared among study groups. BOP score scale=0-1**

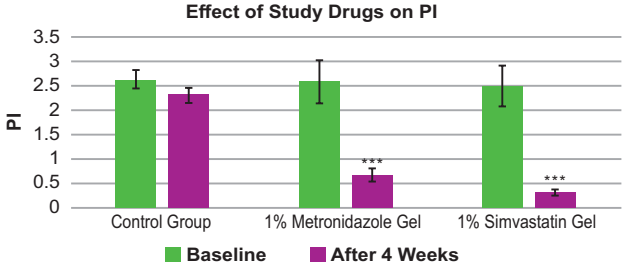



**Figure 05. n=30, Mean ± SD, score scale 0-3. *** p<0.001 when compared to the control group. PI score scale=0-3**

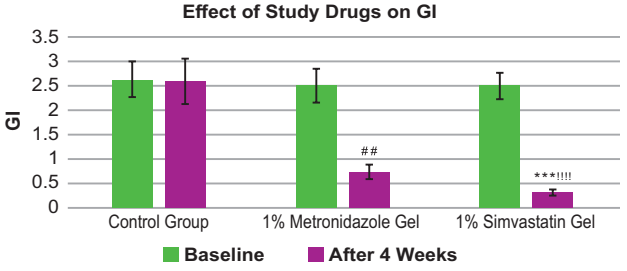



**Figure 06. n=30, Mean ± SD, score scale 0-3. *** p<0.001 when compared to the control group. ## p-value <0.01 when compared within a study groups. !!! p<0.001 when compared among study groups. GI score scale=0-3**

**Table 01. Measurement of TNF-α, $PGE_2$ and NO**

| Variables | Study Groups (n=30) | Mean ± Standard Deviation | | P-value |
|---|---|---|---|---|
| | | Baseline | After 4 Weeks | |
| Measurement of TNF-α (pg/ml) | Control Group | 46.26 ± 1.78 | 41.85 ± 1.78 | 1.0 |
| | 1% Metronidazole Gel | 75.03 ± 1.23 | 31.15 ± 1.19 | 0.03* |
| | 1% Simvastatin Gel | 75.08 ± 2.28 | 11.33 ± 2.13 | 0.3! |
| Measurement of PGE2 (pg/ml) | Control Group | 94.90 ± 2.26 | 93.9 ± 2.46 | 0.6 |
| | 1% Metronidazole Gel | 85.57 ± 1.23 | 8.28 ± 1.56 | 0.01* |
| | 1% Simvastatin Gel | 91.09 ± 1.13 | 21.78 ± 1.53 | 0.01* |
| Measurement of NO (µmol/ml) | Control Group | 62.47 ± 0.75 | 61.72 ± 0.67 | 0.5 |
| | 1% Metronidazole Gel | 64.13 ± 2.29 | 28.35 ± 2.83 | <0.001 |
| | 1% Simvastatin Gel | 65.29 ± 2.24 | 18.8 ± 2.48 | <0.001 |

## DISCUSSION

In the present study the clinical effectiveness of 1% SIMV gel was compared to 1% MET gel after SRP in patients with periodontitis. Many studies were conducted on MET gel since many years but to the best of our understanding, only few studies were conducted on SIMV gel in treating periodontitis.

In this study a significant reduction was found in PPD in 1% MET gel group as compared to control group after treatment of four weeks (P<0.001). Bergamasch et al.[18] measured the PPD and found that after the topical administration of 15% metronidazole gel PPD reduced significantly in periodontitis patients as compared to placebo group. The results of their study are same as that of our study but less concentration of gel improved the PPD in our study because the mode of administration of gel is different in both studies (gel administered in to the periodontal pocket versus drug applied topically). The administration of gel into the periodontal pocket provides good drug penetration and prevent the emergence of resistance bacteria at the diseased site.

In the present study 1% SIMV gel reduced the PPD and CAL very effectively (p<0.001) as compared to control after four-week treatment. 1% SIMV gel was found to be more effective in reducing PPD (p<0.05) as compared to 1% MET gel. No significant changes in CAL were found when comparing among both the study groups. Amy et al.[19] also found the same results that after the administration of 1% SIMV gel the PPD and CAL in patients with periodontitis was reduced significantly as compared to placebo group.

BOP is very reliable sign of a certain degree of sulcus lining erosion and/or sulcular epithelium ulceration. It is also an indicator of significant residual deposits of calculus in the subgingival area. In our present study, 1% SIMV gel reduced BOP to significantly high level as compared to control group (p<0.001) and 1% MET gel group. Jambhekar et al.[20] in a recent study also found that on comparison between the control group, SIMV group, and tetracycline group (another conventional drug used to treat periodontitis locally), the modified sulcular bleeding index was changed to a significant level by SIMV group after one month as compared to other groups.

In this study, PI was highly decreased by both gel groups as compared to control group (p<0001). 1% SIMV gel reduced GI to very high significant level as compared to 1% MET gel (p<0.001). 1% SIMV gel showed decreased in GI reduction to a significantly high level (p<0.001) as compared to 1% MET gel. Our results are in accordance with the results of Gunjiganur et al.[21] who also found reduction in PI and GI in patients with periodontitis following the administration of 1.2% SIMV gel as an adjunct to SRP as compared to control group who received only SRP. Thus, it has been suggested that SIMV may have an outstanding role in the treatment of periodontal infections due to its numerous anti-inflammatory properties.

Numerous anabolic effects of statins on bone metabolism have been thoroughly reported. Statins induce the development of osteoblastic bone marrow stem cells (BMP-2) by upregulating the bone morphogenic prot-2 gene expression. They also encourage the formation of new bone by keeping osteoblasts from going through apoptosis. Therefore, it is well known that statins have a negative effect on osteoclast cells during the remodeling of bone, thereby slowing down the rate of bone resorption. Previous studies showed that anabolic effect produced by systemic administration of statins in rats in vivo has not been confirmed by several investigations. But there was an increase formation of cortical bone and a partial suppression of osteoporosis, when statins were given locally.[22] Larger human trials, however, did not support statins' favorable effects on bone. Our research showed that TM was reduced to significant level by 1% SIMV gel after 4 weeks (p<0.01) but we found no significant reduction when we compared SIMV gel group with 1% MET gel group and control group. It has been suggested that no positive results were found in terms of tooth mobility due to short duration of the study.

TNF-α is secreted by activated macrophages and monocytes. It has a role in immune response regulation, substance metabolism regulation, inflammatory response regulation, and many other processes in addition to its antitumor action. TNF-α is higher in chronic periodontitis and activates osteoclasts and hence bone resorption. It can also stimulate formation of osteoclast-like cells, dissolve and cause destruction of connective tissue by producing $PGE_2$ and metalloproteinases as mediators. Thus, TNF-alpha plays a leading role in resorption of alveolar bone, the breakdown of periodontal ligaments, and the loss of periodontal attachment. In addition to stimulating cytokine synthesis and secretion, the endotoxin generated by G-anaerobes during periodontitis can also raise TNF-α concentrations in patient peripheral blood, gingival crevicular fluid, and local periodontal tissue. The results of our study showed that TNF-alpha levels were reduced significantly by 1% SIMV gel as compared to conventional 1% MET gel (p<0.05). The results of this study are in accordance with the study done by Bahammam etal.[23] who also found that TNF-α levels were reduced with SIMV usage in patients with periodontitis. Yang et al.[24] used Dendropanax morbiferus leaves extract, which has anti-inflammatory and antioxidant property in ligature induced periodontitis in rats. He observed decrease levels of $PGE_2$ in rat models. We also observed in our study that $PGE_2$ levels decreased by both study groups as compared to control (p<0.05) which shows the anti-

inflammatory and anti-oxidant properties of SIMV and MET, however we didn't find any significant difference between the two study groups and among the two study groups.

Another inflammatory biomarker in saliva is NO, a free radical gas. Free radicals are species which when secreted in the right amounts are advantageous to the host; they can function as potent antibacterial agents or assist in controlling the endothelium's vascular tone. In healthy individuals, there is an appropriate equilibrium between free radicals and their scavengers. When the generation of free radicals is elevated, this equilibrium can be set off, leading to significant cell damage that can eventually cause inflammatory conditions of the periodontal and periapical tissues, as well as precancerous and cancerous lesions in the oral cavity. In this study we found that use of both 1% SIMV gel and 1% MET gels after SRP reduced the level of NO to a significantly high ($p<0.001$) level as compared to control group who received only SRP. Similar results were also observed by Wadhwa et al.[25] in smokers with chronic periodontitis after SRP.

## CONCLUSION

It was concluded from the study that 1% SIMV gel is found to be better than 1% MET gel in reducing the clinical parameters and inflammatory biomarkers in treating periodontal disease. The potential advantage of locally applied SIMV in residual, inflammatory periodontal pockets in patients undergoing periodontal care has been established based on the findings of this clinical investigation. The significant improvement in periodontal clinical parameters and inflammatory biomarkers combined with the efficiency of the procedure makes its use practical in a clinical setting. Thus, the anti-inflammatory properties of SIMV may have potential role in host regulation, and it may provide a novel approach in the treatment of periodontal disease.

### Ethical Consideration

This study was approved by Institutional Review Board of Karachi University, Pakistan.

### Funding

There is no role of any funding agency in this study.

### Conflict of Interest

Authors declared no conflict of interest.

## REFERENCES

1. Yan Y, Zhan Y, Wang X, Hou J. Clinical evaluation of ultrasonic subgingival debridement versus ultrasonic subgingival scaling combined with manual root planning in the treatment of periodontitis: study protocol for a randomized controlled trial. *Trials.* 2020 Jan 28;21(1):113. https://doi.org/10.1186/s13063-019-4031-y
2. Raj SC, Mishra AK, Mohanty D, Katti N, Pattnaik S, Patra L, et al. Comparative evaluation of the clinical and radiographic efficacy of 0.05% zoledronate gel as local drug delivery system in treating intrabony defects in stage III grade B periodontitis patients with and without type-2 diabetes mellitus-A randomized split-mouth clinical trial. *Clin Adv Periodontics*. 2023 Jul 20. https://doi.org/10.1002/cap.10262
3. Qureshi A, Bokhari SAH, Haque Z, Baloch AA, Zaheer S. Clinical efficacy of scaling and root planning with and without metronidazole on glycemic control: three-arm randomized controlled trial. *BMC Oral Health*. 2021 May 12;21(1):253. https://doi.org/10.1186/s12903-021-01620-1
4. Pavia M, Nobile CG, Bianco A, Angelillo IF. Meta-analysis of local metronidazole in the treatment of chronic periodontitis. *J Periodontol.* 2004 Jun;75(6):830-8. https://doi.org/10.1902/jop.2004.75.6.830
5. Nandan B, Barman RD, Pant VA, Gupta V, Bhaduria U, Kaur H, et al. Comparative Evaluation of Cost-Effectiveness, Clinical and Microbiological Parameters of Systemic Antibiotics Versus Local Drug Delivery in Aggressive Periodontitis. *Cureus*. 2022 Jan 6;14(1):e20985. https://doi.org/10.7759/cureus.20985
6. Rao NS, Pradeep AR, Bajaj P, Kumari M, Naik SB. Simvastatin local drug delivery in smokers with chronic periodontitis: a randomized controlled clinical trial. *Aust Dent J*. 2013 Jun;58(2):156-62. https://doi.org/10.1111/adj.12042
7. Yang CN, Kok SH, Wang HW, Chang JZ, Lai EH, Shun CT, et al. Simvastatin alleviates bone resorption in apical periodontitis possibly by inhibition of mitophagy-related osteoblast apoptosis. *Int Endod J*. 2019 May;52(5):676-688. https://doi.org/10.1111/iej.13055
8. Bradley AD, Zhang Y, Jia Z, Zhao G, Wang X, Pranke L, et al. Effect of Simvastatin Prodrug on Experimental Periodontitis. *J Periodontol*. 2016 May;87(5):577-82. https://doi.org/10.1902/jop.2016.150599
9. Chen N, Ren R, Wei X, Mukundan R, Li G, Xu X, et al. Thermoresponsive Hydrogel-Based Local Delivery of Simvastatin for the Treatment of Periodontitis. *Mol Pharm*. 2021 May 3;18(5):1992-2003. https://doi.org/10.1021/acs.molpharmaceut.0c01196
10. Rahman S, Gv G, Mehta DS. A clinico-microbiological and biochemical study evaluating the adjunctive use of antimicrobial photodynamic therapy and local drug delivery of 1.2 % simvastatin gel compared to scaling and root planning alone. *Photodiagnosis Photodyn Ther.* 2020 Dec; 32:102017. https://doi.org/10.1016/j.pdpdt.2020.102017
11. Pham DT, Phewchan P, Navesit K, Chokamonsirikun A, Khemwong T, Tiyaboonchai W. Development of Metronidazole-loaded In situ Thermosensitive Hydrogel for Periodontitis Treatment. *Turk J Pharm Sci.* 2021 Sep 1;18(4):510-516. https://doi.org/10.4274/tjps.galenos.2020.09623

12. Shetty B, Karegowda P, Khan SF, Yadalam U, Nambiar M. Comparison of simvastatin 1.2% gel and alendronate 1% gel in chronic periodontitis as local drug delivery: A randomized clinical trial. *J Indian Soc Periodontol.* 2022 Nov-Dec;26(6):591-599. https://doi.org/10.4103/jisp.jisp_37_22
13. Yan Y, Zhan Y, Wang X, Hou J. Clinical evaluation of ultrasonic subgingival debridement versus ultrasonic subgingival scaling combined with manual root planing in the treatment of periodontitis: study protocol for a randomized controlled trial. *Trials*. 2020 Jan 28;21(1):113. https://doi.org/10.1186/s13063-019-4031-y
14. Peikert SA, Fischer A, Kruse AB, Al-Ahmad A, Woelber JP, Vach K, et al. Adjuvant Transgingival Therapy with Visible Light Plus Water-Filtered Infrared-A (VIS + wIRA) in Periodontal Therapy-A Randomized, Controlled, Stratified, Double-Blinded Clinical Trial. *Antibiotics (Basel).* 2021 Mar 3;10(3):251. https://doi.org/10.3390/antibiotics10030251
15. Chen X, Wang L, He Z, Zhao H, Cai Y, Song S, et al. Effects of xipayi mouth rinse combined with minocycline on localized aggressive periodontitis' therapeutic effect and the levels of CRP, TNF-α, IL-6 in serum. *Ann Palliat Med*. 2020 Sep;9(5):3410-3417. https://doi.org/10.21037/apm-20-1653
16. Sánchez GA, Miozza VA, Delgado A, Busch L. Salivary IL-1β and PGE2 as biomarkers of periodontal status, before and after periodontal treatment. *J Clin Periodontol*. 2013 Dec;40(12): 1112-7. https://doi.org/10.1111/jcpe.12164
17. Fuentes-Lerma MG, Zamora-Pérez AL, Robles-Gómez C, Guerrero-Velázquez C, Peregrina-Sandoval J, Gutiérrez-Angulo M, et al. Serum nitric oxide concentration in generalized chronic and aggressive periodontitis in the Mexican population is not related to the severity of the disease. *Biomedica.* 2023 Mar 30;43(1):61-68. https://doi.org/10.7705/biomedica
18. Bergamaschi CC, Santamaria MP, Berto LA, Cogo-Müller K, Motta RH, Salum EA, et al. Full mouth periodontal debridement with or without adjunctive metronidazole gel in smoking patients with chronic periodontitis: A pilot study. *J Periodontal Res*. 2016 Feb;51(1):50-9. https://doi.org/10.1111/jre.12278
19. Killeen AC, Krell LE, Bertels M, Christiansen MM, Anderson L, Hattervig RL, etal. Effect of locally applied simvastatin on clinical attachment level and alveolar bone in periodontal maintenance patients: A randomized clinical trial. *J Periodontol.* 2022 Nov;93(11):1682-1690. https://doi.org/10.1002/JPER.21-0708
20. Jambhekar S, Soman M, Shrivastava R, Ventrapragada R, Sarate S, Kodem T. Comparative Evaluation of Tetracycline Hydrochloride Fiber and Simvastatin Gel as an Adjunct to Scaling and Root Planning in Periodontitis Patients. *Cureus*. 2023 Jul 22;15(7): e42314. https://doi.org/10.7759/cureus.42314
21. Gunjiganur Vemanaradhya G, Emani S, Mehta DS, Bhandari S. Effect of 1.2% of simvastatin gel as a local drug delivery system on Gingival Crevicular Fluid interleukin-6 & interleukin-8 levels in non surgical treatment of chronic periodontitis patients. *Arch Oral Biol*. 2017 Oct;82:55-61. https://doi.org/10.1016/j.archoralbio.2017.05.022
22. Kabra S, Thosar NR, Malviya NS. Exploring the Synergistic Effect of Simvastatin in Oral Health Applications: A Literature Review. *Cureus*. 2023 Aug 30;15(8): e44411. https://doi.org/10.7759/cureus.44411
23. Bahammam MA, Attia MS. Effects of Systemic Simvastatin on the Concentrations of Visfatin, Tumor Necrosis Factor-α, and Interleukin-6 in Gingival Crevicular Fluid in Patients with Type 2 Diabetes and Chronic Periodontitis. *J Immunol Res*. 2018 Aug 15; 2018:8481735. https://doi.org/10.1155/2018/8481735
24. Yang YJ, Song JH, Yang JH, Kim MJ, Kim KY, Kim JK, et al. Anti-Periodontitis Effects of Dendropanax morbiferus H.Lév Leaf Extract on Ligature-Induced Periodontitis in Rats. *Molecules*. 2023 Jan 14;28(2):849. https://doi.org/10.3390/molecules28020849
25. Wadhwa D, Kumar V, Hasija MK, Bey A. Levels of nitric oxide in smokers and nonsmokers with chronic periodontitis before and after nonsurgical periodontal treatment. *Natl J Maxillofac Surg*. 2023 Sep-Dec;14(3):450-453. https://doi.org/10.4103/njms.njms_405_21


**DATA SHARING STATEMENT:** The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

**AUTHORS' CONTRIBUTION**

The following authors fulfill authorship criteria as per ICMJE guidelines;

**Hasan F, Ikram R:** Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.

**Abbas A, Alam SM:** Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.

**Zain S, Kamran H:** Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.

**Kamran H:** Analysis and interpretation of data, critical revision, final approval, agreed to be accountable for all the work.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License, which permits unrestricted use, distribution & reproduction in any medium provided that original work is cited properly.