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EFFECT OF CIPROFLOXACIN AS AN ADJUNCTIVE ANTIBIOTIC ON PERIODONTAL CLINICAL PARAMETERS AND CREVICULAR FLUID INTERLEUKIN-8 AND SOLUBLE INTERCELLULAR ADHESION MOLECULE-1 LEVELS IN THE TREATMENT OF GENERALIZED CHRONIC PERIODONTITIS

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ABSTRACT

Background and Aim: To evaluate the effect of adjunctive ciprofloxacin (CIP) therapy to periodontal clinical parameters, and gingival crevicular fluid (GCF) interleukin-8 (IL-8) and soluble intercellular adhesion molecule-1 (sICAM-1) levels in subjects with chronic periodontitis.

Subjects and Methods: Twenty eight patients with chronic periodontitis were included. The patients were assigned into two treatment groups. The treatment groups consisted of scaling and root planing (SRP) combined with systemically administered CIP (SRP+CIP group) and SRP group alone. They were monitored at baseline (before therapy) and at one and three months after therapy. Clinical parameters were measured and GCF samples were collected at each session. IL-8 and sICAM-1 levels in GCF were also determined.

Results: In both groups, all periodontal clinical parameters decreased from baseline to three months visit. Total amount of IL-8 and the volume of GCF in SRP+CIP group were found higher at baseline than first and third month measurements. In SRP group, only the volume of GCF decreased from baseline to the third month. sICAM-1 levels did not show significant change during whole study period.

Conclusion: Both methods were effective in the treatment of mild/moderate chronic periodontitis. Compared to SRP alone, use of CIP in addition to SRP decreased the amount of IL-8. No significant relationship between present therapeutic modalities and sICAM-1 levels in GCF was observed.

Key words: Chronic Periodontitis, Ciprofloxacin, Gingival Crevicular Fluid, Interleukin-8, Soluble Intercellular Adhesion Molecule-1.

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CLINICAL DENTISTRY AND RESEARCH 2013; 37(2): 13-22 Orjinal Araştırma

GENERALİZE KRONİK PERİODONTİTİS TEDAVİSİNDE SİPROFLOKSASİNİN EK ANTİBİYOTİK OLARAK KULLANILMASININ KLİNİK PERİODONTAL PARAMETRELER, DİŞETİ OLUĞU SIVISI İNTERLÖKİN-8 DÜZEYİ VE ÇÖZÜNEBİLİR İNTERSELÜLER ADEZYON MOLEKÜLÜ-1 DÜZEYİ ÜZERİNE ETKİSİ

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ÖZET

Amaç: Kronik periodontitisli bireylerde birleşik siprofloksasin (SIP) tedavisinin klinik periodontal parametreler, dişeti oluğu sıvısı (DOS) interlökin-8 (IL-8) düzeyi ve çözünebilir interselüler adezyon molekülü-1 (sICAM-1) düzeyi üzerine etkisini değerlendirmek.

Bireyler ve Yöntem: Çalışmaya kronik periodontitisli yirmi sekiz birey dahil edildi. Hastalar iki tedavi grubuna ayrıldı. Bir gruba sadece diş yüzeyi temizliği ve kök yüzeyi düzleştirmesi (DKYD) yapılırken (DKYD grubu), diğer gruba DKYD'ne ek olarak sistemik olarak siprofloksasin (SIP) verildi (DKYD+SIP grubu). Hastalar tedaviden önce (başlangıç) ve tedaviden bir ve üç ay sonra muayene edildi. Her randevuda klinik periodontal parametreler ölçüldü, DOS örnekleri toplandı ve DOS içerisindeki IL-8 ve sICAM-1 düzeyleri ölçüldü.

Bulgular: Her iki grupta da tüm klinik periodontal parametrelerin başlangıca göre üç aylık değerlendirmelerde düştüğü gözlendi. DKYD+SIP grubunda toplam IL-8 düzeyinin ve DOS hacminin başlangıçta, birinci ve üçüncü aydan daha fazla olduğu tespit edildi. DKYD grubunda, başlangıca gore üçüncü ayda DOS hacmi azalırken, sICAM-1 düzeyinde çalışma süresi boyunca anlamlı bir değişiklik gözlenmedi.

Sonuç: Orta şiddetli kronik periodontitis tedavisinde her iki yöntem de etkili bulundu. Tek başına DKYD'ne kıyasla, DKYD'ne ilave olarak SIP kullanılması IL-8 düzeyini azalttı. Bu çalışmadaki tedavi yöntemleri ile DOS içerisindeki sICAM-1 düzeyi arasında anlamlı bir ilişki bulunmadı.

Anahtar Kelimeler: Kronik Periodontitis, Siprofloksasin, Dişeti Oluğu Sıvısı, İnterlökin-8, Çözünebilir İnterselüler Adezyon Molekülü-1

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INTRODUCTION

Chronic periodontitis has been defined as 'an infectious disease' resulting in inflammation, progressive attachment and bone loss within the supporting tissues of the teeth.[1] In last decades, local host response to periodontitis has been studied by biochemical analysis of gingival crevicular fluid (GCF). Among many inflammatory and immune mediators identified in GCF, cytokines have attracted particular attention and are known to be involved in both inflammation-related alteration and repair of the periodontal tissues. Certain cytokines have been proposed as potentially useful diagnostic or prognostic markers of periodontal destruction.[2,3]

Interleukin-8 (IL-8) is a major pro-inflammatory cytokine that activates neutrophils and T lymphocytes and then attracts them to inflammatory site. Compared to healthy sites, its level is known to increase in the GCF of inflamed areas.[4] IL-8 has been shown to be highly important in the initiation and development of inflammatory response and tissue destruction in periodontal diseases, due to its critical role in recruitment and functional activation of neutrophilic granulocytes.[5] Studies that examined the GCF concentrations of IL-8 reported conflicting data. For instance, studies indicated that the total amount of GCF IL-8, suggesting a role for this cytokine in the disease process,[5] whereas other studies reported an opposite or absent relationship between GCF levels of IL-8 and periodontal disease.[6-8] In a recent study, Goutoudi et al.[9] analysed the levels of IL-8 in GCF of patients with chronic periodontitis prior to and following surgical and/or nonsurgical periodontal therapy. According their data, periodontal therapy reduced the levels of IL-8 in GCF. However, a strong relationship between IL-8 amount in GCF and periodontal destruction and inflammation was not found.

Intercellular adhesion molecule-1 (ICAM-1), a member of the immunoglobulin superfamily and a cell surface receptor for lymphocyte function associated with antigen-1 and Mac1, is expressed by many cell types including fibroblasts and gingival epithelial cells.[10,11] The expression of ICAM-1, which is upregulated by IL-1β, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) plays a key role in the retention and activation of leukocytes at inflamed gingival sites.[12,13] Soluble form of this adhesion molecule (sICAM-1) has also been identified and is considered to have an important immunoregulatory function.[14] Previous studies have shown that sICAM-1 increases during inflammation in a number of tissues including lung and gingiva.[15] Although their expression has not been extensively investigated during periodontal repair and regeneration, presence of sICAM-1 in GCF of periodontally compromised patients was reported by Hannigan et al.[16] in 2004. In their study, authors examined the relationship of soluble adhesion molecules with periodontal inflammation and also investigated the effect of periodontal treatment on the levels of these molecules. The results of the study indicated that changes in the levels of adhesion molecules may be a sensitive indicator to differentiate healthy sites from those with periodontitis. Moreover, significant differences were observed in the sICAM-1 levels following periodontal therapy.[16]

Quinolones are one of the main groups of antibiotics that have been introduced for use in urinary tract infections in the 1970s. Quinolones have several advantages such as good penetration into the tissues and ability to show antibacterial activity within the cells. The first and second generations only act on gram-negative aerobic bacteria.[17] The primary aim of periodontal treatment is to reduce the infection, resolve inflammation and prevent further destruction of the tissues.[18] Adjunctive antibiotic use is a therapeutic option to improve treatment outcomes in patients with severe chronic and aggressive periodontitis.[19,20] Ciprofloxacin (CIP), a quinolone antibiotic, is active against gram-negative rods, including all facultative and some anaerobic putative periodontal pathogens. It accumulates and remains active inside PMNs and retains its bactericidal activity inside PMNs by enhancing intracellular destruction of susceptible bacteria.[21,22] Its concentration was found higher in GCF than it was in serum.[23] Tezel et al.[24] evaluated GCF CIP levels of subjects with gingivitis and periodontitis, and effects of CIP on periodontal clinical parameters. Results of their study did not demonstrate significant contribution of systemic CIP to the clinical parameters of the subjects with gingivitis. On the other hand, a significant decrease in the clinical attachment level scores of the subjects with periodontitis was observed following CIP administration.[24]

Influence of systemic antibiotic use in combination with periodontal therapy to GCF IL-8 levels has not been an overemphasized subject yet. In 2010, Ho et al.[25] evaluated the influence of azithyromycin to several cytokines including IL-8 in a short-term follow-up study and found a transient decrease in the GCF levels of IL-8 after azithyromycin treatment. In a recent study, Goutoudi et al.[9] analysed the levels of IL-6 and IL-8 in GCF of patients

with chronic periodontitis prior to and following surgical and/or nonsurgical periodontal therapy. As a conclusion the authors reported that surgical or nonsurgical periodontal therapy may reduce the levels of IL-8 in GCF.[9]

All these information may let the investigators to think about a possible effect of CIP in addition with non-surgical periodontal therapy to IL-8 and sICAM-1. However, to our knowledge, there is no clinical trial investigating this relationship. Therefore, the present study aimed to evaluate the effect of adjunctive ciprofloxacin therapy on periodontal clinical parameters, GCF IL-8 and sICAM-1 levels in subjects with chronic periodontitis.

SUBJECTS AND METHODS

Study Population

Twenty eight patients with chronic periodontitis were recruited from the Department of Periodontology at Kırıkkale University, Faculty of Dentistry. Prior to participation, the purpose and procedures were fully explained to patients. All patients agreed to participate in the study and signed an appropriate consent form in agreement with the Helsinki Declaration on human experimentation. The approval of the Local Ethics Committee of Kırıkkale University, Faculty of Dentistry was also obtained. Patients were diagnosed as having chronic periodontitis according to clinical and radiographic findings. Participants, having more than 20 remaining teeth, with moderate to advanced periodontal disease as evidenced by multiple sites with a probing depth of 4 mm or more and with extensive radiographic bone loss and bleeding on gentle probing were included. Subjects were excluded if they had a history of systemic disease, had a known hypersensitivity to any type of quinolones or if they had received antibiotics, other medicines and periodontal treatment within the past 3 months. Women who were pregnant or lactating were also excluded. All participants were non-smokers.

Study Design and Therapeutic Procedures

In the present double-blind, prospective, randomized controlled clinical trial, the treatment groups consisted of scaling and root planing alone (SRP group) and SRP combined with CIP (SRP+CIP group). The patients were randomly assigned into two treatment groups. The first patient was selected in one of the two experimental groups by coin toss, and the next patient was consecutively added to the opposite group by one of the authors (TA). The CONSORT guidelines for clinical trials were followed and the study flow chart was given in Figure 1. SRP+CIP group was assigned to receive ciprofloxacin (500 mg twice-daily for 8 days, Siprosan, Drogsan, Ankara, Turkey), whereas SRP group received placebo tablets following standard non-surgical periodontal therapy. SRP was performed with manual instruments on all teeth by one of the authors (HGK). Oral hygiene instructions including toothbrushing and the use of interdental flossing or interdental brushing as appropriate were given to the patients at each session.

Clinical Data Collection and GCF analysis

Subjects were monitored at baseline (before therapy) and at the first and the third month follow-up visits. Following indices were taken from the whole dentition: plaque index (PI)[26], gingival index (GI)[27], bleeding on probing (BOP)[28], probing depth (PD) and clinical attachment level (CAL). BOP was measured dichotomously and PD and CAL measures were obtained from six points around a tooth using a Williams periodontal probe by directing the probe parallel to the long axis of the tooth. CAL measurements were made from the cemento-enamel junction to the bottom of the sulcus. All clinical data were recorded by one examiner (EOE). Before the treatment, four teeth with interproximal PD ≥ 4mm were selected for GCF collection. The sample sites were isolated with cotton rolls and air-dried gently. Then, each sterile paper point was inserted into the periodontal pockets and waited for 30 seconds. Care was taken to avoid mechanical injury. Strips contaminated with blood were discarded. For volume determination, the strips transferred to the chair-side located Periotron 8000 (Oraflow Inc., Plainview., NY, USA) which was calibrated using known volumes of phosphate-buffered saline (PBS). For determination of inflammatory parameters, the paper point was removed from the pocket and was placed into 500 µl phosphate buffered saline (PBS, pH: 7.0) transport solution. The total amount measurements of GCF levels of IL-8 and sICAM were determined with ELISA test.

Data analysis

Twenty eight subjects were involved in the analysis. All statistical analyses were performed with a commercial statistical program (SPSS for Windows version 15.01, 2006, SPSS Inc., Chicago, IL, USA). Data were expressed as mean values and standard deviations. The intra and intergroup differences in GCF cytokine levels and clinical parameters

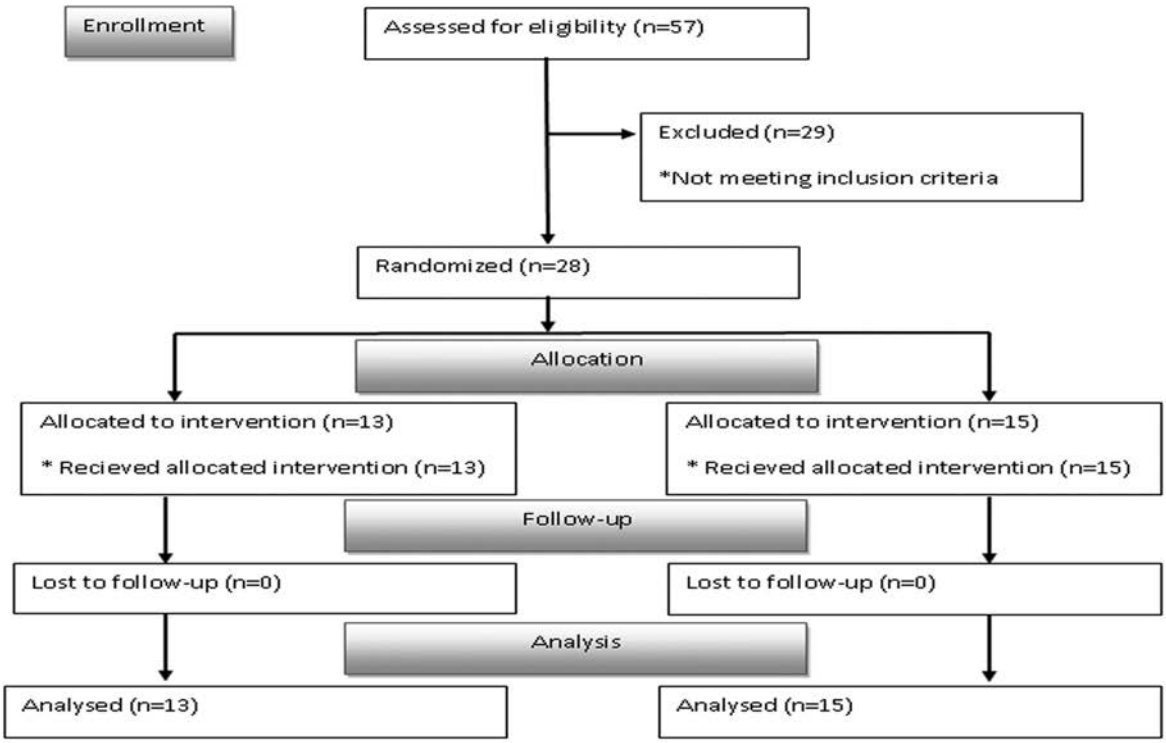

Figure 1. Flow chart of the study

were analyzed by using repeated measures ANOVA. The null-hypothesis was rejected at $p<0.05$.

Power Analysis

Power calculations between two main groups were done by using G*Power 3.0.10 and Sample Size Calculations Software (Franz Faul, Universitat Kiel, Germany) considering that the test and control groups were independent, under the hypothesis of normality for the variables examined. Calculations at $\alpha=0.05$ significance level showed that 28 patients were sufficient to detect a difference of 1.0±1.5 mm in change in CAL, with a 81% statistical power. This level of statistical power was assumed to be acceptable to demonstrate differences between the test and control groups.

RESULTS

Clinical characteristics

A total of 28 subjects were enrolled the study. The SRP group consisted of 15 subjects and the SRP+CIP group had 13 subjects. Clinical characteristics of the study at baseline, first and third months after non-surgical periodontal treatment were shown in Table 1. At baseline, there were no significant differences between groups for all clinical parameters. In both groups, all clinical parameters showed decreases from baseline to third month visit after treatment ($p<0.05$). However, no intergroup differences were observed in follow-up periods (Table 1)

GCF sample levels of IL-8 and sICAM-1

The total amount measurements of GCF levels of IL-8 and sICAM-1 and intra-group comparisons of these molecules are shown in Table 2. Although not significant at three months visit, the total amount of IL-8 decreased in the SRP+CIP group from initial visit to the first ($p<0.05$) and the third month follow-ups. sICAM levels did not show statistically significant change during all study period in both study groups (Table 2). Except baseline IL-8 levels, no intergroup differences were detected in terms of GCF volume and cytokines between SRP+CIP and SRP groups.

Table 1. Baseline and follow-up clinical parameters (mean ± SD)

	Groups/Parameters	PD	CAL	PI	GI
Baseline	SRP+CIP (n=13)	4.20±0.34	3.27±0.39	1.58±0.34	1.78±0.31
	SRP (n=15)	4.08±0.43	3.43±0.53	1.75±0.36	1.81±0.32
1st Month	SRP+CIP (n=13)	3.23±0.33¥	2.78±0.49¥	1.17±0.21¥	1.65±0.27
	SRP (n=15)	3.06±0.26¥	2.94±0.32¥	1.34±0.58¥	1.46±0.29¥
3rd Month	SRP+CIP (n=13)	2.94±0.27¥	2.52±0.40¥	1.22±0.16¥	1.44±0.20¥,§
	SRP (n=15)	2.97±0.29¥	2.76±0.33¥	1.26±0.15¥	1.38±0.21¥

¥ Significantly lower compared to baseline ($p<0.05$)
§ Significantly lower compared to first month ($p<0.05$)
PD, probing depth; CAL, clinical attachment level; PI, plaque index; GI, gingival index;
CIP, ciprofloxacin; SRP, scaling and root planing

Table 2. Baseline and follow-up GCF parameters (mean ± SD)

	Groups/Parameters	GCF (µl)	IL-8 (pg/4 sites)	sICAM-1 (pg/4 sites)
Baseline	SRP+CIP (n=13)	0.38±0.07	0.033±0.024*	0.012±0.006
	SRP (n=15)	0.34±0.09	0.017±0.008	0.013±0.008
1st Month	SRP+CIP (n=13)	0.23±0.08¥	0.016±0.087¥	0.013±0.009
	SRP (n=15)	0.28±0.07	0.029±0.032	0.013±0.007
3rd Month	SRP+CIP (n=13)	0.22±0.05¥	0.022±0.012	0.014±0.008
	SRP (n=15)	0.24±0.07¥	0.023±0.012	0.015±0.008

* Significantly higher compared to CIP group ($p<0.05$)
¥ Significantly lower compared to baseline ($p<0.05$)
IL, interleukin; sICAM, soluble intercellular adhesion molecule;
GCF, gingival crevicular fluid; pg, picograms; µl, microliters; CIP, ciprofloxacin;
SRP, scaling and root planing

DISCUSSION

The effectiveness of conventional periodontal therapies, such as non-surgical mechanical debridement (SRP), may not be enough to debride bacteria from infected sites and the soft-tissue wall of a periodontal pocket may act as a harbour for residual periodontal pathogens.[29,30] Systemic antimicrobial agents can help to eradicate these inaccessible bacteria.[31] A large number of reports have indicated beneficial effects of systemic antibiotics for patients with periodontal diseases in various clinical situations. Amoxicillin (with or without clavulanic acid), azithromycin, clindamycin, doxycycline, metronidazole, spiramycin, tetracycline, ciprofloxacin, and certain combinations of these are the investigated drugs for this purpose.[32] In several studies, adjunctive antibiotics enhanced the clinical outcomes of SRP thereby reducing the need for further therapy which is frequently surgical.[33] In contrast, similar efficacy of SRP and SRP plus systemic antibiotics was also reported.[34-36] According to the previous studies, GCF concentration of ciprofloxacin was found significantly higher than its serum concentration.[23] Ciprofloxacin is particularly effective against many invasive pathogens because of its ability to

penetrate cells and produce bactericidal effects.[37] In general, controlled trials evaluating the clinical and microbiological effects of quinolone antibiotics and mechanic periodontal treatment combination demonstrated positive contributions of the systemic drug administration to the improvement of periodontal variables.[24,38] When the clinical indices and volume of GCF were considered, both treatment approaches were found effective in the elimination of periodontal inflammation in the present study. However, adjunctive antibiotic use did not influence the clinical results in addition to non-surgical periodontal treatment of mild to moderate level chronic periodontitis. These results were in accordance with the results of Serrano et al.[34] and Dannewitz et al.[39]

IL-8 has been shown to be important for the initiation and development of inflammation and tissue destruction in periodontal diseases, due to its critical role in recruitment and functional activation of neutrophilic granulocytes.[7,40,41] In periodontal patients, IL-8 has been reported in both GCF and periodontal tissues. McGee et al.[6] found that IL- 8 concentrations were significantly higher in gingiva adjacent to probing pocket depth ≤3mm and lowest adjacent to >6mm sulci. According to Rosalem et al.[42] GCF IL-8 levels failed to show any significant change following non-surgical periodontal treatment of generalized chronic periodontitis patients from baseline to 3 months later, despite the reduction in inflammatory clinical parameters. On the contrary, Goutoudi et al.[9] showed reduced levels of IL-8 after non-surgical periodontal therapy in the same group of patients. According to the present findings, total amount of IL-8 did not remarkably change with the application of SRP to the patients having mild and/or moderate level of periodontitis. The limited data evaluating the effect of systemic antibiotics to IL-8 revealed a transient decrease in the GCF IL-8 content simultaneous with GCF volume following administration of antibiotics.[25] However, information regarding the influence of systemic CIP, as an adjunct to non-surgical periodontal therapy or alone, to the levels of IL-8 in GCF is not readily available. In the present study, IL-8 showed a remarkable decrease following utilization of CIP in addition to SRP. This result might be attributed to the possible mechanism involving the reductive effect of quinolone antibiotics on IL-8 by inhibition of the nuclear factor-κB (NF-κB) pathway activation.[43]

The levels of sICAM-1 were shown to be elevated in inflammation, infection and cancer, indicating that sICAM-1 may be a useful parameter for diagnosis and evaluation of these pathological conditions.[44] Previous studies investigating the involvement of inflammatory mediators have shown elevated levels of sICAM-1 in sites with deep periodontal pockets.[45,46] In another study high amounts of sICAM-1 were correlated with the presence of dental plaque and increased inflammation indices. In this clinical trial, Fraser et al.[15] also found the impact of smoking to the levels of sICAM-1 in serum and GCF in subjects with chronic periodontitis. According to these findings, sICAM-1 can be considered as a marker that emerges due to inflammation or tissue damage. In 2005, Kuru et al.[47] evaluated the presence and possible changes of SCAM-1 in GCF following surgical periodontal treatment. Their results presented a temporal decrease in GCF sICAM-1 concentration which might serve to enhance inflammatory reactions at surgically-treated sites, thereby limiting repair and regeneration in the periodontium. A study comparing serum levels of inflammation markers in participants with chronic periodontitis at baseline and following non-surgical periodontal therapy concluded that periodontal disease and healing period is not associated with markers including sICAM-1.[48] In the present controlled clinical trial, any statistically significant alteration regarding the total amount of sICAM-1 in GCF was not observed for both study groups. Although it seems similar with the results of Marcaccini et al.[48], this outcome conflicts with the findings of the several abovementioned reports which largely concluded that a significant change in sICAM-1 levels occurs after periodontal therapy.

The actual role and outcome of the regulatory processes including IL-8 and ICAM-1 in the pathogenesis of periodontal diseases in vivo are unknown. It is thought that up-regulation of IL-8 and ICAM-1 in gingival epithelial cells by several bacteria may stimulate the host immune response by recruiting leukocytes to the site of infection. However, some bacterial causes may also attenuate the expression of IL-8 and ICAM-1, delaying the host defense mechanisms and therefore creating more damage to the surrounding tissue by enhancing the immune response.[49,50] Although a similar alteration of IL-8 and sICAM-1 can be expected according to the previous reports, the exact mechanism of the interaction between these two molecules is not clear.[49,51] In the present study, no correlation was observed in the pre- and post-treatment values of these two molecules.

CONCLUSION

In conclusion, both methods were found effective in the treatment of mild/moderate chronic periodontitis. Compared to SRP alone, use of CIP in addition to the non-surgical periodontal therapy decreased the amount of IL-8 and the volume of GCF. Within the limitations of this trial, no significant relationship between non-surgical periodontal therapy with or without adjunctive CIP use and sICAM-1 levels in GCF was observed. Long-term studies including larger sample sizes are needed to make a more comprehensive assessment of the effects of CIP on clinical parameters, GCF IL-8 and sICAM-1 levels in subjects with chronic periodontitis.

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