Comparison of Topical Metronidazole, Ciprofloxacin, Cimetidine, and Meloxicam Treatment in Plaque-Induced Gingivitis

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Abstract

Objectives: The aim of the present study was to evaluate and compare the clinical effectiveness of newly prepared topical dosage forms as an adjunct to scaling and polishing (S & P) in plaque-induced gingivitis.

Materials and Methods: The study was conducted on 75 patients (35 males and 40 females) with a moderate to severe gingivitis randomly divided into five groups, each including 15 patients. In each group, the patients received (S & P) plus one of the oral gels (1% metronidazole, 1% ciprofloxacin, 1% cimetidine, 0.5% meloxicam) twice daily for seven days, except group 0 which were treated by (S & P) alone without any drug application. All the patients were evaluated before treatment and 7 days after treatment for plaque index [PLI], gingival index [GI], and bleeding on probing [BOP] and biochemical parameters (salivary enzymes) like aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), and lactate dehydrogenase (LDH).

Results: There was a significant improvement following all treatments type when compared to pretreatment records with minor differences in the effects of treatment modalities on the clinical parameters (PLI, GI, and BOP). Combination therapy of (S & P) plus ciprofloxacin gel resulted in the best improvement of PLI and BOP whereas the highest significant improvement in GI was with the combination therapy of (S & P) plus cimetidine gel. Similarly, AST, ALT, CK, and LDH significantly reduced in all five groups, with the most observed reduction of both AST and CK was found in the combination therapy of metronidazole gel along with (S & P). The highest decrease in ALT and LDH was observed with the combination therapy of cimetidine gel along with (S & P). Conclusion: The above studies revealed that adjunctive use of topical gels particularly ciprofloxacin and cimetidine along with (S & P) results in significant benefits in the treatment of plaque-associated gingivitis.

Keywords*: oral gel, metronidazole, ciprofloxacin, cimetidine, meloxicam, gingivitis, and dental plaque.*

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Introduction:

Gingivitis is an inflammatory condition of the soft tissue surrounding the teeth as a direct response to the microbial plaque[(1)]. Plaque-associated gingivitis is the type most commonly encountered[(2)]. Therapy for individuals with plaque-associated gingivitis is initially directed at reduction of oral bacteria and associated calcified and non- calcified deposits[(3, 4)].

Although mechanical and surgical interventions are the most widely used methods of controlling disease progression, they may fail to remove completely the infection due to the failure of instruments to reach the base of deep pockets, diffusion of periodontal pathogens into soft tissue and dentinal tubules, migration of periodontal pathogens from other

sites, and complexity of teeth anatomy which makes it difficult for the instruments to remove all the infected materials [5]. In addition to mechanical and surgical intervention, chemotherapeutic approaches are available including topical or systemic delivery of anti-plaque and antimicrobial agents, which aim to suppress pathogenic species responsible for gingivitis.

Systemic antimicrobial therapy has the advantage that it is simple and easy to administer as it can reach all periodontal sites and may also eliminate or reduce pathogens colonizing on oral mucosa and other extra-dental sites including the tongue and tonsillar areas[6]. However, systemic antimicrobials need large doses to be administered because they are not able to achieve high gingival crevicular fluid (GCF) concentration or to gain sufficient concentration of the drug at the site of disease[7]. Other disadvantages are increased drug-resistant, drug interactions, and inconsistent patient compliance[8] as a result of frequent and repeated daily administration over a prolonged period.

Conversely, Site-specific therapy by local and topical drug administration certainly has three potential advantages: decreased drug doses, increased drug concentration at the site of infection and reduced systemic side effects such as gastrointestinal distress. Local delivery of antimicrobial agents allows the flexibility use of concentrations up to 100 times higher than when systemic routes of administration are employed[9].

Hence the use of a topical antimicrobial agent for treatment is preferred as it allows direct access of high local concentration of antimicrobial agents. Many antimicrobials have been tried as mouth rinses in the treatment of periodontal diseases with poor to moderate degrees of success. Thus, the aim of this study was to evaluate the effect of a new topical dosage form as an adjunct to scaling and polishing in the treatment of plaque-associated gingivitis.

MATERIALS AND METHODS

This study conducted on 75 patients (35 males and 40 females) with moderate to severe gingivitis. Their age ranged between 20-45 years old. The study conducted in Sulaimani City at the Periodontics Department of the Peramerd Specialist Dental Center during six months May-October of 2010.

Preparation of Oral Gels

Preparation of the Base

Methylcellulose (5%) was prepared as a gel bases by dissolving the required quantity in cold distilled water with continuous stirring. The product (mucilage) was kept in the refrigerator for one day. After that, the tested drugs have been mixed and dissolved in it to form an oral gel-like formula

Preparation of the Formulas

In the present study, the concentrations of (1%, 1%, and 0.5%) of ciprofloxacin, cimetidine, and meloxicam were selected respectively to formulate oral gels of them.

Patient Diagnosis

The patients were diagnosed clinically with the aid of a dental mirror and periodontal probe. The probe was gently inserted to the gingival margin for knowing if there was BOP or not. In addition, by using William's Periodontal Probe, the amount of plaque that accumulated on the surfaces of teeth was scored. By inspection of the patient's gum, a moderate and severe gingivitis were differentiated by having one or all of the classic signs of inflammation, which include swollen gums, bright red or purple gums and gum that is tender or painful to the touch. The exclusion criteria were: pregnant and nursing women, chronic diseases such as hypertension, diabetes mellitus, renal failure, etc.), those with any periodontal therapy apart from supragingival scaling in the three months' period before the study, and patients with known or suspected hypersensitivity to metronidazole, ciprofloxacin, cimetidine, or meloxicam.

Patient Grouping

The recruited patients were randomly divided into five groups; each group was treated by one of the topical drug treatment as shown in Table 1. In each group, the patients received (S & P) plus one of the oral gels except group 0 which were treated by (S & P) alone without any drug application. Instruction was given to the patients about the use of the gel for seven days twice daily after brushing teeth by using soft toothbrush with (Lacalute active) ® toothpaste, in the morning after breakfast and in the night before bedtime, the gel remained on the teeth surfaces and whole gingiva for 20 minutes in both times then the mouth was washed thoroughly with water only.

Clinical Procedures

Periodontal examination was carried out utilizing the following clinical parameters:

1. Plaque index (PLI)[10].

Score 0: No plaque:

Score 1: Thin film of plaque at the gingival margin, visible only when scraped with an explorer.

Score 2: Moderate amount of plaque along the gingival margin, interdental space free of plaque: Plaque visible with the naked eye.

Score 3: Heavy plaque accumulation at the gingival margin: interdental space filled with plaque.

2. Gingival index (GI)[10].

Score 0: Normal gingiva, no inflammation, no discoloration, no bleeding.

Score 1: Mild inflammation, slight color change, mild alteration of the gingival surface, no bleeding.

Score 2: Moderate inflammation, erythema, swelling and BOP or when pressure applied.

Score 3: Severe inflammation, severe erythema, and swelling, a tendency toward spontaneous hemorrhage, some ulceration.

3. Bleeding on probing (BOP):

The gingiva of each tooth was gently probed with a periodontal probe to the base of the gingival pocket:

Score 0: if the bleeding did not occur.

Score 1: if bleeding occurs within 30 seconds after probing.

Biochemical Parameter Measurement

Samples of un-stimulated mixed saliva were collected from patient's mouth in sterile test tubes using micropipette samples were taken before and after treatment, three minutes after mouth cleansing and before breakfast. After that, the saliva samples were centrifuged at 10000 rpm for 10 minutes, and the supernatant from the centrifuged samples was separated. The activity of enzymes in saliva was determined spectrometrically by the International Federation of Clinical Chemistry (IFCC) method on the Hitachi 911 Automatic Analyzer.

Measurement of ALT activity

The activity of ALT was measured by a method developed by Wrobleski and LaDue, optimized by (Henry and Bergmeyer) following modified IFCC recommendation[11]. The decrease in absorbance due to the conversion of NADH to NAD^+ and proportional to ALT activity in the specimen was measured at 340nm. The absence of P5P allowed a better stability of working reagent.

Measurement of AST activity

The activity of AST was measured by a special method developed by Karmen et al. 1955[12] and optimized by (Henry and Bergmeyer) following modified IFCC recommendation[11]. The decrease in absorbance due to the conversion of NADH to NAD^+ and proportional to AST activity in the specimen was measured at 340nm. The absence of P5P allowed a better stability of working reagent.

Measurement of LDH activity

The activity of LDH was measured by a special method, and Henry optimized this method according to SFBC recommendation[13]. The reaction scheme is as follows. The decrease in absorbance due to the conversion of NADH to NAD^+ and proportional to LDH activity in the specimen was measured at 340nm.

Measurement of CK activity

The activity of CK was measured by an enzymatic method was first described by Oliver, modified by Rosalki, and further improved for optimal test conditions by Szasz[14]. The decrease in absorbance, proportional to CK activity in the specimen was measured at 340nm.

Statistical Analyses

Paired samples t-test was used to analyze statistical differences between mean scores of clinical data, before and after treatment. For comparison among treatment groups, one-way analysis of variance (ANOVA) tests or when appropriate the LSD (least significant difference) test was used for multiple comparisons between groups. The threshold for the significant difference was set at $P<0.05$. SPSS® 19.0 software (SPSS Inc., Chicago, IL, USA) was used to carry out the statistical analyses.

RESULTS

Comparison of clinical parameters (PLI, GI, and BOP) before and after treatment

When compared to pretreatment measurements all clinical parameters (PLI, GI, and BOP) were significantly reduced ($P<0.05$) after treatment with (S & P) alone or plus (metronidazole, ciprofloxacin, cimetidine, and meloxicam) twice daily for 7 days, as shown in Figures (1, 2, 3 and 4) and Table 2.

Comparison of effect of topical drugs (metronidazole, ciprofloxacin, cimetidine, and meloxicam gels) plus (S & P) on clinical parameters

There were significant improvement ($P<0.05$) following all patients of five treated groups with one of the topically tested drugs (metronidazole, ciprofloxacin, cimetidine, and meloxicam gels) twice daily for 7 days along with (S & P) when compared to pretreatment records with minor differences in the effects of treatment modalities on the clinical parameters (PLI, GI, and BOP) as shown in Figures 6, 7 and 8. Ciprofloxacin gel along with (S & P) (Group 2) resulted in the best improvement of PLI and BOP as shown in Table 2. The effect of treatment groups on the reduction in PLI and BOP was in the following order: (Group 2 > group 3 > group 1> group 0 > group 4), (Group 2> group 3> group 1> group 4> group 0) respectively. The highest significant improvement in GI was with the combination therapy of (S & P) plus cimetidine gel (group 3). The order of treatment groups' effects on GI was (Group 3> group 2> group 1> group 4> group 0).

Comparison of saliva biochemical parameters (AST, ALT, CK and LDH) before and after treatment

The results of paired-samples t-test within all study groups revealed that there were significant decreases ($P<0.05$) in all saliva biochemical parameters (AST, ALT, CK, and LDH) after treatment as shown in Table 3. The results also indicated that there were reductions in the value of those parameters after doing only (S & P).

Comparison of effect of topical drugs (metronidazole, ciprofloxacin, cimetidine, and meloxicam gels) plus (S & P) on saliva biochemical parameters

There was a significant reduction ($p<0.05$) in AST, ALT, CK and LDH enzyme activity following all treatments type when compared to pretreatment records as shown in Figures (8, 9, 10 & 11) with minor differences among treatment groups in their effect on particular enzyme as shown in Table 3. Metronidazole (group 1) had more effect on decreasing AST and CK activity; the order of effect of treatment groups on AST was as following: (group 1> group 3> group 2> group 4> group 0). The order of effect of treatment groups on CK was as following: (group 1> group 4> group 3> group 2> group 0). Apparently, cimetidine (group 3) was more effective for lowering ALT and LDH activity. The order of effect of treatment groups on ALT was as following: (group 3> group 1> group 4> group 0> group 2). The order of effect of treatment groups on ALT was as following: (group 3> group 4> group 2> group 1> group 0).

DISCUSSION

In the present study topical drug treatment was used instead of systemic drug administration due to known systemic drugs treatment disadvantages like increased bacterial resistant against antibiotic, drug interaction, and inconsistent patient compliance[8].

All drugs used in this study were prepared as a gel formulation instead of toothpaste or mouth rinses due to the latter's short time remain within the mouth, They do not offer significant concentration and for sufficient time at the site of the disease and hence make them poorly effective in the treatment of chronic gingivitis [15].

Effects on PLI

The results of the present study revealed that the PLI was significantly reduced in all groups. However, combination therapy of ciprofloxacin plus (S & P) produced significantly higher significant reduction compared to (S & P) alone. In addition, ciprofloxacin plus (S & P) showed a higher reduction in PLI than the other drug treatments, which might be due to the better antimicrobial effect of ciprofloxacin against Enterobacteriaceae[16]. Our data support earlier results obtained by Raghavendra et al. in 2009[17].

Following ciprofloxacin, the more noticeable reduction in PLI than (S & P) alone was seen with combination therapy of cimetidine gel plus (S & P); this result might be due to the effect of topical cimetidine which was a potent inhibitor of P. gingivalis[18].

The 3rd reduction of PLI was with the combination therapy of (S & P) plus metronidazole gel. The reduction may depend on the reduction of supra and subgingival plaque and removal of calculus. Also, this could be due to the role of metronidazole in the reduction of sensitive microorganisms such as bacteriodes species and spirochetes which are the main factors in plaque-associated gingivitis[19]. This result is in agreement with Al-Mubarak et al. in 2000[20].

The 4th reduction of PLI was in (S & P) alone, and this was due to the removal of pathogenic organisms found in dental plaque and calculus[21].

The least reduction of PLI, when compared with (S & P) alone, was seen with combination therapy of (S & P) plus meloxicam gel, this might be explained by the fact that meloxicam gel is ineffective against bacterial dental plaque; thereby it is ineffective in reducing PLI[22].

Effects on GI

The significant reduction in GI was seen in all groups with the highest reduction in GI seen in (S & P) plus cimetidine gel. This might be due to the anti-inflammatory effect of cimetidine by modulating T-cell function through inhibition of suppressor T-lymphocyte activity, an increase in interleukin-2 production, and enhancement of natural killer cell activity[23]. These observations suggest that H2 receptor antagonists may enhance host defenses through both humoral and cellular pathways and result in reduced inflammation.

The 2nd reduction in GI value after cimetidine was seen with the combination therapy of (S & P) plus ciprofloxacin gel; this could be due to the collective effect of ciprofloxacin and scaling. This result was in agreement with Raghavendra et al. in 2009[17].

The 3rd reduction in GI was the result of the combination therapy of (S & P) with metronidazole gel. This result was in agreement with the results obtained by Awartani and Zulqarnain in 1998[24], and this result could be related to the role of metronidazole in the reduction of sensitive microorganisms which is one of the main factors in chronic gingivitis.

The combination therapy of (S & P) plus meloxicam gel had the least effect in reducing GI when compared with ciprofloxacin, cimetidine, and metronidazole gel; this might be related to the fact that meloxicam results in a high reduction in GI only when systemically administered to the patients[25].

In (S & P) alone, this improvement was noticed by improvement in the condition of marginal gingival tissue by a decrease of inflammation since a controlled scaling itself result in some shrinkage of the gingival tissue due to the reduction of inflammation[26].

Effects on BOP

In all groups, significant decreasing of BOP was observed, but the highest reduction was with the combination therapy of (S & P) plus ciprofloxacin gel, this might be due to the antibacterial effect of

ciprofloxacin, this was in accordance with the results obtained by Raghavendra et al. in 2009[17].

After ciprofloxacin, the combination therapy of (S & P) plus cimetidine gel also resulted in decreasing of BOP.

The 3rd reduction of BOP was observed when metronidazole gel used as the adjunctive therapy to (S & P), this was in agreement with Stelzel et al. in 2000[19].

Regarding the effect of meloxicam gel when compared with the (S & P) alone, it had nearly the similar effect to that of (S & P) alone, this may be related to the low doses or concentration of the drug.

(S & P) without gel application resulted in decreasing BOP; this was explained by the fact that mechanical therapy has been used as the main treatment for chronic gingivitis as justified by Vinholis et al. in 2001[27].

In the present study, ciprofloxacin gel in reducing PLI and BOP was superior to metronidazole, cimetidine, and meloxicam gels, while for improvement of GI, cimetidine gel had the superior effect to metronidazole, ciprofloxacin, and meloxicam gels.

Effects on Salivary Enzymes

Numerous markers in saliva have been proposed as diagnostic tests for periodontal disease (gingivitis and periodontitis) such as intracellular enzymes (CK, LDH, AST, ALT).

In the present study, saliva was collected rather than gingival crevicular fluid GCF. Contrary to the GCF, there is plenty of saliva, and the procedure of its sampling is much easier and more bearable for the patient. In addition, the same enzymes as those in the GCF can be detected because of the simple and non-invasive method of collection.

In this present study the pretreatment activities of AST, ALT, CK, and LDH were increased in the saliva of all patients in each group with chronic gingivitis; but after treatment, the activity of examined salivary enzymes was significantly decreased for all five groups which probably resulted in gingival tissue repair after treatment. This result coincided with the results obtained by Todorovic et al. in 2006[28].

Moreover, metronidazole gel was more effective in decreasing the enzymatic activity of both AST and CK. Such finding might be explained by the presence of a high absorbance of metronidazole at the wavelength at which nicotinamide adenine dinucleotide [NADH] was determined. Therefore, lowering values of AST and CK might occur when these enzymes were measured by continuous flow methods based on endpoint decrease in reduced NADH [29, 30].

Furthermore, the findings of this study showed that cimetidine was more effective in reducing the enzymatic activity of both ALT and LDH, and this might be related to the local anti-inflammatory effect of cimetidine which helps in reducing gingival inflammation and decreasing the value of GI (31), after that by decreasing the value of GI. The activity of ALT and LDH was linearly decreasing depending on the good correlation between the activities of ALT and LDH in saliva and the value of GI. This fact was obtained by Todorovic et al. in 2006[28].

In summary, Ciprofloxacin and cimetidine gels prepared for this study promised to be the new candidate for the effective treatment of plaque-induced gingivitis, and they were superior to both metronidazole and meloxicam gels. For reduction in salivary enzymatic activity, metronidazole and cimetidine gels were superior to ciprofloxacin and meloxicam gels. Further studies are needed to evaluate the effect of (metronidazole, ciprofloxacin, cimetidine, and meloxicam) gels in the treatment of chronic periodontitis rather than gingivitis.

Acknowledgments

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Table 1. Patient grouping with their treatments S&P: Scaling & Polishing

Groups	Male	Female	Total	Treatment	Dose of drug
0	4	11	15	S & P alone	
1	7	8	15	S & P plus Metronidazole gel 1% w/w	1.5 gm Twice daily
2	7	8	15	S & P plus Ciprofloxacin gel 1% w/w	1.5 gm Twice daily
3	8	7	15	S & P plus Cimetidine gel 1% w/w	1.5 gm Twice daily
4	9	6	15	S & P plus Meloxicam gel 0.5% w/w	1.5 gm Twice daily

Table 2. Comparison of clinical parameters (PLI, GI and BOP) before and after treatment in all five groups.

Groups	Visits	Clinical Parameters (Mean ± SE)		
		PLI	GI	BOP
Group 0	Before	1.28 ± 0.091	1.14 ± 0.067	**0.92 ± 0.021**
	After	0.91 ± 0.034*	0.89 ± 0.022*	**0.78 ± 0.019***
Group 1	Before	1.21 ± 0.110	1.31 ± 0.078	**0.89 ± 0.026**
	After	0.54 ± 0.047*	0.57 ± 0.038*	**0.44 ± 0.045***
Group 2	Before	1.28 ± 0.076	1.19 ± 0.075	**0.93 ± 0.024**
	After	0.52 ± 0.029*	0.49 ± 0.048*	**0.15 ± 0.054***
Group 3	Before	1.32 ± 0.092	1.15 ± 0.075	**0.92 ± 0.020**
	After	0.54 ± 0.050*	0.41 ± 0.049*	**0.25 ± 0.045***
Group 4	Before	1.34 ± 0.112	1.31 ± 0.126	**0.93 ± 0.023**
	After	**0.99 ± 0.94***	**0.89 ± 0.078***	**0.77 ± 0.045***

* = Significant difference (P<0.05), PLI= plaque index, GI= gingival index, BOP= bleeding on probing, Group 0 = scaling & polishing alone, Group 1= scaling & polishing + metronidazole gel, Group 2 = scaling & polishing + ciprofloxacin gel, Group 3 = scaling & polishing + cimetidine gel, Group 4 = scaling & polishing + meloxicam gel.

Table 3 Comparison of biochemical parameters (AST, ALT, CK, and LDH) before and after treatment in all five groups.

Groups	Visits	Biochemical parameters (Mean ± SE)			
		AST	ALT	CK	LDH
Group 0	Before	21.20 ± 3.81	10.98 ± 2.44	1.73 ± 0.29	**317.6 ± 53.2**
	After	15.57 ± 2.78*	9.30 ± 1.87*	1.42 ± 0.23*	**266.3 ± 41.7***
Group 1	Before	24.00 ± 5.89	12.80 ± 3.21	4.14 ± 0.89	**233.1 ± 28.5**
	After	14.57 ± 2.45*	8.39 ± 1.77*	2.71 ± 0.54*	**161.5 ± 20.81***
Group 2	Before	25.02 ± 3.52	10.43 ± 2.30	2.37 ± 0.55	**317.7 ± 57.28**
	After	18.05 ± 3.15*	9.71 ± 2.03*	1.53 ± 0.20*	**244.2 ± 41.59***
Group 3	Before	28.69 ± 4.25	16.03 ± 2.34	3.70 ± 0.87	**233.8 ± 35.85**
	After	19.70 ± 2.88*	10.40 ± 1.41*	2.75 ± 0.61*	**159.4 ± 23.56***
Group 4	Before	34.20 ± 2.79	17.02 ± 2.65	3.47 ± 0.83	**385.6 ± 47.80**
	After	**27.53 ± 2.44***	**13.90 ± 1.72***	**2.13 ± 0.52***	**311.3 ± 43.91***

* = Significant difference (P<0.05), Group 0 = scaling & polishing alone, Group 1= scaling & polishing + metronidazole gel, Group 2 = scaling & polishing + ciprofloxacin gel, Group 3 = scaling & polishing + cimetidine gel, Group 4 = scaling & polishing + meloxicam gel.

Figure 1. Anterior view of gingival condition before and afer treatment with metronidazole gel.

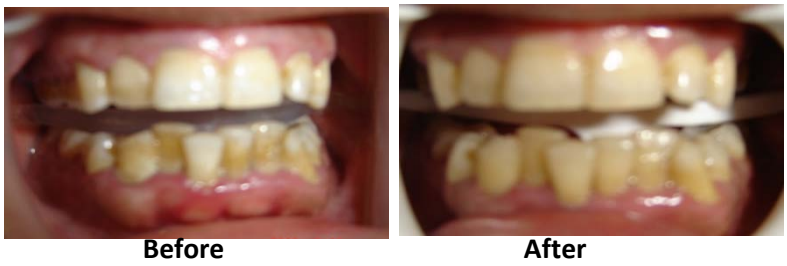


Figure 2. Anterior view of gingival condition before and afer treatment with ciprofloxacin gel.

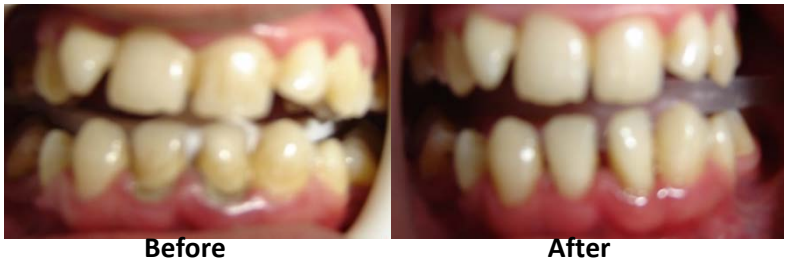


Figure 3. Anterior view of gingival condition before and afer treatment with cimetidine gel.

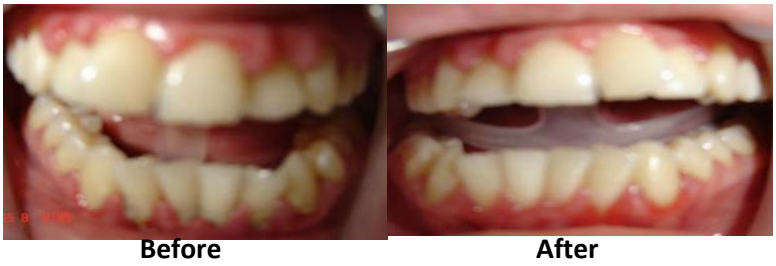
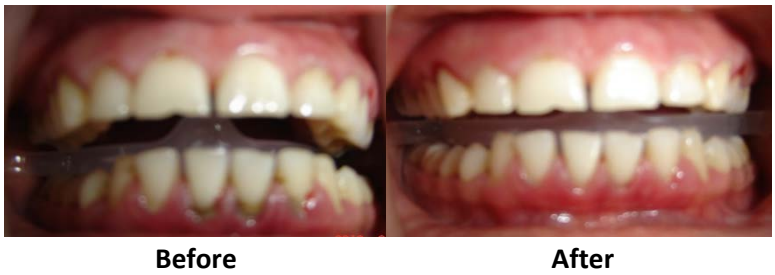
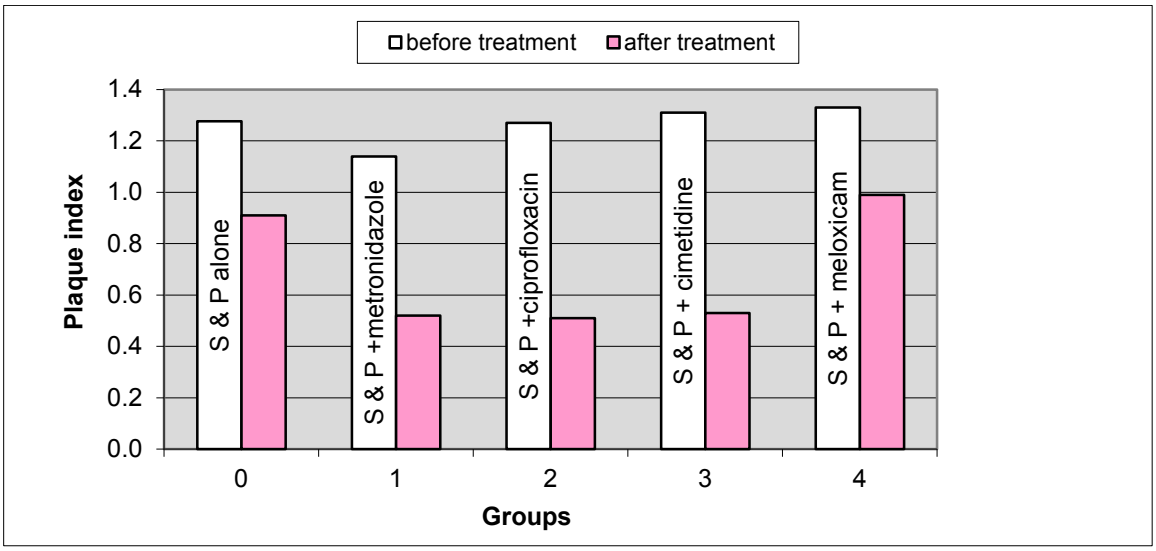


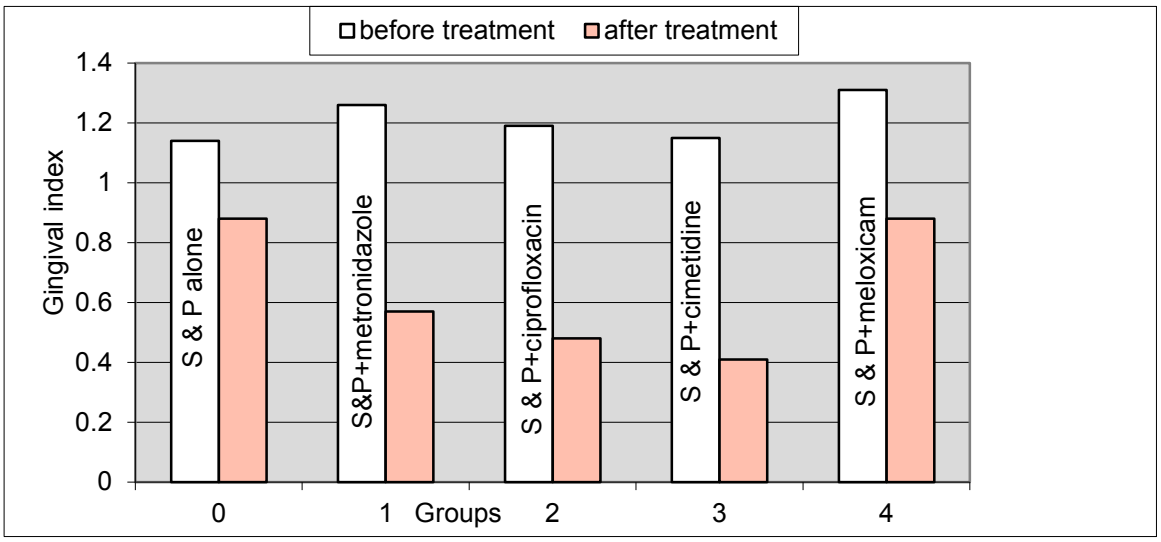
Figure 4. Anterior view of gingival condition before and afer treatment with meloxicam gel.





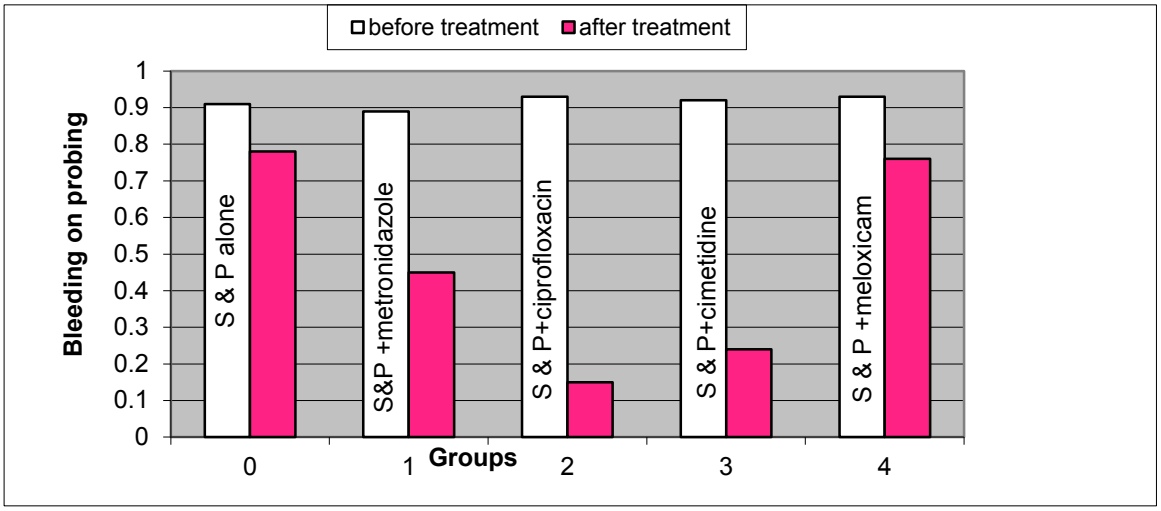
S & P: scaling & polishing, 0: S &P alone; 1: S & P + metronidazole gel; 2: S & P + ciprofloxacin; 3: S & P + cimetidine; 4: S & P + meloxicam

Figure 5. Mean Plaque Index (PLI) for all five groups collectively before and after treatment



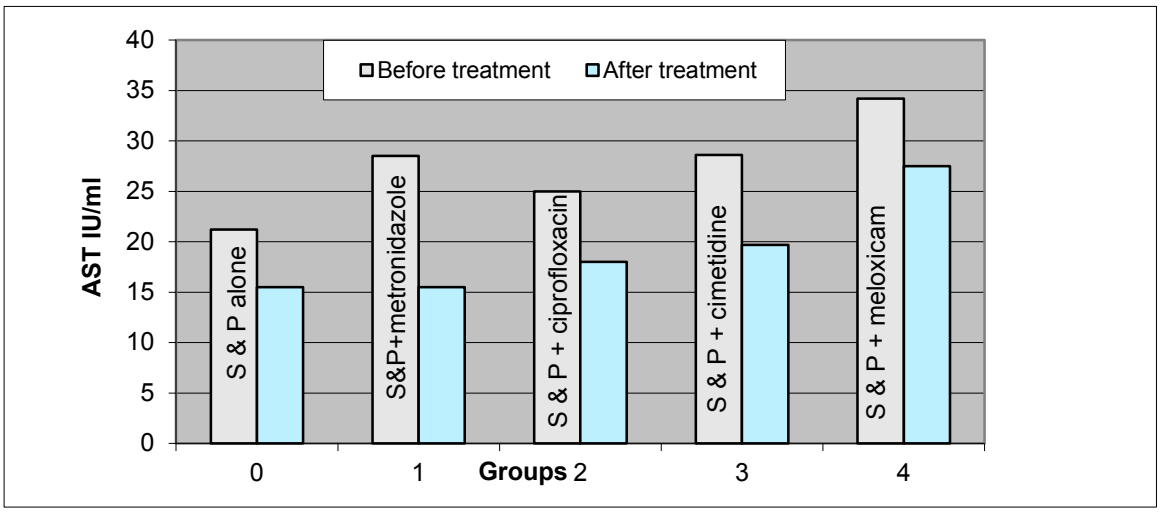
S & P: scaling & polishing, 0: S &P alone; 1: S & P + metronidazole gel; 2: S & P + ciprofloxacin; 3: S & P + cimetidine; 4: S & P + meloxicam

Figure 6. Mean Gingival Index (GI) for all five groups collectively before and after treatment



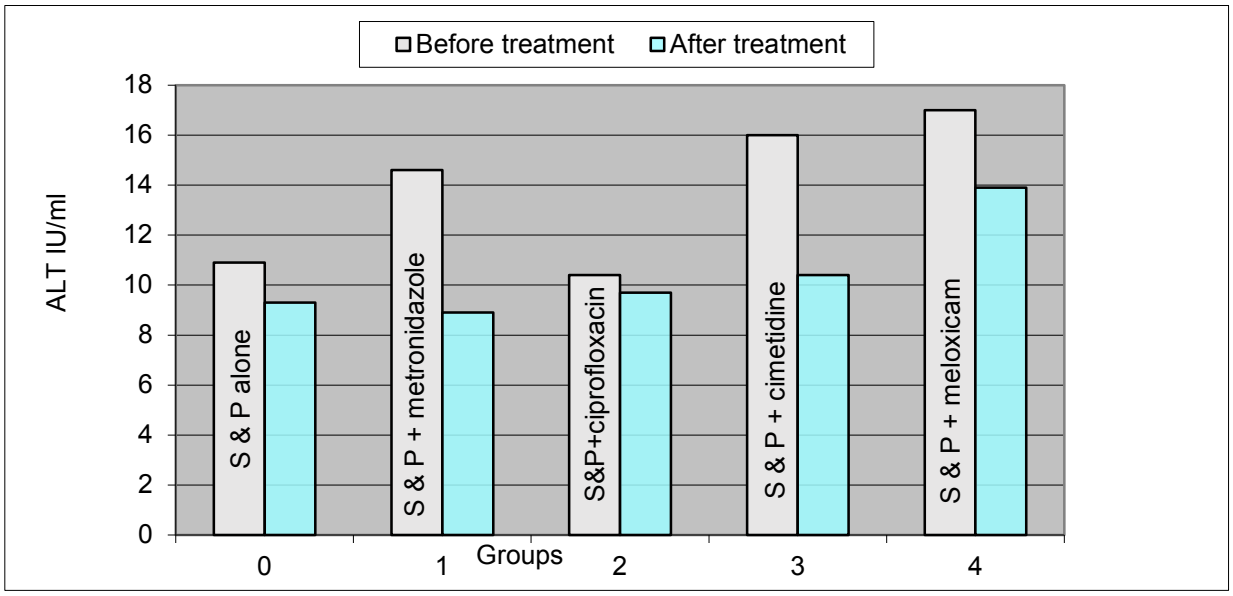
S & P: scaling & polishing, 0: S &P alone; 1: S & P + metronidazole gel; 2: S & P + ciprofloxacin; 3: S & P + cimetidine; 4: S & P + meloxicam

Figure 7. Mean Bleeding on probing (BOP) for all five groups collectively before and after treatment



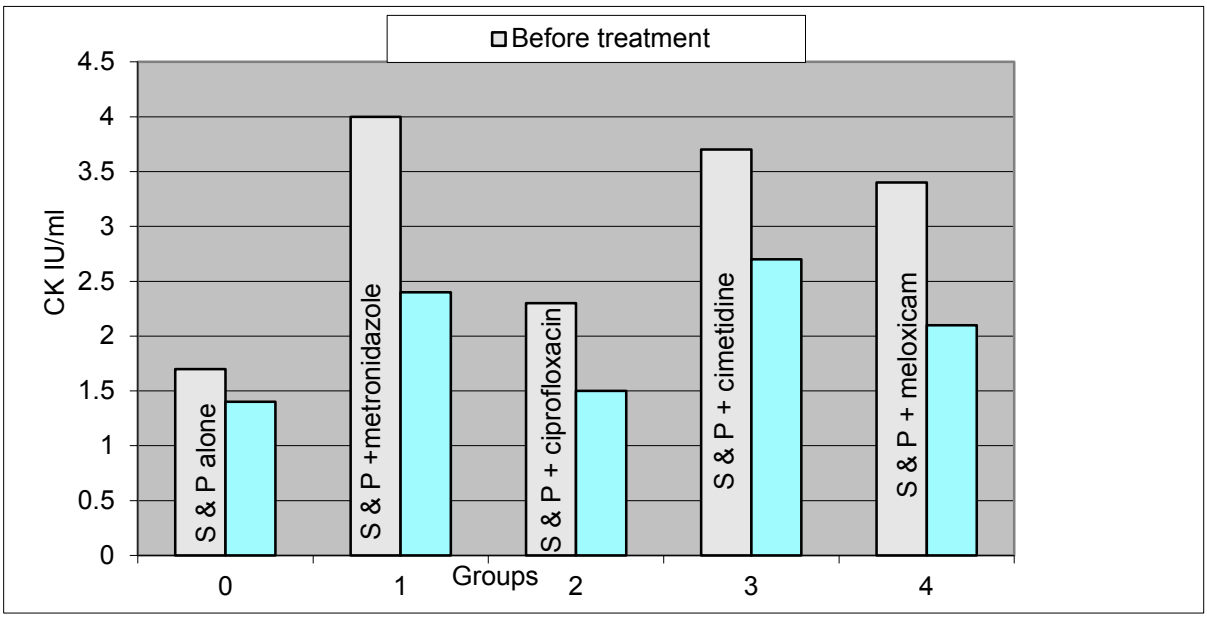
S & P: scaling & polishing, 0: S &P alone; 1: S & P + metronidazole gel; 2: S & P + ciprofloxacin; 3: S & P + cimetidine; 4: S & P + meloxicam

Figure 8. AST for all five groups before and after treatment



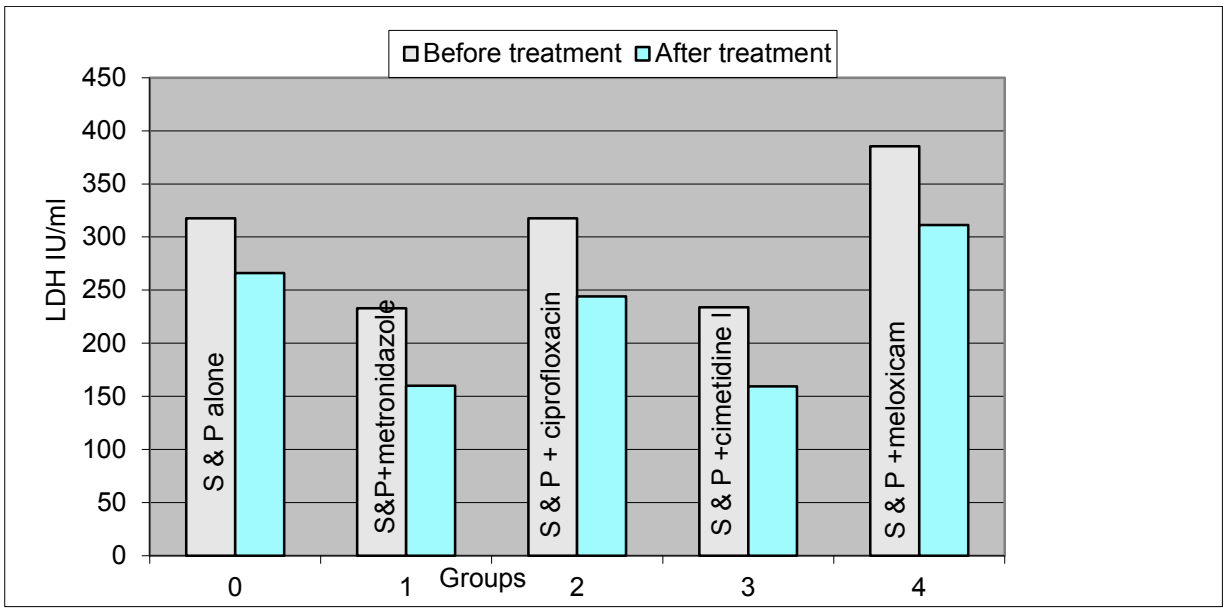
S & P: scaling & polishing, 0: S &P alone; 1: S & P + metronidazole gel; 2: S & P + ciprofloxacin; 3: S & P + cimetidine; 4: S & P + meloxicam

Figure 9. ALT for all five groups before and after treatment



S & P: scaling & polishing, 0: S &P alone; 1: S & P + metronidazole gel; 2: S & P + ciprofloxacin; 3: S & P + cimetidine; 4: S & P + meloxicam

Figure 10. CK for all five groups before and after treatment



S & P: scaling & polishing, 0: S &P alone; 1: S & P + metronidazole gel; 2: S & P + ciprofloxacin; 3: S & P + cimetidine; 4: S & P + meloxicam

Figure 11. LDH for all five groups before and after treatment

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