Herbal anti-inflammatory immunomodulators as host modulators in chronic periodontitis patients: a randomised, double-blind, placebo-controlled, clinical trial

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Purpose: Host modulatory therapy has been proposed as a treatment for periodontal diseases. A class of herbal medicines, known to be immunomodulators, alters the activity of immune function through the regulation of informational molecules such as cytokines. In the current study, we tested the hypothesis that herbal immunomodulator drugs act as an adjuvant to scaling and root planing (SRP) in alleviating periodontal inflammation by improving clinical and biochemical parameters.

Methods: Sixty healthy subjects (30 in each group) with moderate and severe chronic periodontitis were enrolled in a double-blind, placebo-controlled, double-masked randomised controlled trial. The control group was treated with SRP and a placebo, whereas the test group was treated with SRP followed by dietary supplementation of Septilin for 3 weeks. Periodontal clinical parameters and serum C-reactive protein (CRP) levels were evaluated for all patients at the baseline, 3 weeks, and 6 weeks.

Results: Improved gingival index scores found in the test group as compared to the control group were found to be statistically significant only after 3 weeks ($P<0.001$). In contrast, the decrease in the sulcus bleeding index and pocket depth scores was statistically highly significant in the test group as compared to the control group after 3 weeks and 6 weeks ($P<0.001$). However, reduced clinical attachment level and CRP scores, as reflected in the test group as compared to the control group, were not found to be statistically significant after both 3 weeks ($P>0.05$) and 6 weeks ($P>0.05$).

Conclusions: The results of this clinical-biochemical study suggest that dietary supplementation with herbal immunomodulatory agents may be a promising adjunct to SRP and may aid in improving periodontal treatment outcomes.

Keywords: C-reactive protein, Herbal medicine, Periodontitis, Randomized controlled trial.

INTRODUCTION

Until the 1970s, treatment strategies for periodontal disease were based on the understanding that plaque bacteria and their products primarily mediated the tissue destruction in affected patients. This concept changed when investigators began to document the host's contribution to disease pathogenesis [1]. Thus, it was postulated that it is the host's immuno-inflammatory reaction to the presence of bacteria that mediates tissue destruction and a number of factors, including environmental (e.g., tobacco use), acquired (e.g., systemic diseases), or genetic risk factors, can influence this host response. Since the destruction of the periodontal tissues is believed to be due to the immuno-inflammatory re-

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sponse, it is logical to consider therapeutic approaches that modulate the host immuno-inflammatory response in addition to antibacterial approaches in the management of chronic periodontitis [2].

Accordingly, host modulation therapy (HMT) has emerged as a new concept for the treatment of periodontal diseases. HMT aims to reduce tissue destruction and stabilize or even regenerate the periodontium by modifying or downregulating destructive aspects of the host response and upregulating the protective or regenerative responses [3]. HMT comprises systemically or locally delivered pharmaceuticals prescribed as a part of periodontal therapy and are used as adjuncts to conventional periodontal treatment [4].

Ayurveda is a prehistoric science popular in Asia and Europe and is fast gaining recognition worldwide. In ayurveda, naturally occurring herbs and shrubs are used to provide a cure for medical ailments without causing any undue side effects. Nowadays, suitable drugs and preparations from natural sources are the centre of attraction in the field of research for preventing immunological complications of various organs [5]. Herbal drugs exert their effect by modulating both humoral and cellular immune functions. They also have the capacity to control the production of proinflammatory mediators, thereby managing many inflammatory processes [6].

More recently, herbal drugs have been found to be promising in managing inflammatory disorders [7,8]. Herbal immunomodulator drugs (HID), such as *Balsamodendron mukul, Maharasnadi quath, Trikuta, Tinospora cordifolia, Phyllanthus emblica, Saussurea lappa, Rubia cordifolia*, and *Glycyrrhiza glabra*, have been reported to possess antibacterial, anti-inflammatory, antiexudative, and immunomodulation properties [9]. A combination of these drugs, i.e., Septilin (The Himalaya Drug Co., Bangalore, India) (Table 1), has shown some potency in modulating immune functions in animal models [10,11]. It includes various herbal products, each with its own unique immunomodulatory effect (Table 1). Prolonged use of antibiotics is associated with numerous adverse effects [12]. HIDs have been reported to increase the phagocytic coefficient [11], which is related to the clinical improvement in chronic infections that are resistant to the commonly used broad-spectrum antibiotics. C-reactive protein (CRP) is an extremely sensitive and nonspecific acute-phase marker for inflammation. A positive association between CRP and periodontitis has been established in the past [13,14]. The mechanism of Septilin in regulating the production of proinflammatory mediators such as interleukin (IL) 6, IL-8, tumor necrosis factor (TNF)-α, nitric oxide, cycloxygenase (COX-2), and phosphodiesterase in lipopolysaccharides-stimulated macrophage and monocyte cell lines has been investigated in *in vitro* studies [15]. The present study is undertaken to evaluate the immunomodulatory effects of Septilin as an adjunct to scaling and root planing (SRP) on periodontal parameters and on serum CRP.

Table 1. Composition of a Septilin.

	Constituent	Quantity (mg)
Powder	*Balsamodendron mukul*	162
	Shankha bhasma	32
Extract	*Maharasnadi quath*	65
	Tinospora cordifolia	49
	Rubia cordifolia	32
	Emblica officinalis	16
	Moringa pterygosperma	16
	Glycyrrhiza glabra	6

Thus, in the current study, we tested the hypothesis that HIDs act as an adjuvant to SRP in alleviating periodontal inflammation by (1) improving clinical periodontal parameters and (2) reducing the serum CRP levels.

MATERIALS AND METHODS

This study is a parallel double-blind placebo-controlled randomised controlled trial (RCT) carried out on patients reporting to the outpatient department of Tatyasaheb Kore Dental College and Research Centre, New Pargaon. The approval of the Institutional Ethics Committee was obtained. Each patient was explained about the study and enrolled in the study after the patient provided informed consent. This clinical trial is registered in U.S. National Institutes of Health Clinical Trials Registry with the registration number NCT01997814.

Sample size

The study was powered at 80% to detect a mean pocket depth (PD) difference of 0.8 mm after treatment assuming a 30% within-group change in the primary outcomes PD and clinical attachment level (CAL). The minimum required sample size was calculated to be 26 patients for each group; to compensate for potential drop-outs, 30 patients were recruited for each group.

Eligibility criteria

Sixty patients with moderate (≥2 interproximal sites with CAL of ≥4 mm [not on the same tooth] or ≥2 interproximal sites with PD of ≥5 mm [not on the same tooth]) or severe (≥2 interproximal sites with CAL of ≥6 mm [not on the same tooth] and ≥1 interproximal site with PD of ≥5 mm) chronic periodontitis (defined using the center for disease control Centers for Disease Control and Prevention 2007 criteria [16]) were selected for the study. Patients were required to be nonsmokers in the age group of 30–60 years with a lack of systemic illnesses, allergies, pregnancy, history of any drug intake, and periodontal treatment in the past 6 months.

Randomization

The participants attended clinic visits at the time of randomization (baseline), and at 3-week and 6-week intervals until July 2013. The subjects were classified into two groups (30 patients in each group); test group: patients who received two HID capsules (Septilin) twice a day for 3 weeks and control group: patients who re-

ceived two placebo capsules- twice a day for 3 weeks.

The randomization was done in accordance with the CONSORT 2010 guidelines [17]. The entire study was supervised and monitored by the data monitoring group (DMG) consisting a panel of two investigators. The allocation of patients was done using a random key generator (Quick Calcs, Graph Pad software, San Diego, CA, USA). The allocation and the examination of the subjects were carried out by different individuals who were completely blinded, thus ensuring double blinding.

Each patient was given a number which was already assigned to either the test group or the control group by the DMG. Both the allocator and the examiner were unaware of the group to which the patient was allotted.

Intervention

After allocation of patients to the test and the control group, periodontal parameters like plaque index (PI), gingival index (GI), sulcus bleeding index (SBI), PD, and CAL were recorded at baseline (before treatment). Out of these parameters, serum CRP, PD, and CAL were primary outcome measures, whereas PI, oral hygiene index simplified, GI, and SBI were secondary outcome measures. The same periodontal parameters were recorded 3 and 6 weeks after treatment in both the test and the control group. UNC-15 periodontal probe (GDC-AC-007-CP15, GDC Marketing, Hoshiarpur, Punjab, India) was used to measure PD and CAL. PI, SBI, GI, PD, and CAL were checked on four sites per tooth (mesiobuccal, buccal, distobuccal, and palatal or lingual). The sum of all the readings was calculated, and then, the average was calculated by dividing the sum by the total number of surfaces recorded. All the clinical parameters were recorded full mouth. At each visit, the serum CRP levels were evaluated. Initial therapy was performed on all patients at baseline and consisted of full-mouth SRP; local anaesthesia was used whenever deemed appropriate. SRP was performed by hand and with ultrasonic instrumentation (Satelec India Private Limited, Gandhinagar, India) as necessary, and oral hygiene instructions were given. The protocol called for SRP to be completed within a 14-day interval. All initial therapy procedures were performed by the same periodontist. After completion of the initial therapy session, the patient was referred to the DMG for the dispensing of drugs; the DMG was unaware of the readings of the parameters recorded in patients, thereby ensuring that there was no bias.

The test group received oral administration of HIDs (Septilin), and the control group received a placebo. Both the drugs were dispensed in similar packets ensuring the blinding of the patients.

Both the groups received thorough oral hygiene instructions without the prescription of mouthwash.

At the subsequent visits of 3 and 6 weeks, the periodontal parameters were recorded and the oral hygiene instructions were reinforced.

All examinations were performed by a single dentist who received prior training from a periodontist. At the start of the data gathering, the measurements on 10% of the sample were repeated by the examiner for the within-examiner evaluation. The reproducibility and concordance of clinical measurements were calculated by means of the within-examiner κ index.

The value obtained for probing depths was 0.87, which was considered to be a strongly positive association, thereby proving the efficacy of the calibration.

Laboratory tests

Blood samples for laboratory tests on CRP were obtained by means of antecubital puncture. A 10-mL blood sample was centrifuged at 500×g for 10 minutes separating the cells from the serum. The serum samples were then collected and stored at −70˚C, until required for analysis.

CRP was assayed using a highly sensitive CRP turbilatex kit (CRP-CAL, Spinreact, Girona, Spain) with a sensitivity of 0.01 μg/mL on a fully automatic turbilatex analyser. This kit is a latex-particle-enhanced turbidometric immunoassay. The test is based on the photometric measurement of the agglutination between the anti–hu-CRP-coated latex particles and the CRP present in the sample. The agglutination is detected as an absorbance change, which allows for the quantification of CRP in the sample via a calibration curve.

The same procedure was repeated at recall visits of 3 and 6 weeks for the CRP evaluation.

Statistical analysis

A descriptive and inferential statistical analysis was carried out in the present study. The results of the continuous measurements are presented as mean±standard deviation (min–max) and the results of the categorical measurements are presented as number (%). Significance is assessed at the 5% level of significance. The following assumptions on the data were made: (1) Dependent variables should be normally distributed; (2) Samples drawn from the population should be random; (3) Cases of the samples should be independent.

A Student *t*-test (two-tailed, independent) was used to find the significance of the study parameters on a continuous scale between the two groups' intergroup analysis of the metric parameters. Levene test for the homogeneity of variance was performed to assess the homogeneity of the variance, and another Student *t*-test (two-tailed, dependent) was used to find the significance of the study parameters on a continuous scale within each group. The final model constructed using the repeated measures analysis of variance. The chi-squared/Fisher exact test was used to find the significance of the study parameters on a categorical scale between two or more groups. Pearson correlation of changes in clinical variables with changes in CRP (the change in variable was computed on the basis of the baseline and the 6th week measurement) was also performed.

The statistical software programs called SAS 9.3 (SAS Institute Inc., Cary, NC, USA) and PASW ver. 18.0 (SPSS Inc., Chicago, IL, USA) were used for the analysis of the data, and Microsoft Word and Excel were used to generate graphs, tables, etc.

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RESULTS

Sixty patients (31 males and 29 females) in the age group of 33–55 years (mean age, 45.73±5.50 years) were included in this study. Age-eligible participants were recruited from March 2012 to May 2013. The participants attended clinic visits at the time of randomization (baseline) and at 6-week and 12-week intervals till July 2013. The subjects were classified into two groups (30 patients in each group).

Test group

Patients received two HID capsules (Septilin) twice a day for 3 weeks.

Control group

Patients received two placebo capsules twice a day for 3 weeks.

The primary analysis was intention-to-treat and involved all patients who were randomly assigned. Two patients from the test group and one patient from the control group did not continue with the follow-ups after the second visit. However, the ITT method required all the subjects to be allocated. Hence, all the subjects were included in the final analysis. The participant flow in the study is shown in Fig. 1. The demographic distribution within the test and the control groups revealed no statistical differences between groups with respect to age and sex ($P>0.05$) (Table 2). None of the patients had any known systemic conditions, infections, or any other factors known to increase the CRP level. None of the patients reported any change in their general health or medical status during the period of the study.

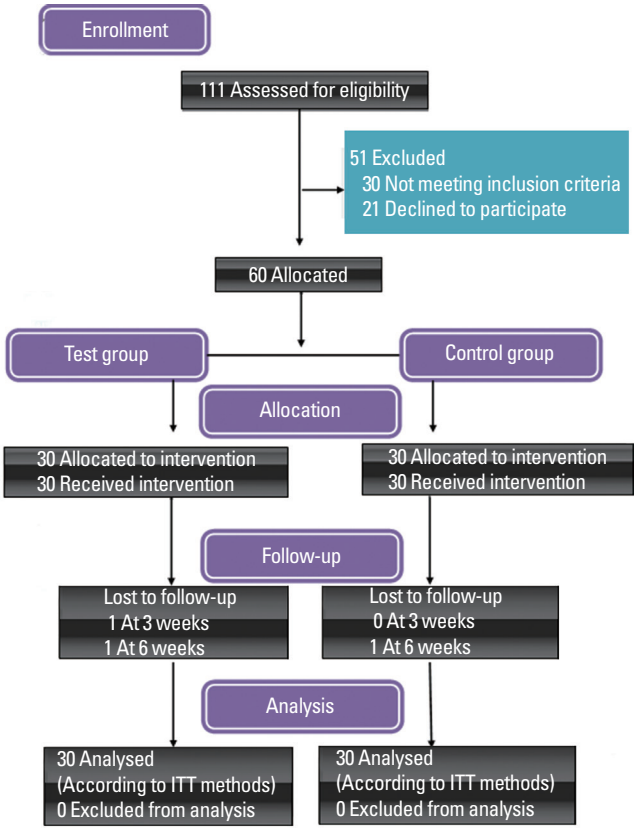

Figure 1. Participant flow.

As stated earlier, all the clinical and biochemical parameters were assessed in both groups at the baseline, after 3 weeks, and after 6 weeks. No significant difference ($P>0.05$) was found in any of the parameters between the groups at the baseline. With thorough SRP therapy followed by regular maintenance, the plaque control in all the patients was satisfactory. Throughout the study, plaque accumulation was at a minimum with no significant differences ($P>0.05$) between the two groups. There was no statistically significant difference in PI in the test group and the control group ($P>0.05$) after 3 and 6 weeks (Table 3). Improved GI scores found in the test group as compared to the control group, were found to be statistically significant only after 3 weeks ($P<0.001$) (Table 3). In contrast, the decrease in SBI and PD scores was statistically highly significant in the test group than in the control group after 3 weeks and 6 weeks ($P<0.001$) (Table 3). However, reduced CAL and CRP scores as reflected in the test group as compared to the control group, were not found to be statistically significant after both 3 weeks ($P>0.05$) and 6 weeks ($P>0.05$) (Table 3).

The data were further analysed to determine the distribution of changes in PD. The frequency distributions of PD between groups were compared before and after treatment. A significant shift to greater PD reduction was noted for the test group as compared to the control group. The percentage of PD of <4 mm was 100% in the test group at 3 weeks versus 80% in the control group ($P=0.03$); however, the same changes were not significant at 6 weeks ($P=0.24$). These findings suggest that clinically approximately 20% sites showed better changes in PD in the test group as compared to the control group at 3 weeks (Table 4).

The changes in CRP were correlated vis-a-vis with changes in periodontal parameters using Pearson correlation (Table 5). In the test group and the control group, PD and CAL were found to have

Table 2. Demographics of subject population and baseline periodontal parameters.

Baseline characteristic	Test group (n=30)	Control group (n=30)
Age (year)	46.47±6.01	45.00±4.91
Plaque index	2.51±0.25	2.44±0.33
Gingival index	2.19±0.41	2.32±0.36
Sulcus bleeding index	2.89±0.79	3.21±0.86
Pocket depth	3.96±0.61	4.24±1.06
Clinical attachment level	5.22±0.76	4.83±1.06
C-reactive protein	3.66±2.28	3.59±1.49

Values are presented as mean±standard deviation. Student *t*-test.
There were no significant differences between groups ($P>0.05$).

Table 3. Full-mouth values for periodontal measurements before and after treatment.

Parameter	Test group (n=30)	Control group (n=30)	*F*-value (*P*-value)
Plaque index			0.007 (0.94)
Baseline	2.51±0.25	2.44±0.33	
3 Weeks	1.91±0.30[a]	1.92±0.34[a]	
6 Weeks	1.67±0.36[a]	1.61±0.31[a]	
Gingival index			5.32 (0.03)
Baseline	2.19±0.41	2.32±0.36	
3 Weeks	1.58±0.46[a,b]	1.90±0.47[a]	
6 Weeks	1.47±0.42[a]	1.49±0.39[a]	
Sulcus bleeding index			14.82 (<0.001)
Baseline	2.89±0.79	3.21±0.86	
3 Weeks	1.81±0.54[a,b]	2.45±0.57[a]	
6 Weeks	1.55±0.54[a,b]	1.97±0.46[a]	
Pocket depth			7.14 (<0.001)
Baseline	3.96±0.61	4.24±1.06	
3 Weeks	2.81±0.55[a,b]	3.48±0.99[a]	
6 Weeks	2.53±0.67[a,b]	3.07±0.96[a]	
Clinical attachment level			0.69 (0.40)
Baseline	5.22±0.76	4.83±1.06	
3 Weeks	4.18±0.76[a]	4.15±1.08[a]	
6 Weeks	3.89±0.72[a]	3.69±1.04[a]	
C-reactive protein			0.10 (0.75)
Baseline	3.66±2.28	3.59±1.49	
3 Weeks	2.58±1.78[a]	2.91±1.30[a]	
6 Weeks	2.55±1.79[a]	2.70±1.28[a]	

[a]$P<0.05$ compared to baseline. [b]$P<0.05$ compared to the control group.

Table 4. Categorical analysis of pocket depth in two groups in three different time periods.

Variable	Baseline	6 Weeks	12 Weeks	% Change
Test group (n=30)	30	29	28	-
<4 mm	19 (63.3)	29 (100)	28 (100)	36.7
4–6 mm	11 (36.7)	0 (0)	0 (0)	–36.7
>6 mm	0 (0)	0 (0)	0 (0)	0
Control group (n=30)	30	29	29	-
<4 mm	15 (50)	24 (80)	27 (90)	40.0
4–6 mm	11 (36.7)	4 (13.3)	3 (10)	–26.7
>6 mm	4 (13.3)	2 (6.7)	0 (0)	–13.3
P-value	0.159	0.024[a]	0.238	-

Values are presented as number (%).
[a]$P<0.05$.

Table 5. Pearson correlation of change in clinical variables with a change in CRP.

Variable	Case		Control	
	r	*P*-value	*r*	*P*-value
Change in PI with change in CRP	–0.016	0.937	0.311	0.094
Change in GI with change in CRP	0.180	0.359	0.545	0.002[a]
Change in OHIS with change in CRP	–0.184	0.349	–0.250	0.183
Change in SBI with change in CRP	0.312	0.106	0.189	0.316
Change in PD with change in CRP	0.399	0.036[a]	0.483	0.007[a]
Change in CAL with change in CRP	0.520	0.005[a]	0.499	0.005[a]

PI: plaque index, GI: gingival index, OHIS: oral hygiene index simplified, SBI: sulcus bleeding index, PD: pocket depth, CAL: clinical attachment level, CRP: C-reactive protein level.
[a]$P<0.05$ compared to baseline.

a statistically significant positive correlation coefficient with CRP.

DISCUSSION

Herbal extracts have been used to cure human illness for ages. A number of these preparations are thought to promote positive health and maintain organic resistance against infection by re-establishing the body's equilibrium and conditioning the body tissues.

Immuno-modulating agents have been reported to act primarily on cellular rather than on humoral immune responses and to restore the immuno-competency of impaired hosts without hyper-stimulating normalcy. These agents accentuate macrophage chemotaxis and phagocytosis, and promote interaction with other related immuno-regulatory lymphoid cells [18]. Since the exacerbated immune response plays a salient role in periodontal breakdown, it was decided to evaluate the immunomodulatory effects of Septilin on the periodontal disease process through RCT.

Activation of local macrophages and other cells (including fibroblasts and endothelial cells) leads to initiation of an acute phase response, which is a nonspecific process that may occur in the initial host response to periodontal infection. This response ultimately causes the release of mediators such as TNF-α and IL-6, leading to systemic changes such as hepatic release of plasma proteins like CRP, activation of complement proteins, and various metabolic changes. Usually, acute phase molecules like CRP are present at relatively low levels in the plasma; however, their levels may rise dramatically within 72 hours of tissue injury or infection [19]. After the onset of acute tissue injury, CRP levels increase within 4 to 6 hours in serum. Studies have shown high levels of CRP in periodontal infections [20,21]. The risk of cardiovascular disorders is directly proportional to the serum CRP levels [22]. CRP levels in the range of 1–3 mg/L can be considered risk factors for cardiac and cere-

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brovascular events [19]. The present study found serum CRP levels ranging from 1 to 14 mg/L in both the test and the control groups in the pretreatment phase, which definitely emphasizes the need to reduce these levels in periodontal disease.

The literature shows that several herbal formulations have the capacity to control the production of proinflammatory mediators, thereby managing many inflammatory processes [6]. The use of such herbal anti-inflammatory formulations for a longer period of time was found to be safer than that of chemical anti-inflammatory drugs [23]. Septilin is an ayurvedic preparation which contains various herbs and minerals. These medicinal plants possess immunomodulatory and anti-inflammatory properties that aid in strengthening the immune system and potentiating the nonspecific immune responses of the body [24]. Septilin has been shown to have antibacterial, anti-inflammatory, antiexudative, and immunostimulatory effects [9,25] and is effective in respiratory tract infections, tonsillitis, and other infections [11,26,27].

Shetty et al. [27] have reported a non–randomized non—placebo-controlled pilot study using Septilin in chronic periodontitis patients. No patient reported any untoward and unpleasant reactions to Septilin, indicating that it was relatively safe.

The external validity of the study has been justified by including both the sexes and a wide age range (30–60 years). Thus, we have included a broad spectrum of chronic periodontitis cases, increasing the generalizability of the results. The dosage regimen for the use of this formulation in chronic periodontitis has to be established, but we have adopted the conventional two capsules twice daily for 3 weeks.

The test group, which was administered Septilin, showed significant improvement in SBI and PD during the various time intervals considered in this study. Further, a decrease in the GI score was significant in the test group as compared to the control group during the period of drug administration (baseline to 3 weeks). However, the same changes were not significant at 6 weeks when drug administration was stopped. This shows a definitive effect of Septilin in reducing the inflammatory load in the test group patients, which substantiates the host modulation effect of Septilin in chronic periodontitis patients. The findings of our study are in agreement with clinical and laboratory studies which have shown that Septilin possesses anti-inflammatory properties [11,26,27].

An *in vitro* study has shown that Septilin also exhibits COX-2 enzyme inhibitory activity by down-regulating *COX-2* gene expression [11]. Herbal drugs with COX-2 inhibiting activity have been suggested for use as an alternative to nonsteroidal anti-inflammatory drugs for chronic inflammatory conditions [28]. On the other hand, SRP basically targets the removal of local factors only without having any direct effect on the inflammatory mediators [29], whereas host modulation therapies block the pathways responsible for periodontal tissue destruction [30]. This possibly explains the reason why the test group showed greater improvement than the control group with respect to the inflammatory clinical parameters.

In a study by Shetty et al. [27], the results of the same formulation were not checked during the period when drug administration was stopped. Interestingly, changes in GI were not significant in the test group as compared to the control group during this period (3–6 weeks). This may explain the short-term effectiveness of the drug. Further, although a decrease in the CAL and CRP scores was greater in the test group than in the control group at 3 weeks and 6 weeks, these changes were not statistically significant. A long-term study of the same kind may be necessary to check the effectiveness of the drug.

There was no significant difference postoperatively between the test group and the control group for the serum CRP levels. CRP appears in the serum only during the acute phase of inflammatory diseases [31,32]. The CRP level decreases and eventually disappears with the subsidence of the disease process and the recovery of the patient [33,34]. This could possibly explain why changes in CRP levels did not show significant changes over a period of time (baseline to 6 weeks).

This study also assesses the change in the levels of serum CRP with the treatment provided, and determines its correlation with the clinical parameters in either group over a period of time. In the present study, the CRP levels in moderate and severe periodontitis patients fell significantly after periodontal therapy (from baseline to 6 weeks) in both the groups. Moreover, the percentage of subjects with a CRP level of >3 mg/L decreased significantly. This is in agreement with other studies [35-40] that reported a significant reduction in the serum CRP level after treatment.

To the best of our knowledge, this is the first double-blind placebo-controlled RCT on Septilin as an adjunctive to periodontal therapy. This preparation can open new frontiers in the immunomodulatory therapy of periodontal disease as an adjuvant to conventional therapeutic measures. Further long-term studies with a larger sample size are necessary to corroborate the results of this study. In addition, the use of a more sensitive diagnostic medium such as gingival crevicular fluid to assess the levels of the disease markers is recommended.

In conclusion, the results of this placebo-controlled double-blind RCT project suggest that Septilin (a herbal immunomodulatory agent) may be a promising adjunct to SRP and may aid in improving periodontal treatment outcomes because the preparation is safe and has shown beneficial effects on the clinical and biological markers of periodontal disease. The results warrant long-term studies with an examination of osseous changes in a larger population.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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