Role of Orthoboon (glucosamine sulfate + collagen + Vitamin C): A novel host-modulating agent in the management of chronic periodontitis

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INTRODUCTION

The treatment concept wherein drug therapies are used as an adjunct to conventional periodontal treatments in order to ameliorate the restrictive aspects of host inflammatory response is the basic concept of host modulation therapy.1 This concept of host modulation which is not new to the field of medicine with its application in the treatment of number of chronic disorders such as arthritis and osteoporosis has percolated even to the field of dentistry by Williams in 1990 and Golubin 1992, which was later expanded by many other researchers.2 This strategy which is not new in the treatment of periodontitis has advocated nonsteroidal anti-inflammatory drugs (NSAIDs) with evidence of reduction in alveolar bone resorption when used for prolonged period of time. A variety of drug classes including the NSAIDs, bisphosphonates, tetracyclines, enamel matrix proteins, bone morphogenetic proteins (BMPs), and growth factors have been evaluated as host-modulating agents.3 These host-modulating pharmaceutical agents have received much interest in the treatment strategy for periodontal disease because of their potential to move periodontal treatment strategies to a new level. However, with numerous NSAIDs emerging and proving their positive association in the treatment of periodontitis, the risk of significant unwanted effects precluded their use.4 As of now, to date, subantimicrobial-dose doxycycline is the only available adjunctive host response modulator that is licensed for the treatment of periodontitis.

Abstract:

Background: Recent trends suggest using novel host-modulating agents as a treatment strategy for chronic periodontitis. Glucosamine sulfate (GS) was proven to have anti-inflammatory actions related to its ability to suppress neutrophil functions. Orthoboon, an anti-arthritic and anti-inflammatory drug, has shown to have a positive therapeutic effect due to its constituents made of a combination of GS, Vitamin C, and collagen. The aim of the study was to evaluate the host modulatory effects of Orthoboon on periodontal status and to estimate the C reactive protein (CRP) levels before and after nonsurgical periodontal therapy (NSPT). Materials and Methods: A total number of 40 patients with chronic periodontitis were randomly divided into two groups of 20 patients each. The test group patients (n = 20) received 500 mg Orthoboon three times daily for 45 days. Prior to the initiation of Orthoboon, all patients in both test group and control group were subjected to Phase I periodontal therapy. CRP levels were estimated immediately after phase I therapy and 45 days after therapy. Clinical parameters including plaque index, gingival index, and bleeding index were recorded before and after NSPT for the two groups. Results: The mean CRP levels were reduced significantly in the test group before and after administration of Orthoboon and also there were statistically significant differences in the mean CRP levels at the end of 45 days between the test group and the control group. Conclusion: Administration of Orthoboon, i.e., GS, with a combination of Vitamin C and collagen was proved to be of a significant benefit in the test group than in the control group. Key words: C-reactive protein, glucosamine sulfate, host modulation therapy.
Due to this inhibitory action on matrix metalloproteinases, its clinical benefits in randomized controlled clinical trials have yet to be determined.[6]

With the number of local host modulatory agents, such as enamel matrix derivatives, growth factors, and BMPs, being investigated for their potential use as adjuncts to surgical therapy; glucosamine sulfate (GS) is one novel compound which has proven its anti-inflammatory actions related to its ability to suppress neutrophil function and is widely used in the field of orthopedics for its pain relieving abilities in arthropathies. On the other hand, GS has also shown to exhibit minimal side effects. GS with a combination of collagen and Vitamin C, commercially known as Orthoboon, is one such unique preparation widely used in the treatment of osteoarthritis and rheumatoid arthritis.[6]

As periodontitis being an inflammatory disease, C-reactive protein (CRP) levels tend to rise with the severity of the disease. CRP being a prime marker of inflammation, analyses and evaluation of its values can be of use in determining progression of disease or the efficiency of treatments. As of now, only one study in the literature has been available till date regarding the use of GS. However, not even a single study exists advocating the use of this unique preparation of Orthoboon (GS + Collagen + Vitamin C) in the treatment of periodontitis.

Therefore, the current study was proposed to assess the host modulatory effects of GS along with collagen and Vitamin C on periodontal status and also to estimate the CRP levels before and after nonsurgical periodontal therapy (NSPT).

MATERIALS AND METHODS

Study design and study population
The study was single-centered, placebo-controlled, randomized, single-blinded, parallel-group clinical trial, wherein each participant was randomly assigned into a group with an allocation ratio of 1:1.

Inclusion criteria
Patients above the age of 35–55 years diagnosed with chronic generalized periodontitis and absence of occlusal trauma associated with malocclusion were included in the study.

Exclusion criteria
Patients excluded were those diagnosed with diabetes mellitus, peptic ulcer, blood dyscrasias, nutritional deficiencies, infected with immunodeficiency virus, acquired immunodeficiency syndrome, lactating or carrying women, those on diuretics, steroid use, oral-contraceptive users, or those addicted to tobacco.

The case definition adopted for periodontitis used in the present study was according to the CDC/AAP working group 1999, wherein CAL ≥3 mm and PD ≥4 mm in at least 2 interproximal sites (not on the same tooth) or one site with PD ≥5 mm for mild periodontitis; CAL ≥4 mm and PD ≥5 mm in at least 2 interproximal sites (not on the same tooth) for moderate chronic periodontitis and CAL ≥6 mm in at least 2 interproximal sites (not on the same tooth) and PD ≥5 mm in at least one site for severe chronic periodontitis.

The study was carried out in the department of periodontics and implantology. It was reviewed and approved by the institutional ethical committee and was conducted from February 2018 to May 2018. The participants received detailed information regarding the proposed research who also provided signed informed consent. All the participants were screened by a principal clinical investigator.

Sample size
The sample size was calculated using G Power 3.1 software (Heinrich Heine University, Düsseldorf, Germany). At a level of significance set at 5%, power of the study 80%, and for an expected effect size difference of 0.996 (obtained from the pilot study), it was calculated that 17 samples per group were required to perform the study. However, to compensate for dropouts, 20 patients per group were enrolled, thus totaling to an effective sample size of 40.

Using convenient sampling technique, 40 patients of chronic periodontitis attending the outpatient department of department of periodontics were randomly divided into two groups of 20 patients each, after obtaining the informed consent. The patients were randomly allocated into the test and control groups using coin toss method by the clinical investigator. The participants were blinded regarding the sequence of subject allocation. The control group were subjected to phase-I therapy and CRP levels were estimated immediately after scaling and root planing (SRP) and 45 days after SRP. In the test group, the patients were subjected to 500 mg of Orthoboon for a period of 45 days and CRP levels were estimated after phase I therapy and 45 days after SRP. The following clinical parameters were recorded before and after NSPT for the two groups, bleeding index: Muhlemann and Sons 1971 (BI), plaque index: Silness and Loe: 1964 (PI) and gingival index: Loe and Silness: 1963 (GI).

Statistical analysis
The collected data were compiled in Microsoft Excel and analyzed using SPSS version 20.0 (IBM, Chicago, USA). The data were summarized using descriptive statistics and presented as mean, standard deviation, and percentage. The primary and secondary outcome variables, i.e., CRP levels and PI, GI, and BI were determined at different time intervals using unpaired and paired t-tests, respectively. Unpaired t-test was used to evaluate the differences in mean CRP, GI, PI, and BI scores between the test and control groups. The mean difference comparisons between baseline and 45 days in each group were estimated using the paired t-test.

RESULTS
The present study intended to evaluate the host modulatory effects of GS along with collagen and Vitamin C on periodontal parameters and inflammatory status, by the evaluation of CRP levels before and after NSPT. The study had proved that administration of Orthoboon containing GS, collagen, and Vitamin C combination had statistically significant reduction in CRP scores than in the control group.
Table 1 shows the intergroup comparison of the study variables between the test and control groups. The mean CRP level at baseline (after SRP) in the Orthoboon test group was 3.48 ± 2.05, whereas in the control group, it was 3.93 ± 3.49. However, this difference was statistically nonsignificant (P ≥ 0.05). After the initial SRP treatment, no statistically significant difference in the mean scores of CRP, PI, GI, and BI was observed between the test and control groups ensuring baseline comparability between the groups (P ≥ 0.05). The mean CRP level at the end of 45 days in the Orthoboon/test group was 1.24 ± 0.69, whereas in the control group, it was 3.37 ± 3.32. This difference was statistically significant (P = 0.08). This indicates that administration of Orthoboon for 45 days resulted in high reduction in CRP scores than without administration. After 45 days, there were no statistically significant differences in the mean GI, PI, and BI scores in the Orthoboon/test group and the control group, suggesting that the administration of Orthoboon for 45 days in addition to SRP had no effect on PI, GI, and BI scores (P ≥ 0.05); however, the effect was seen only in relation to CRP levels.

Table 2 shows the intragroup comparison of the study variables between the baseline and 45 days. The mean CRP levels and PI, GI, and BI scores showed an average reduction of 1.96, 0.40, 0.34, and 0.41 units, respectively, after 45 days of administration of Orthoboon after SRP. This reduction of the above parameters in test group was significant statistically (P = 0.001). The highest reduction of 56.32% in the CRP levels was seen after administration of Orthoboon. In the control group, the mean CRP levels and PI, GI, and BI scores had shown an average reduction of 0.55, 0.77, 0.60, and 0.54 units, respectively, after 45 days after SRP even without administration of Orthoboon. This differentiation was also statistically significant (P = 0.001).

**DISCUSSION**

The host immune-inflammatory response against bacterial plaque can be viewed as a “dual-edged sword,” ultimately being responsible for perpetuating the destruction of the periodontium. Importance on host response has led to growth of host modulatory therapies. This can lead to improved therapeutic results, delay the progression of diseases, and aid in better predictability in patient management. A novel way of managing periodontal health concerns apart from mechanical debridement is the use of pharmacological tools called “Perioceutics,” which is noninvasive, with the least side effects, without complicated methods of application, when compared to other therapeutic modes against infection. The role of host-modulating agents in the treatment of periodontitis in conjunction with conventional therapy was concluded in systemic reviews.

Glucosamine is one of the nonvitamins, nonmineral amino monosaccharide sugar that is essential for the biosynthesis of glycosylated proteins and lipids supplements and is most commonly taken along with chondroitin as a single supplement in the treatment of osteoarthritis. Glucosamine has also been found to be used in colorectal and lung cancer. GS was proven to have anti-inflammatory actions related to its ability to suppress neutrophil functions and this explains its claimed pain-relieving ability in arthropathies. Moreover, GS inhibits nuclear factor-kappa B activation and prostaglandin E2 synthesis induced by interleukin 1β (IL-1β). Fibrillated cartilage chondrocyte adhesiveness to fibronectin is restored by glucosamine by the suggested activation of protein kinase C, thereby augmenting the process of repair. GS induced a 2-fold increase in the steady levels of both perlecan and aggrecan mRNA, which caused a meek but consistent decrease in the quantity of stromelysin mRNA, thus emphasizing on its anti-inflammatory capacity.

Dietary consumption of nutrients required in microquantities such as minerals and vitamins adjunctive to periodontal therapy has been expected to help maintain a balanced immune system through involvement of several biological processes in host, particularly the innate immunity. The role of Vitamin C, a water-soluble vitamin, in maintaining a balanced redox potential via acting as electron donor and scavenging reactive oxygen species helps downstream inflammatory...
responses.\textsuperscript{11,12} In addition, it promotes the synthesis of mature type I collagen by preventing iron-dependent oxidation; inhibits the cross-linking of collagen fibers; modifies the role of fibroblast proliferation, thereby aiding in wound healing; and improves host resistance to infection.\textsuperscript{13} Nutrients such as Vitamin C which include major extracellular antioxidants can also act as modulators of inflammation by scavenging free radicals formed as a part of oxidative stress and sequestration of transition metal ions.\textsuperscript{14} Thus, Vitamin C being one of the potential reducing agents has the capacity to regulate inflammatory process, thereby stimulating repair of the tissues.

The present study intended to evaluate the host modulatory effects of GS along with collagen and Vitamin C on periodontal status and inflammatory parameter by the evaluation of CRP levels before and after NSPT. Although there was sparse literature on the evaluation of effect of glucosamine on periodontal tissues, the study had proved that administration of Orthoboon containing GS, collagen, and Vitamin C combination had statistically significant reduction in CRP scores than the control group. The additional benefit of Orthoboon over plain GS is the presence of combination of factors such as Vitamin C and collagen, which substantiates for its added benefits. A 30-day study conducted by Wijayanto et al., on the use of supplements such as glucosamine–chondroitin sulfate orally in osteoarthritic patients who experienced chronic periodontitis after SRP, showed decreased GI and PD.\textsuperscript{15} The conference report published by the International Association for Dental Research (IADR) Asia/Pacific Regional Meeting and Co-Annual Scientific Meeting of IADR Divisions 2013, on the efficacy of GS in the management of chronic periodontitis, by investigating its effect on gingival crevicular fluid level of IL-1β for a period of 3 months, proved the beneficial effects of GS in the modulation of inflammatory response in chronic periodontitis patients, via its inhibitory effect on IL-1β level. A 4-month prospective cohort study conducted by Kantor et al. concluded that the use of glucosamine and chondroitin supplements was associated with reduced high-sensitivity-CRP and PGE-metabolite concentrations.\textsuperscript{16} Arthrocare forte, capsule containing chondroitin and GS potassium (500 mg), methyl sulfonyl methane, and chondroprotective and anti-arthritic drug when used in the treatment of chronic periodontitis over a period of 5 years showed significant benefit as it speeds up the regenerative capacity and stability of the periodontium.\textsuperscript{17} A randomized, double-blinded, placebo-controlled, crossover study to assess the effects of glucosamine hydrochloride plus chondroitin sulfate for 28 days in healthy, overweight adults had showed 23% statistically significant reduction in the CRP levels with decrease in the cytokine activity on proteomic analysis.\textsuperscript{18,19}

Although the domain of periodontitis has limited number of host modulation therapies such as subantimicrobial dose of doxycycline, and Emodogain administered locally, the future of antiresorptive treatments is quite hopeful in the treatment of periodontal diseases.\textsuperscript{20} Further long-term trials in different populations with improved sample size are required to substantiate the use of Orthoboon in periodontal conditions.

**CONCLUSION**

Administration of Orthoboon, i.e., GS with a combination of Vitamin C and collagen, proved to be of noteworthy benefit in the test group than in the control group, as assessed by the stability of the periodontium through periodontal and inflammatory parameters. However, further studies are warranted to assess its safety and prolonged efficacy.

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**Conflicts of interest**

There are no conflicts of interest.

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