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Efficacy of Azithromycin in Comparison with Metronidazole in the Treatment of Chronic Periodontitis

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الخلاصة

الاهداف:تهدف الدراسة الى تقييم الفعالية السريرية للمضاد الحيوي (أزيثرومايسين) عند اعطائه كعلاج اضافي بعد عملية تقليح و تسطيح الجذور و مقارنته بالمضاد الحيوي (الميترونايديزول) في علاج الالتهاب المزمن للأنسجة الرابطة للأسنان.**المواد و طرائق العمل**: اختير اربع و اربعون مريضا مشخصين بالتهاب الأنسجة الرابطة المزمن و قبل البدء بالعلاج تلقى المرضى تنظيفا" شاملا" للأسنان و تقليحا" و تسطيحا" لجذور الأسنان. بعد التنظيف قسم المرضى الى ثلاث مجاميع علاجية: المجموعة الأولى تحتوي على عشرين مريضا اعطى جرعة الأزيثرومايسين(٥٠٠ ملغم مرة واحدة في اليوم) لمدة ثلاثة أيام كعلاج اضافي الى التقليح و تسطيح الجذور. المجموعة الثانية تحتوي على احد عشر مريضا" اعطى جرعة الميترونايديزول (٥٠٠ ملغم ، ٣ مرات في اليوم) لمدة سبعة أيام كعلاج اضافي الى التقليح و تسطيح الجذور. أما المجموعة الثالثة تحتوي على ثلاثة عشر مريضا" اعطى لها جرعة (بلاسيبو كبسول) مرة واحدة باليوم لمدة ثلاثة أيام كمجموعة ضابطة (سيطرة) فضلا عن التقليح و تسطيح الجذور. **النتائج** : كان تقييم النتائج السريرية للطرائق العلاجية بواسطة تسجيل مؤشرات ماحول الأسنان كمؤشر قياس التهاب (gingival index) التعرف على النزف اللثوي باستخدام مؤشر الموجود أو المفقود عند التسمير ثم قياس عمق الجيب. هذه القياسات أخذت من المرضى قبل بدء العلاج و بعد اربعين يوما من تلقي العلاج. التحليل الأحصائي للبيانات أوضح وجود تحسنا ملحوظا من كافة المؤشرات السريرية لدى المجاميع الثلاثة بعد أربعين يوما من العلاج مقارنة بقيمتها عند الفحص من القاعدة باستثناء المجموعة الضابطة التي اظهرت عدم تحسن ووجود نزف من الجيوب اللثوية عند التسمير. و عند المقارنة بين المجاميع الثلاثة لوحظ وجود فروقات احصائية معنوية في مؤشر التهاب اللثة و نسبة وجود نزف من الجيوب اللثوية عند التسمير عند المرضى الذين تلقوا علاج (الأزيثرومايسين) مقارنة بالمجموعة الضابطة، و لم تظهر اية فروقات معنوية في كافة المؤشرات السريرية عند المرضى الذين تلقوا علاج (الميترونايديزول) مقارنة بالمجموعة الضابطة. **الأستنتاجات** : اظهرت هذه الدراسة أظهرت أن استخدام الأزيثرومايسين كعلاج اضافي الى التقليح و تسطيح الجذور، اعطى تحسنا ملحوظا للأنسجة الداعمة الرابطة حول الأسنان مقارنة بالتقليح و تسطيح الجذور بمفرده، و أن الأزيثرومايسين له فعالية ايجابية و مفضلا على (الميترونايديزول) عند المرضى المصابين بالتهاب الأنسجة الرابطة المزمن.

ABSTRACT

Aims: The aim of this study was to evaluate the clinical effects of systemic azithromycin as an adjunct to scaling and root planning (SRP) and compared it with metronidazole in the treatment of chronic periodontitis. **Materials and Methods**: Forty four patients with clinical diagnosis of chronic periodontitis underwent scaling and root planing were divided into three groups. The first group (n = 20) patients received azithromycin 500 mg once daily for 3 days plus SRP. The second group (n= 11) received metronidazole 500 mg 3 times daily for 7 days plus SRP. The third control group (n= 13) patient received SRP plus placebo treatment once daily for 3 days. Clinical measurement including gingival index, bleeding on probing and probing pocket depth were performed at the base line visit and 40 days after taking the treatment. **Results**: The results obtained at 40 days from the base line showed better significant improvement in all clinical parameters ($p \leq 0.05$) in the treated groups, except for bleeding on probing in control group were no significant improvement was reported. Azithromycin plus SRP give the greatest improvement in mean gingival index and bleeding on probing ($p < 0.05$) when compared with the control group but no significant differences were observed between metronidazole treated group and the control group. **Conclusions**: The adjunctive use of azithromycin with SRP has potential to improve periodontal health over SRP only and could be an interesting alternative to metronidazole from patients with chronic periodontitis.

Key Words: Azithromycin, metronidazole, chronic periodontitis.

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INTRODUCTION

Chronic periodontitis is an infectious inflammatory diseases of tooth supporting apparatus with progressive attachment loss and loss of alveolar bone.(1) Chronic periodontitis is characterized by gingival enlargement, redness, bleeding during brushing, bad taste in the mouth, sensitive tooth, gingival bleeding upon probing, periodontal pocket formation, bone loss and the end

result tooth mobility and gradual loosing of the tooth.[2] Chronic periodontitis occur frequently after the age of 30 years and may also occur in children and adolescents. Periodontal destruction correlates to the amount of local etiological factors that are frequently subgingival calculus and various associated microflora.[3] Periodontal diseases are caused by a number of microorganism, anaerobic bacteria which are often referred to as indicator microorganism have been implicated in initiation and progression of periodontitis.[4] Most of periodontal investigators agree that bacteria are the primary etiological agent of destructive periodontal disease it have been reported that periodontal pocket is colonized by a host of different bacteria, approximately 500 different bacterial species were associated with subgingival plaque.[5] The most common periodontal pathogens are anaerobic which indicates that the periodontitis can be diagnosed and treated as an anaerobic infection, microorganisms are commonly recognized as *Prophyromonas gingivalis*, *Tannerella forsythia*, *Actinobacillus actinomycetemcomitans and various spirochetes*.[6]

The treatment of periodontal disease has been carried by a non surgical debridment and regular periodontal maintenance care.[7] The vast majority of periodontal cases respond well to conventional non surgical periodontal therapy, i.e. scaling and root planning, improve oral hygiene and supportive periodontal recall.[8] However, certain patients for various reasons don't respond favorably to mechanical therapy alone, for those patients. the use of an appropriate adjunctive antimicrobial agents is often beneficial.[9] The use of chemical agents in the control of periodontal pathogenic microorganisms can provide more effective and predictable clinical results as they are less expensive and more easily accepted by many patients than others complex and traumatic treatment like periodontal surgeries.[10,11] Moreover, systemic antibiotic therapy can be essential in eliminating pathogenic bacteria that invade gingival tissue and help in control periodontal pathogens that residing in various domains of the mouth from where they can translocate to the periodontal sites.[12] Various antimicrobial and antiseptic agents were identified; they have beneficial effect in chronic periodontitis include tetracycline[13], doxycycline[14], chlorhexidine[15], clindamycin[16,17], metronidazole[18], combination of metronidazole and amoxicillin[19] and azithromycin.[20]

Metronidazole is a synthetic antimicrobial drug has antibacterial activity against gram negative anaerobic pathogens responsible for both acute orofacial infections and chronic periodontitis. [21]

Azithromycin is an azalid antibiotic with excellent in vitro activity against a wide variety of oral bacteria, it has long half life good tissue penetration.[22] In addition, azithromycin is taken up by phagocytes and released over long periods in inflamed tissue ,it requires a total of only three doses of 500 mg to produce its therapeutic effects.[23] Haas *et al*. (2008) reported that the use of azithromycin has potential to improve periodontal health of young patients with aggressive periodontitis.[24] Moreover, Schmidt and Bretz (2007) showed that using additional courses of azithromycin has beneficial effects in the treatment of periodontal abscesses.[25]

MATERIALS AND METHODS

Forty four systemically healthy patients 22 female and 20 male participate in this study,their age range between(20-45years) with chronic periodontitis were divided into three treatment groups: the first group (n= 20) received SRP plus azithromycin (500 mg 1x day) for 3 days. The second group (n= 11) received SRP plus metronidazole (500 mg 1x 3) for 7 days. The third group (control n= 13) received SRP plus placebo (glucose capsule 1x day) for 3 days.

Clinical examination was done for each patient at base line (0 day) and 40 days post therapy in total of 95 teeth/ 190 sites represented at least two periodontal sites in anterior and posterior teeth with probing pocket depth $\geq$ 4mm.

Clinical parameters were evaluated which include gingival index (Loe index, 1967)[26], bleeding on probing (detected after 30 second of probe insertion into gingival sulcus) and probing pocket depth according to Ainemo *et al*.[3] After completion of the base line recording, all se-

lected teeth were scaled and root planed and the patients were instructed to take azithromycin, metronidazole and placebo separately according to study groups, all parameters were evaluated 40 days after treatment.

Data were expressed as the mean ± standard deviation (± SD). Means were compared using sample student t – test as appropriate to compare changes in different parameters, this relative change may result in different *p* values ($p \leq 0.05$). Anova and duncan test was used to compare the differences in parameters among three different groups.

RESULTS

The data in table (1) represented the mean ±SD of the three parameters(gingival index, bleeding on probing and probing pocket depth) in all treated groups participated in the study at base line visit (0day) and those values obtained after 40 days of treatment.

Table (1): Mean ± standard deviation of gingival index, bleeding on probing and probing pocket depth (in mm) at the baseline sample and after 40 days of treatment in all study groups

Treatment Groups	Time (Day)	Gingival Index	Bleeding on Probing	Probing Pocket Depth
		Mean ± SD		
Group 1: SRP + Azithromycin n = 20	0	1.65 ± 0.587	0.95 ± 0.224	4.13 ± 0.897
	40	0.40 ± 0.503	0.25 ± 0.444	1.99 ± 0.609
Group 2: SRP + Metronidazole n = 11	0	1.55 ± 0.522	0.64 ± 0.505	3.93 ± 1.034
	40	0.82 ± 0.603	0.18 ± 0.405	1.98 ± 0.583
Group 3 (Control): SRP + Placebo n = 13	0	1.54 ± 0.519	0.62 ± 0.506	3.75 ± 0.819
	40	1.80 ± 0.641	0.46 ± 0.519	2.36 ± 0.773

In Table (2) all parameter showed significant differences ($p \leq 0.05$) in azithromycin treated group.

For metronidazole group, all the parameters were significantly different ($p \leq 0.05$) after 40 days from the base line.

There were significant differences ($p \leq 0.05$) detected in placebo treated group for gingival index and probing pocket depth between the tow day (0) and after 40 days of treatment. However, no significant differences demonstrated in bleeding on probing as shown in Table (2).

Table (2): Comparison the changes in gingival index, bleeding on probing and probing pocket depth between the baseline and after 40 days of treatment in all study groups

Treatment Groups	Parameter	t–value (Paired Test)	d.f.	*p*–value
Group 1: SRP + Azithromycin n = 20	Gingival Index	8.753	19	0.000*
	Bleeding on Probing	6.658	19	0.000*
	Probing Pocket Depth	9.564	19	0.000*
Group 2: SRP + Metronidazole n = 11	Gingival Index	2.667	10	0.024*
	Bleeding on Probing	2.887	10	0.016*
	Probing Pocket Depth	5.885	10	0.000*
Group 3 (Control): SRP + Placebo n = 13	Gingival Index	3.207	12	0.008*
	Bleeding on Probing	1.477	12	0.165
	Probing Pocket Depth	5.885	12	0.000*

* Significant difference existed at $p \leq 0.05$.

ANOVA test in table (3) revealed that there were significant differences ($P \leq 0.05$) in both gingival index and bleeding on probing among different groups, but there was no significant difference ($P > 0.05$) in probing pocket depth level.

Table (3): Analysis of variance (ANOVA) for the difference between baseline and after 40 days of treatment among different study groups

Parameter	S.O.V.	SS	d.f.	MS	F–value	*p*–value
Gingival Index	Between Groups	5.269	2	2.635	5.637	0.007*
	Within Groups	19.163	41	0.467		
	Total	24.432	43			
Bleeding on Probing	Between Groups	2.358	2	1.179	5.607	0.007*
	Within Groups	8.620	41	0.210		
	Total	10.977	43			
Probing Pocket Depth	Between Groups	4.611	2	2.305	2.513	0.093
	Within Groups	37.616	41	0.917		
	Total	42.226	43			

* Significant difference existed at $p \leq 0.05$. S.O.V. source of variance. SS: sum of square. d.f: degree of freedom. MS: mean square

Table (4) and Figure (1) showed comparison between the changes in parameters studied in three treated groups. There were significant differences in both gingival index and bleeding on probing between azithromycin treated group and placebo group ($p \leq 0.05$). However, there were no significant differences in probing pocket depth between the three groups.

Table (4): Mean ± standard deviation and Duncan's Multiple Range Test of gingival index, bleeding on probing and probing pocket depth among different study groups

Parameters	SRP + Azithromycin	SRP + Metronidazole	SRP + Placebo (Control)
		Mean ± SD	
Gingival Index	1.250 ± 0.639 ^{B}	0.727 ± 0.905 ^{AB}	0.462 ± 0.519 ^{A}
Bleeding on Probing	0.700 ± 0.470 ^{B}	0.455 ± 0.522 ^{AB}	0.154 ± 0.376 ^{A}
Probing Pocket depth	4.143 ± 1.002 ^{A}	1.946 ± 0.995 ^{A}	1.385 ± 0.848 ^{A}

Means with different letters horizontally were statistically significant at $p \leq 0.05$.

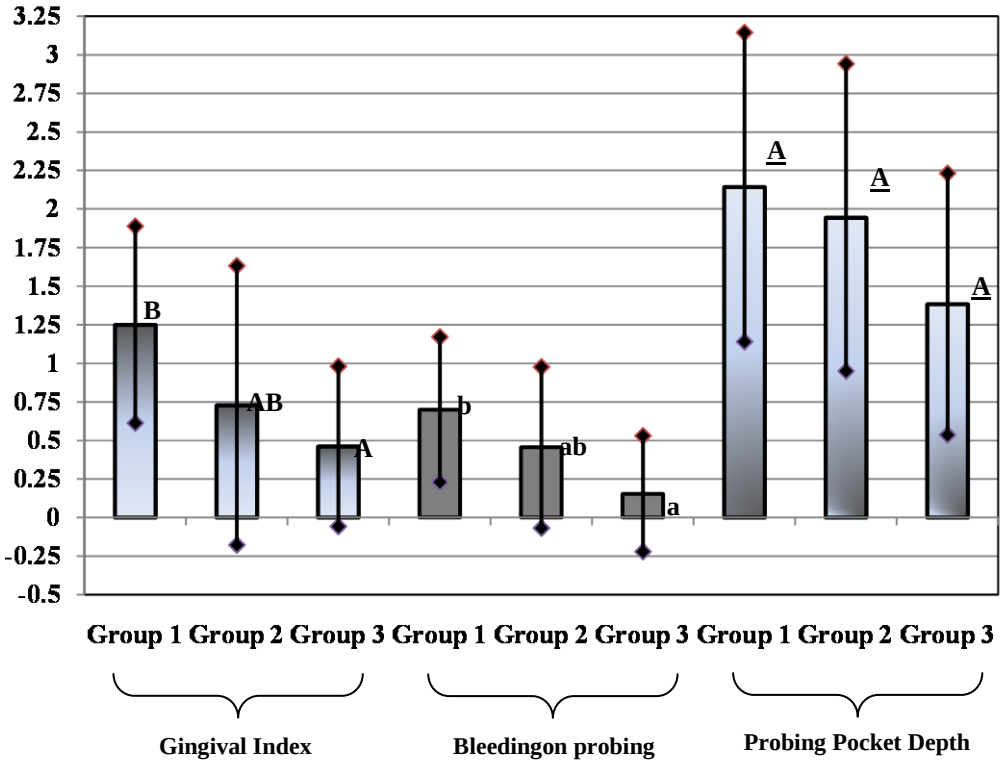

Figure (1): Mean ± standard deviation and Duncan's Multiple Range Test of gingival index, bleeding on probing and probing pocket depth among different study groups
Means with different letters were statistically significant at $p \leq 0.05$.

DISCUSSION

In the present study, assessment was made on base line and after 40 days of treatment in patients with chronic periodontitis. treatment give improvement in gingival index, bleeding on probing and probing pocket depth, these were supported by other studies.[27,28] The mechanism of this improvement detected by many researchers which revealed that azithromycin retained in target tissues for a long time and detectable in the inflamed periodontal tissues after systemic treatment with antibiotic.[29,30] Moreover, azithromycin has been reported to penetrate both healthy and diseases periodontal tissue exceeded the minimum inhibitory concentration of most pathogens involved in the pathophysiology of chronic inflammatory periodontal disease.[31] Recent study reported that azithromycin was effective in vitro biofilm model of periodontal disease and suggest the feasibility of azithromycin for treatment of periodontal disease as abiofilm infectious disease.[32] In metronidazole treated group the decrease of gingival inflammation was related to the reduction of gingival index, bleeding on probing,with Reduction in pocket depth which is appeared after 40 of treatment l. These results agreed with other studies.[19] Carvalho *et al*. (2004) suggested that a significant clinical benefit in combing SRP with metronidazole with weekly professional supragingival plaque removal for treatment of chronic periodontitis.[18] another study demonstrated that the adjunct use of metronidazole conjunction with SRP result in reduction of spirochetes and gram negative anaerobic bacteria and were effective in treating adult periodontitis patients exhibiting deeper pockets that contain a susceptible gram negative anaerobic bacteria.[33]

Significant differences could be observed in the treatment of group with pla-

cebo in gingival index and probing pocket depth from the base line. However, lower but not significant improving observed in bleeding on probing and have fewer sites still bleed on probing. These results were consistent with the finding of other study[34], this could explain that supragingival dental plaques and bacteria are removed by professional mechanical tooth cleaning, but it will not be effective because subgingival dental plaque and bacteria invading periodontal tissues are difficult to be remove and need adjunct systemic treatment.[35] Bonito *et al*. (2004) detected that SRP is intended to reduce the bacterial load, shrink swollen and inflamed gingival, and recondition the subgingival ecology, making it biologically compatible with optimal healing and reattachment of epithelium to the root surface.[11] Another study demonstrated that the reduction in gingival inflammation seem to be directly associated with a decrease in plaque formation and decrease in gingival index and the treatment by scaling and root planning results in significant clinical improvement, but may not arrest the progression or recurrence of disease whether pathogen microorganism are still present at local subgingival site at completion of active treatment.[36] However, systemic antibiotics significantly accelerate the suppression of the periodontal microflora but have limited effect on the elimination of target isolates during healing.[37]

In comparison with azithromysin treated group and placebo group, the clinical changes observed significant differences in gingival index, bleeding on probing between two groups. However, no significant difference detected in probing pocket depth. These results were similar to those observed by other studies.[10,11,27] Simth *et al*. (2002) conducted that treated patients with azithromycin showed an improvement in gingival inflammation with fewer sites continuing to bleed on probing and fewer failing to improve in probing depth when compared with the control (placebo) group.[29] However, Plaza *et al*. (2003) showed that significant superiority only in the gingival index[38]. These results may be explain by other study which revealed that the count of anaerobes and spirochetes were significantly lower throughout the treatment with azithromycin compared to the placepo group.[39]

All parameters showed no significant differences between patients take azithromycin and patients take metronidazole. These results supported by Haffajee *et al*. (2008) found that both azithromycin and metronidazole give similar reduction of some species of bacteria after 2 weeks of treatment and had better clinical response in periodontal tissue[40], this could explain the improvement in periodontal tissue in two groups.

There were no significant difference demonstrated in all clinical parameters between placebo group and metronidazole treated group, this was in agreement with Salonge *et al*. (2004) who concluded that the use of systemic metronidazole resulted in clinical improvement but could not observed additional effects of metronidazole comparing with the control group.[41]

CONCLUSIONS

This study concluded that azithromycin treated group resulted in abetter clinical improvement of periodontal health of the patient after 40 days of treatment. Azithromycin provide significant advantage over metronidazole or SRP alone and might be useful agent for treatment of chronic periodontitis and other type of bacterial infection.

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