Original Article

ADJUNCTIVE EFFECT OF RANITIDINE HYDROGEL ON CLINICAL PARAMETERS AND PORPHYROMONAS GINGIVALIS LEVELS IN PERIODONTAL DISEASE

Jennifer Jeyaruby Joyson[1], Arvina Rajasekar[1]*

[1]*Department of Periodontology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, India.*
arvinar.sdc@saveetha.com

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ABSTRACT

Periodontitis is a chronic infectious disease affecting human health and oral wellbeing, with *Porphyromonas gingivalis* as a key pathogen. Effective local therapies are essential to improve clinical outcomes and reduce disease burden, with implications for public health. To evaluate the clinical and microbiological efficacy of subgingivally delivered ranitidine hydrogel as an adjunct to scaling and root planing in Stage II Grade A periodontitis. Fifty systemically healthy patients (30–60 years) were divided into control (scaling and root planing) and test (scaling and root planing + ranitidine hydrogel) groups. Clinical parameters—plaque index, gingival index, probing pocket depth, and clinical attachment level—were recorded at baseline and 3 months. Subgingival *P. gingivalis* levels were assessed via real-time PCR. Statistical significance was set at $p < 0.05$. Both groups showed significant improvement in clinical and microbiological parameters ($p < 0.05$). The test group demonstrated greater reductions in clinical indices and *P. gingivalis* load compared to the control ($p < 0.05$). Subgingival ranitidine hydrogel enhanced non-surgical periodontal therapy outcomes, reducing microbial burden and supporting its role as an adjunctive medicine in managing periodontal disease, thereby promoting oral health, wellbeing, and broader public health.

Key words: Disease, Histamine, Infectious disease, Non-surgical periodontal therapy, Periodontal disease, Wellbeing.

Introduction

Periodontitis is a chronic, multifactorial inflammatory disease characterised by the progressive destruction of the tooth-supporting tissues, ultimately culminating in clinical attachment loss and alveolar bone resorption. The disease arises from a dysbiotic subgingival biofilm that triggers an exaggerated host immune response, rather than direct microbial insult alone [1]. Among the periodontal pathogens implicated, *Porphyromonas gingivalis* plays a central role owing to its virulence factors, immune-evasive strategies, and ability to orchestrate microbial dysbiosis within the periodontal niche [2].

Mechanical debridement through scaling and root planing remains the cornerstone of periodontal therapy. Although effective in reducing microbial load and inflammation, its clinical outcomes may be compromised by anatomical limitations such as deep periodontal pockets, furcation involvements, and root surface irregularities. These sites provide a favourable environment for bacterial persistence and recolonisation, thereby predisposing to disease recurrence [3]. Consequently, adjunctive therapeutic approaches aimed at enhancing the biological response to conventional therapy have garnered increasing attention [4-6].

Local drug delivery systems have emerged as a rational strategy to overcome the shortcomings of systemic pharmacotherapy by achieving high drug concentrations directly at the disease site while minimising systemic exposure and adverse effects [7, 8]. Among various delivery platforms, injectable hydrogels have demonstrated considerable promise owing to their biocompatibility, ease of placement, sustained drug release, and ability to conform to the periodontal pocket architecture [9, 10]. Such systems offer a conducive microenvironment for tissue healing while facilitating prolonged therapeutic action.

Histamine has been recognised as a key inflammatory mediator in periodontal disease, influencing vascular permeability, immune cell activity, and osteoclastogenesis. Elevated histamine levels within inflamed periodontal tissues have been associated with enhanced inflammatory signalling and accelerated bone resorption. Blockade of histamine H_2 receptors has therefore been proposed as a novel host-modulatory approach in periodontal therapy [11]. Ranitidine, a selective H_2 receptor antagonist with a long-standing clinical safety profile, has demonstrated immunomodulatory and anti-inflammatory properties beyond its conventional gastrointestinal applications [12]. Emerging experimental evidence suggests that H_2 receptor inhibition may attenuate periodontal inflammation, suppress osteoclastic activity, and modulate pathogenic bacterial responses [13].

Building upon previously established in-vitro evidence demonstrating the biocompatibility and safety of a

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ranitidine-based hydrogel formulation [14], clinical validation of its therapeutic efficacy is warranted. However, clinical data evaluating the adjunctive use of ranitidine hydrogels in periodontal therapy, particularly with respect to microbiological outcomes, remain sparse. Given the pivotal role of *P. gingivalis* in disease progression, assessing its quantitative reduction provides meaningful insight into treatment effectiveness.

Therefore, the present prospective clinical study was undertaken to evaluate the effectiveness of a locally delivered ranitidine hydrogel as an adjunct to scaling and root planing in patients with chronic periodontitis, with specific emphasis on its impact on *Porphyromonas gingivalis* levels. This study aims to contribute clinical evidence supporting histamine receptor modulation as a novel adjunctive strategy in periodontal management.

Materials and Methods

Study design and patient selection
This prospective clinical study was conducted in the Department of Periodontology, Saveetha Dental College and Hospitals, Chennai, India. Fifty systemically healthy outpatients of both sexes, aged between 30 and 60 years, diagnosed with Stage II Grade A periodontitis and possessing a minimum of 20 natural teeth, were recruited. Patients who had received systemic antibiotics or antimicrobial therapy within the preceding three months, individuals with systemic diseases, pregnant or lactating women, and smokers were excluded from the study.

The study protocol was approved by the Institutional Review Board of Saveetha Dental College and Hospitals, Chennai. Written informed consent was obtained from all participants before enrolment. Sample size estimation was performed using G*Power software (version 3.1.9.4), based on mean and standard deviation values obtained from a previously published study [15], yielding a total sample size of 50 subjects with 80% power at a 95% confidence level. Participants were divided into two groups of 25 subjects each. The control group received scaling and root planing alone, while the test group received scaling and root planing followed by adjunctive subgingival application of ranitidine hydrogel [16-21].

Clinical examination
Clinical examination was performed by a single calibrated examiner (AR) at baseline and at three months. The clinical parameters assessed included plaque index (PI), gingival index (GI), probing pocket depth (PPD), and clinical attachment level (CAL).

Periodontal therapy
All periodontal therapeutic procedures were carried out by a single operator (JJJ). Scaling and root planing were performed using ultrasonic scalers and hand instruments (Gracey curettes; Hu-Friedy®, Chicago, IL, USA). In the test group, ranitidine hydrogel was delivered subgingivally into the periodontal pockets following mechanical debridement using a blunt cannula syringe to ensure atraumatic placement. A periodontal dressing was placed in both groups following treatment. Participants were instructed to avoid brushing in the treated areas, refrain from using interdental aids, and avoid consumption of hard or sticky foods for one week. The periodontal dressing was removed after seven days. All patients were recalled for follow-up evaluation after three months [22-27].

Microbiological sample collection
Subgingival plaque samples were collected by a single examiner (AR) at baseline and at three months. The sampling sites were isolated using cotton rolls, and supragingival plaque was gently removed before sampling. A sterile paper point was inserted into the deepest part of the periodontal pocket and left in situ for 60 seconds. The collected samples were immediately transferred to sterile microcentrifuge tubes and stored at −20°C until further processing [28-35].

Microbiological analysis
Quantitative analysis of *Porphyromonas gingivalis* was performed using real-time polymerase chain reaction (RT-PCR). The reaction mixture consisted of 20 µL of 1× SYBR Premix (Takara Bio Inc., Shiga, Japan), 1 µL of extracted genomic DNA, and appropriate primers. Universal primers used were forward 5′-GATTAGATACCCTGGTAGTCCAC-3′ and reverse 5′-TACCTTGTTACGACTT-3′. Species-specific primers for *P. gingivalis* were forward 5′-ACCTTACCCGGGATTGAAATG-3′ and reverse 5′-CAACCATGCAGCACCTACATAGAA-3′. The RT-PCR assay was performed using a Bio-Rad CFX96 real-time PCR system under the following cycling conditions: initial denaturation at 95 °C for 3 minutes, followed by 39 cycles of denaturation at 95 °C for 10 seconds and annealing at 54 °C for 30 seconds. Fluorescence signals were measured at the end of each cycle. Data analysis was carried out using CFX Maestro Software (Bio-Rad, California, USA).

Statistical analysis
Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 23.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro–Wilk test. As the data followed a normal distribution, parametric statistical tests were employed. Descriptive statistics were expressed as mean and standard deviation. Intergroup comparisons of age, Plaque Index, Gingival Index, probing pocket depth, clinical attachment level, and *Porphyromonas gingivalis* copy numbers between the control and test groups were carried out using the independent samples *t*-test. Intragroup comparisons between baseline and three-month values were analysed using the paired *t*-test. Gender distribution between the groups was assessed using the chi-square test. A *p*-value of less than 0.05 was considered

statistically significant.

Results and Discussion

The mean age of participants in the control group was 44.28 ± 7.16 years, while that of the test group was 43.92 ± 6.84 years, with no statistically significant difference between the groups ($p = 0.84$). The control group comprised 14 males and 11 females, whereas the test group included 13 males and 12 females. Gender distribution was comparable between the two groups and did not show a statistically significant difference ($p > 0.05$), indicating baseline demographic homogeneity.

The mean plaque index values were 2.16 ± 0.04 in the control group and 2.09 ± 0.08 in the test group. Gingival index scores were 2.22 ± 0.19 and 2.18 ± 0.20 in the control and test groups, respectively. The mean probing pocket depth was 5.97 ± 0.17 mm in the control group and 5.93 ± 0.19 mm in the test group, while the mean clinical attachment level values were 6.54 ± 0.16 mm and 6.49 ± 0.18 mm, respectively. The baseline *P. gingivalis* load was comparable between the groups, with values of 5.13 ± 0.93 × 10^2 copy count/µL in the control group and 5.06 ± 0.89 × 10^2 copy count/µL in the test group. At baseline, no statistically significant differences were observed between the control and test groups for any of the assessed clinical or microbiological parameters ($p > 0.05$) **(Table 1)**.

Table 1. Intergroup comparison of outcome parameters at baseline and 3 months

Variable	Time point	Group 1 (Control) Mean ± SD	Group 2 (Test) Mean ± SD	t value	p value[a]
Plaque Index (PI)	Baseline	2.16 ± 0.04	2.09 ± 0.08	3.91	0.06
	3 months	1.29 ± 0.14	0.39 ± 0.06	29.54	0.00*
Gingival Index (GI)	Baseline	2.22 ± 0.19	2.18 ± 0.20	0.72	0.47
	3 months	1.32 ± 0.13	0.41 ± 0.04	33.45	0.00*
Probing Pocket Depth (PPD) (mm)	Baseline	5.97 ± 0.17	5.93 ± 0.19	0.78	0.44
	3 months	4.39 ± 0.11	3.02 ± 0.09	48.20	0.00*
Clinical Attachment Level (CAL) (mm)	Baseline	6.54 ± 0.16	6.49 ± 0.18	1.04	0.30
	3 months	4.83 ± 0.06	3.32 ± 0.04	104.70	0.00*
***P. gingivalis* load (copy count/µL)**	Baseline	5.13 ± 0.93 × 10^2	5.06 ± 0.89 × 10^2	0.27	0.79
	3 months	2.11 ± 0.10 × 10^2	0.78 ± 0.04 × 10^2	61.74	0.00*

[a]Independent *t*-test; *Statistically Significant

At the 3-month follow-up, both groups demonstrated statistically significant intragroup improvements in all clinical and microbiological parameters compared with baseline ($p < 0.05$). Intergroup analysis revealed significantly greater reductions in plaque index, gingival index, probing pocket depth, clinical attachment level, and *P. gingivalis* load in the test group compared to the control group ($p < 0.05$). The test group exhibited lower mean plaque index (0.39 ± 0.06) and gingival index (0.41 ± 0.04) scores than the control group (1.29 ± 0.14 and 1.32 ± 0.13, respectively). Similarly, probing pocket depth and clinical attachment level were significantly reduced in the test group (3.02 ± 0.09 mm and 3.32 ± 0.04 mm) compared to the control group (4.39 ± 0.11 mm and 4.83 ± 0.06 mm). The *P. gingivalis* load showed a significantly greater reduction in the test group (0.78 ± 0.04 × 10^2 copy count/µL) than in the control group (2.11 ± 0.10 × 10^2 copy count/µL) **(Table 2)**.

Table 2. Intragroup comparison of outcome parameters from baseline to 3 months

Variable	Group	Baseline (Mean ± SD)	3 Months Mean ± SD	t value	p value
Plaque Index (PI)	Control	2.16 ± 0.04	1.29 ± 0.14	42.25	0.00*
	Test	2.09 ± 0.08	0.39 ± 0.06	120.21	0.00*
Gingival Index (GI)	Control	2.22 ± 0.19	1.32 ± 0.13	27.64	0.00*
	Test	2.18 ± 0.20	0.41 ± 0.04	61.36	0.00*
Probing Pocket Depth (PPD) (mm)	Control	5.97 ± 0.17	4.39 ± 0.11	55.18	0.00*
	Test	5.93 ± 0.19	3.02 ± 0.09	97.87	0.00*
Clinical Attachment Level (CAL) (mm)	Control	6.54 ± 0.16	4.83 ± 0.06	70.76	0.00*
	Test	6.49 ± 0.18	3.32 ± 0.04	121.56	0.00*
***P. gingivalis* load (copy count/µL)**	Control	5.13 ± 0.93 × 10^2	2.11 ± 0.10 × 10^2	22.83	0.00*
	Test	5.06 ± 0.89 × 10^2	0.78 ± 0.04 × 10^2	33.97	0.00*

[a]Paired *t*-test; *Statistically Significant

The present prospective clinical study was undertaken to evaluate the effectiveness of a locally delivered ranitidine hydrogel as an adjunct to scaling and root planing in the management of chronic periodontitis, with particular emphasis on its influence on *Porphyromonas gingivalis* levels. The rationale for exploring ranitidine in periodontal therapy is grounded in the growing recognition of histamine as a key mediator of inflammation, immune modulation, and bone metabolism within periodontal tissues. By targeting histamine receptor–mediated pathways, ranitidine may offer a novel host-modulatory approach to complement conventional mechanical debridement.

The results of the present study demonstrated that the test group receiving adjunctive ranitidine hydrogel showed significantly greater reductions in PI, GI, PPD, and CAL, and *P. gingivalis* copy counts at the three-month evaluation compared with the control group treated with scaling and root planing alone. These findings indicate that local ranitidine delivery enhances both clinical periodontal healing and microbial control, suggesting a synergistic effect when combined with mechanical plaque removal.

Histamine plays a pivotal role in periodontal inflammation by influencing vascular permeability, leukocyte recruitment, cytokine release, and osteoclast differentiation. Periodontal tissues have been shown to express multiple histamine receptor subtypes, enabling them to respond dynamically to fluctuating histamine levels during inflammation. Experimental studies have demonstrated that histamine stimulation increases the expression of pro-inflammatory cytokines, prostaglandins, and receptor activator of nuclear factor-κB ligand (RANKL), thereby promoting connective tissue degradation and alveolar bone resorption. Consequently, antagonism of histamine receptors represents a biologically plausible strategy to attenuate periodontal inflammation and tissue destruction [36].

The clinical improvements observed in the present study are consistent with experimental evidence supporting the beneficial role of histamine receptor antagonists in periodontal disease. Hasturk *et al*. demonstrated that topical application of cimetidine significantly inhibited *P. gingivalis*-induced periodontal inflammation and alveolar bone loss in an animal model, with marked reductions in inflammatory infiltrate and tissue destruction [37]. These findings support the concept that histamine receptor blockade can effectively suppress periodontal inflammation and limit disease progression.

Similarly, Sharma *et al*. reported significant reductions in gingival inflammation following topical application of ranitidine gel as an adjunct to scaling and root planing in patients with plaque-induced gingivitis [38]. Although their study evaluated short-term inflammatory outcomes, the present investigation extends these observations to patients with chronic periodontitis and further demonstrates concomitant reductions in periodontal pocket depth, clinical attachment loss, and *P. gingivalis* burden. This highlights the potential of ranitidine not only as an anti-inflammatory agent but also as a modulator of the subgingival microbial environment.

At the cellular level, histamine has been shown to stimulate gingival and periodontal ligament fibroblasts to produce inflammatory mediators such as interleukin-6 and interleukin-8, while also enhancing osteoclastogenesis through upregulation of RANKL expression [39]. Studies by Minami *et al*. [40] and Groeger *et al*. [41] have elucidated histamine-mediated signaling pathways involving mitogen-activated protein kinases and nuclear factor-κB, which amplify inflammatory responses within periodontal tissues. By antagonizing histamine receptors locally, ranitidine may downregulate these pathways, thereby reducing inflammatory burden, limiting connective tissue breakdown, and promoting periodontal healing [42].

Additional experimental evidence further supports the therapeutic relevance of histamine receptor modulation in periodontal disease. Studies investigating H3 and H4 receptor antagonists have demonstrated significant reductions in inflammatory cell infiltration, prostaglandin E2 levels, RANKL expression, and alveolar bone resorption in experimental periodontitis models [43-45]. These findings collectively reinforce the concept that histamine signaling contributes substantially to periodontal disease pathogenesis and that receptor-specific antagonism may offer a targeted host-modulatory benefit.

The microbial findings of the present study are of particular clinical relevance, as *P. gingivalis* is recognized as a keystone pathogen capable of disrupting periodontal homeostasis and perpetuating dysbiosis even at low abundance [46]. The significant reduction in *P. gingivalis* copy counts observed in the test group suggests that ranitidine may indirectly influence the subgingival microbial ecosystem, possibly through suppression of inflammation-driven ecological changes that favor pathogenic colonization. This dual effect on host response and microbial burden underscores the therapeutic value of adjunctive local drug delivery.

This prospective study's strengths include its clinical design and simultaneous evaluation of clinical and microbiological parameters, providing a comprehensive assessment of ranitidine hydrogel as a targeted adjunctive therapy with minimal systemic exposure. Limitations include a short follow-up, lack of radiographic and biochemical inflammatory assessments, and microbiological analysis limited to *Porphyromonas gingivalis*, which restricts insights into long-term stability, bone-level changes, and broader microbial shifts. Future studies should involve larger, long-term trials, incorporate radiographic and biomarker evaluations, compare with other histamine receptor antagonists, and optimize hydrogel formulations and controlled-release kinetics to enhance clinical outcomes and expand therapeutic applications [47-52].

Conclusion

Within the limits of this study, adjunctive subgingival application of ranitidine hydrogel along with scaling and root planing produced superior clinical outcomes and a greater reduction in *Porphyromonas gingivalis* levels compared to scaling and root planing alone in patients with Stage II Grade A periodontitis.

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Conflict of interest: None

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Ethics statement: The study protocol was approved by Institutional Ethics Committee, Saveetha Dental College and Hospitals, Chennai, India.

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