

Effects of Cefepime Versus Doxycycline on Alveolar Bone Loss and Gingival Recession in Smoker Dental Patients: Clinical Trial.

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الخلاصة

أهداف الدراسة: تهدف الدراسة الى تحديد شدة فقدان العظم السنخي ومدى انتشاره بين المرضى المدخنين ومقارنة بغير المدخنين وتقييم تأثير عقار السفييم مقارنة بعقار الدوكسيسايكلين على شفاء أمراض اللثة عند المرضى المدخنين. **المواد والطرائق:** أجريت هذه الدراسة على 80 مريضاً، (40) منهم كانوا من المدخنين والنصف الأخر (40) كانوا من غير المدخنين. تراوحت أعمار المرضى بين 20-50 سنة وقد تم اختيارهم من المرضى المراجعين لعيادات طب الأسنان/كلية طب الأسنان/جامعة الموصل. تم تحديد المدخنين من خلال استفتاء اجري على هؤلاء المرضى، وبعد ذلك تم قياس نسبة التصاق اللثة بالعظم حسب (1959) Ramfjord gingival sulcus measurement index كما تم قياس ذوبان العظم السنخي بواسطة أشعة X. المجموع الكلي للمرضى المدخنين (40) تم علاجهم بواسطة علاج اللثة المساعد ثم تم تقسيمهم عشوائياً إلى مجموعتين، المجموعة الأولى (20) مريضاً تم علاجهم بواسطة مسحوق عقار السفييم المخلوط بالماء المقطر بينما تم علاج المجموعة الثانية (20) مريضاً بواسطة مسحوق عقار الدوكسيسايكلين المخلوط بالماء المقطر. تم حقن كلا العقارين داخل جيوب اللثة وتمت المحافظة عليه داخل الفم لمدة 15 دقيقة وبعد ذلك تم غسله بالماء المقطر. أجريت لكل مريض على جلسة علاج واحدة لك ل أسبوع ولمدة 6 اشهر وبعدها تم إجراء القياسات السريرية وقياس الأشعة لكل مريض عند بداية الدراسة وبعد 2,4,6 أشهر. **النتائج:** تم إجراء التحليل الإحصائي للنتائج حسب طريقة unpaired t-test ووجدت فروقات معنوية في نسبة التصاق اللثة $p \leq 0.000$ وذوبان العظم $p \leq 0.001$ بين المدخنين وغير المدخنين، بينما لم يوجد فرق معنوي بين المدخنين المعالجين بعقار السفييم مقارنة بأولئك المعالجين بعقار الدوكسيسايكلين لكل من التصاق اللثة قبل العلاج $p \leq 0.893$ و(بعد العلاج $p \leq 0.668$). اما بالنسبة إلى ذوبان العظم فقد كان (قبل العلاج $p \leq 1.000$) و(بعد العلاج $p \leq 0.849$). **الاستنتاج:** يعد التدخين متغير أساسي ومهم في التأثير على صحة أنسجة اللثة والاستخدام الموضعي للمضادات الحيوية في مواضع الإصابة بأمراض اللثة يمكن أن يكون عاملاً مساعداً للعلاج التقليدي لأمراض اللثة.

ABSTRACT

Aims: To determine the prevalence and severity of attachment loss and bone loss among smokers and to compare them with non smokers and to assess the effect of cefepime compared to doxycycline in the outcomes of healing of these periodontal diseases in smoker patients. **Materials and Methods:** This study was carried out on 80 patients, half of which were smokers(40) and the other were nonsmokers, aged from 20 – 50 years, attending the teaching dental clinics in the College of Dentistry, University of Mosul. Questionnaire of smoking habit was applied on smoker patients. Clinical measurements were done including attachment loss and carried out according to Ramfjord gingival sulcus measurement index, Bone loss was measured radiographically with an x – ray unit. A total of 40 smoker patients were received supportive periodontal therapy and then randomly divided into 2 groups, first group (20 patients) were treated by cefepime powder mixed with distilled water and second group (20 patients) were treated by doxycycline powder mixed with distilled water. Both drugs were injected into periodontal pocket and remained in the oral cavity for 15 min then rinsed with distilled water. Each patient receive one session of treatment / once a week for 6 months. Clinical and radiographical parameters of attachment and bone loss were measured at baseline , 2, 4 and 6 months recall visits. **Results:** Unpaired t – test was used for statistical analysis of the data and there were significant differences of attachment loss ($p \leq 0.000$) and bone loss ($p \leq 0.001$) between smoker and non smokers . There were no significant differences between smokers treated with cefepime compared to those treated by doxycycline for attachment loss (before treatment $p \leq 0.893$, after treatment $p < 0.668$) and for bone loss (before treatment $p < 1.000$, after treatment $p < 0.849$). **Conclusions:** Tobacco use is an important variable affecting the health of periodontal tissues. Topical application of antimicrobial agents at the site of periodontal diseases may be a useful adjunct to the conventional periodontal treatment.

Key Words: Attachment loss, bone loss, smoking, cefepime, doxycycline , periodontal diseases .

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INTRODUCTION

Smoking is directly related to a variety of medical problems. There has been an increasing awareness of the role of tobacco use in the prevalence and severity of periodontal diseases and subsequent tooth loss.⁽¹⁾ The typical characteristic of smoking – associated periodontal disease is the destruction of the supporting tissues of the teeth, with the ensuing clinical symptoms of bone loss, attachment loss, pocket formation, and eventually tooth loss.⁽²⁾

Those periodontal diseases are infections and thus antibiotics are often employed as adjuncts for their control⁽³⁾. Locally applied antimicrobials have found to produce higher local concentrations of the drug and lower systemic concentrations, increasing the effectiveness at site and decreasing the risk of systemic side effects.⁽⁴⁾ The newer group of tetracyclines which are inhibitors of bacterial protein synthesis includes doxycycline, methacycline and minocycline.⁽⁵⁾ Doxycycline possesses antibacterial properties as well as other biologic actions that may result in an increased production and maintenance of collagen and bone, and enhance treatment of periodontal diseases⁽⁶⁾. Other antibiotic is cefepime which is a fourth generation cephalosporins acts by inhibition of bacterial cell wall synthesis and exhibited antibacterial activity that can be useful for management of periodontal diseases.⁽⁷⁾

The purpose of this study was to determine the prevalence and severity of periodontal disease (attachment loss and bone loss) among smokers and to compare them with non smokers. The effect of cefepime compared to doxycycline in the outcomes of healing of both attachment loss and bone loss in smoker patients has been assessed.

MATERIALS AND METHODS

The subjects of this study were 80 patients aged (20 – 50) years, 40 patients were non smoker while 40 were smokers, attending teaching dental clinics in the College of Dentistry, University of Mosul.

All patients were informed of the purposes of the investigation and treatment.

The selection criteria of patients included the following:

1. All the patients were in good general health and those with any systemic diseases or drug intake were excluded from the study.
2. Patients with allergy to any type of antibiotics were excluded from the study.

Questionnaire about smoking habit has been recorded for smoker patients including number of cigarette smoked / day and duration of smoking. All the clinical measurements were done on a dental unit under light vision, using mirror and periodontal probe.

The measurements included the following:

1. Loss of attachment: This was carried out according to Ramfjord Gingival Sulcus Measurement Index (1959).

The distance between CEJ and the base of the probing depth was measured to the nearest millimeter with calibrated probe. The measurements were made at the interproximal surfaces only of each tooth except third molar which was excluded. The distance was measured indirectly by subtracting the distance from the gingival margin to the CEJ from the probing pocket depth. The level of CEJ could be determined by feeling it with the probe.⁽⁸⁾

2. Bone loss (radiographic examination) each radiograph examination was undertaken with x – ray unit (Trophy 94, type minoRex) operated at 50 KVP and 8 m.a using intra oral film size – 2 – speed – D – .

Two periapical radiographic films have been taken for every subject, one for the upper anterior and one for the lower anterior teeth, 9 bite wing radiographic films for each posterior site had been taken. The radiographs were developed under standardized conditions. The distance from CEJ to the alveolar crest was measured and if it exceeded 2 mm it was considered as bone loss.

A total of 40 smoker patients received supportive periodontal therapy including scaling and root planning. They were randomly divided into 2 groups, first group; (20 patients) were treated by cefepime powder (500mg), LABORATE PHAR-

MACEUTICAL(INDIA), mixed with distilled water (0.5 ml) and the second group (20 patients) were treated by doxycycline powder(500 mg),SDI, mixed with distilled water (0.5) . Both drugs were injected directly into the periodontal pocket and remain for 15 min, then rinsed with distilled water.

Each patient received one session of treatment / week for 6 months. Clinical and radiographical parameters of attachment and bone loss were measured at baseline and 2, 4 and 6 months.

Statistical analysis (unpaired t - test) was used to determine the differences between non smoker and smoker patients in relation to attachment and bone loss. Paired t – test was used to determine the statistical significant differences at $p < 0.05$ of attachment and bone loss before and after treatment with cefepime and doxycycline and to compare the effects of these 2 drugs.

RESULTS

Statistical analysis of the data was carried out using unpaired t – test to examine the differences in attachment and

bone loss between first group (non smokers) and second group (smokers). The mean of age was (34.48 ± 8.61) , (37.13 ± 6.88) , respectively. The mean attachment loss values for non smokers and smokers were (3.23 ± 0.77) , (4.53 ± 1.15) respectively, while for bone loss values they were (4.78 ± 0.70) , (5.30 ± 0.69) respectively. There was a significant difference of attachment loss ($p \leq 0.000$) and bone loss ($p \leq 0.001$) between two groups, (Table 1). The distribution of smokers according to the number cigarette smoked / day and duration of smoking were presented in Table (2) and (3), respectively. Table (4) showed that there were no significant differences between smokers treated with cefepime and those treated by doxycycline for attachment loss and for bone loss .

Both therapies (cefepime and doxycycline) yielded statistical significant differences on attachment loss and bone loss before and after treatment at $p < 0.05$ this is showed in Table (5) and (6).

Table (1): Unpaired t – test in relation to attachment loss and bone loss for both non smoker and smoker dental patients

Periodontal diseases	Non smoker	Smoker	P - value
	Mean \pm SD	Mean \pm SD	
Attachment loss	4.53 \pm 1.15	3.23 \pm 0.77	*0.000
Bone loss	5.30 \pm 0.69	4.78 \pm 0.70	*0.001

SD = standard deviation; *Significant difference at $p \leq 0.05$

Table (2): The distribution of smokers according to the number of cigarette smoked / day.

No. of Cigarette / day	No. (%)
< 10	9 (22.5)
10 – 20	20 (50.0)
\geq 20	11 (27.5)
Total	40 (100.0)

Table (3): The distribution of smokers according to the duration of smoking

Duration (Years)	No. (%)
< 10	3 (7.5)
10 – 20	27 (67.5)
\geq 20	10 (25.0)
Total	40 (100.0)

Table (4): Unpaired t – test in relation to cefepime and doxycycline before and after treatment in smoker dental patients.

Periodontal diseases		Cefepime Mean ± SD	Doxycyclin Mean ± SD	P - value
Attachment loss	Before treatment	4.50 ± 1.05	4.55 ± 1.28	0.893
	After treatment	3.20 ± 1.15	3.35 ± 1.04	0.668
Bone loss	Before treatment	5.30 ± 0.66	5.30 ± 0.73	1.000
	After treatment	4.20 ± 0.77	4.15 ± 0.88	0.849

SD = standard deviation; *Significant difference at $p \leq 0.05$

Table (5): Paired t – test in relation to cefepime (before and after treatment) in smoker dental patients

Periodontal diseases	Before treatment Mean ± SD	After treatment Mean ± SD	P - value
Attachment loss	4.50 ± 1.05	3.20 ± 1.15	*0.000
Bone loss	5.30 ± 0.66	4.20 ± 0.77	*0.000

SD = standard deviation; *Significant difference at $p \leq 0.05$

Table (6): Paired t – test in relation to doxycycline (before and after treatment) in smoker dental patients

Periodontal diseases	Before treatment Mean ± SD	After treatment Mean ± SD	P - value
Attachment loss	4.55 ± 1.28	3.35 ± 1.04	*0.000
Bone loss	5.30 ± 0.73	4.15 ± 0.88	*0.000

SD = standard deviation; *Significant difference at $p \leq 0.05$

DISCUSSION

Tobacco smoking is the main risk factor associated with chronic destructive periodontal diseases. The typical characteristic of smoking – associated periodontal diseases is the destruction of the supporting tissues of the teeth with the ensuing clinical symptoms of attachment loss – bone loss and eventually tooth loss^(2,9). This study was undertaken to prospectively investigate the influence of smoking exposure overtime on the periodontal health condition and to evaluate the effects of locally – delivered antimicrobials (cefepime and doxycycline) in the treatment of periodontal diseases (attachment loss and bone loss) since periodontal disease is a host response to a pathogenic bacterial infection.^(4,10)

This study included the examination of subjects 20 years old and over, as the pres-

ence of smokers under this age is small compared with old age.⁽⁸⁾ The results of this study showed significant difference between non smokers and smokers regarding both attachment loss and bone loss and this was in agreement with many studies^(1, 11-15), and in disagreement with others which showed no significant differences between smokers and non smokers in clinical attachment loss and radiographical bone loss measurements.⁽¹⁶⁾

Nicotine in cigarette affect periodontal tissues and bone health from many angles but the exact mechanisms behind the destructive effects of smoking on the periodontal tissues are not well understood⁽²⁾. However, when compared to non smokers, smokers have more plaque or harbor different or more virulent types of plaque bacteria.⁽¹⁾ Studies demonstrated that the proportion of subjects positive for *Actino-*

bacillus actinomycetem comitans, Porphyromonas gingivalis, and Bacteriodes forsythus was significantly higher among smokers as compared to non smokers and that certain bacteria were more difficult to eradicate among smokers.^(17,21) Although bacteria are the primary etiologic factor in periodontal diseases. The patient's host response is a determinant of disease susceptibility. In general, smoking could lead to increased periodontal destruction by impairment of the normal host response in neutralizing infection and alterations that result in destruction of the surrounding healthy periodontal tissues^(22,23). Smokers appeared to have decreased levels of salivary antibodies (IgA) and serum (IgG) which will increase the risk of periodontitis.^(24,25) Smoking has a deleterious effect on gingival blood flow and medical literatures have demonstrated that tobacco or nicotine impairs revascularization in soft and hard tissues.^(26,27)

Tobacco components may also modify the production of cytokines or inflammatory mediators which play a role in periodontal tissue and bone destruction, one of these important cytokines is osteoprotegerin (OPG), also known as osteoclastogenesis inhibitory factor (OCIF) which can inhibit the production of osteoclasts⁽²⁹⁾, cigarette smoker patients tended to have lower serum concentration of OPG than non smokers patients⁽³⁰⁾, thus promote osteoclastogenesis, accelerate bone resorption and induce alveolar bone loss⁽³¹⁻³³⁾, and associated with pathophysiology of attachment loss and gingivitis.⁽³⁴⁾ Studies also showed that nicotine exerted negative effects on structural trabecular bone parameters due to imbalance in the normal remodeling process with excessive osteoclastogenesis and inadequate osteoblastogenesis.⁽³⁵⁾ Such alterations in host response may affect the reparative and regenerative potentials of periodontium and can decrease response to treatment in tobacco users.⁽¹⁾

It is well recognized that periodontal diseases and degenerative bone diseases are bacterial in nature. Studies showed that marked excessive loss of calcified matrix is often associated with bacterial infections. Radiograph measurements of alveolar bone resorptions in rats infected

by different types of bacteria were greater compared to the resorption in uninfected control rats.^(37,38) An essential component of therapy is to eliminate or control these pathogens. This has been accomplished through mechanical means (scaling and root planning), which is time – consuming, difficult and sometimes ineffective.^(3,35,36)

Locally applied antimicrobials has been found to produce higher local concentrations of the drug and lower systemic concentrations, increasing the effectiveness at the periodontium and decreasing the risk of systemic side effects.⁽⁴⁾ This study evaluated the effectiveness of cefepime versus doxycycline for treating attachment loss and bone loss in smoker dental patients. Cefepime is a fourth – generation cephalosporines antibiotic. It is an effective modern drug with a broad spectrum of activity which makes it suitable for the treatment of infections caused by a wide variety of bacteria^(7,39-40), including treatment of bone infections.⁽⁴¹⁻⁴³⁾

Results of this study showed significant differences in the clinical and radiographical measurements of attachment and bone loss before and after treatment with cefepime which indicated that this drug can be used in the management of these periodontal diseases and this was in agreement with other studies⁽⁴⁴⁻⁴⁶⁾, and in disagreement with other studies⁽⁴⁷⁾, which showed that there was no significant difference in the incidence of infections between patients who had received cephalosporin antibiotic after orthodontic surgery and those who had not.

Tetracycline antibiotic which include newer group called doxycycline are used in dentistry for subgingival administration as an adjunct in patients with periodontitis^(7,48). In this study doxycycline effect on reduction of attachment loss and bone loss was evaluated and there were significant differences between measurement before and after treatment. This was in agreement with many studies^(4,5,49,50), and in disagreement with others.^(51,52) Doxycycline possesses high antibacterial properties against most periodontal bacteria, as well as other biologic actions that may result in an increased production and maintenance of collagen and bone^(5,6). It is effective in reducing inflammation by inhibiting ma-

trix metalloproteinases, preventing excessive angiogenesis, inhibiting apoptosis and stimulating bone formation.^(53,54)

Results of this study showed that there was no significant differences between cefepime and doxycycline in reduction of attachment and bone losses among smoker dental patients . So, cefepime can be used as an alternative to doxycycline only in patients who have allergy to tetracyclines, since doxycycline is safe with no major side effects and it is useful for management of all cases of periodontitis.

CONCLUSIONS

Clinical studies supported the concept that tobacco use is an important variable affecting the prevalence and progression of periodontal diseases such as attachment loss and bone loss . This is related to the fact that certain periopathogens are more prevalent among smokers and tobacco products appear to have direct local effects that can alter host response. Topical application of antimicrobial agents to the site of periodontal disease may be useful adjunctive to conventional periodontal treatment.

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