Original article
J Res Dent Sci
Autumn 2014;11(3): 116-122

Comparison of the Effect of Doxycycline and Licorice on Chronic Periodontitis – A Clinical Trial Study

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Received: March 2014 *Accepted: Jul 2014*

ABSTRCAT

Background and Aim: Host modulatory therapy (HMT) is a new method that has been used as adjunctive therapy for periodontal diseases. Licorice tablet contains an extract with anti-inflammatory effects. Considering that patients prefer herbal medicine consumption, this study aimed to compare the effect of licorice tablet and doxycycline on chronic periodontitis.

Materials and Methods: In this interventional clinical trial study, 45 patients with mild to moderate chronic periodontitis were selected. Plaque Index (PI), Pocket Depth (PD), Clinical Attachment Loss (CAL) and Bleeding on Probing (BOP) were recorded for all periodontal patients. Then scaling and root planning was done and patients were divided into three groups.

In the first group, a 20mg doxycycline capsule was given to each patient daily, the second group was given a 490mg licorice tablet per day and the third group was given a placebo capsule per day. After 6 weeks, all the above-mentioned parameters were recorded again for all patients. Chi-square, paired sample T and one-way ANOVA tests were used for data analysis.

Results: mean of PD, CAL & BOP reduced significantly after treatment in each of three groups ($P < 0.05$).Mean difference of PD, CAL and BOP between two groups of doxycycline and licorice was not significant. ($P = 0.54$), ($P = 0.74$) and ($P = 0.64$) respectively.

Conclusion:licorice decreases periodontal clinical indices similar to doxycycline tab in chronic periodontitis.

Key words: Chronic periodontitis; Doxycycline; Licorice, Clinical Trial

INTRODUCTION

Periodontitis is referred to as inflammation of teeth-supporting tissues that is caused by a group of microorganisms. It is characterized by vast destruction of periodontal ligament and alveolar bone, associated with pocket formation and gingival recession or both. Its clinical distinction from gingivitis is significant loss of clinical attachment in periodontitis which usually leads to pocket formation, changes in density and height of the adjacent alveolar bone. [1] Inflammatory destruction of tissues is due to the activity of neutrophils and it is accompanied by infiltration of monocytes and development of an acquired immune lesion. [2] Despite the association between periodontal diseases and certain pathogenic bacteria, studies enrolled over the past two decades, have revealed that most of the tissue damage is due to the host response to infection and that it is not directly caused by

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infectious agents. [3]

Following these studies, host modulatory therapy (HMT) is a new method applied as adjunctive treatment for periodontal diseases. HMT aims to decrease the tissue destruction, stabilize or even regenerate the periodontium through modifying or preventing the formation of destructive aspects of host response and enhancing protective or regenerative responses.[4] HMT is a collection of local or systemic application of drugs that is a part of the treatment of periodontal diseases and is used as adjunctive treatment besides the conventional treatments of periodontal diseases. [5]

Several medications are used in the field of HMT among which tetracyclines, low-dose doxycycline in particular; along with non-surgical treatments have been helpful [6]. In this regard, Deo et al. studied 60 patients with chronic periodontitis and concluded that prescribing 10% doxycycline in addition to periodontal non-surgical treatments can decrease the pocket depth (PD) and clinical attachment loss (CAL).[7]

Also Emingil et al. prescribed sub-antimicrobial dose of doxycycline (SDD) for 46 patients with chronic periodontitis and found that using SDD beside periodontal non-surgical treatments can decrease pro-inflammatory cytokines and increase anti-inflammatory cytokines. [8]

In a study by Tavakoli et al., the effects of various concentrations of tetracycline and different washing times on bacterial growth in extracted teeth of chronic periodontitis patients were evaluated. They reported that presence of tetracycline in mentioned condition leads to its dentinal absorption and following gradual release of it, antibacterial activity of tetracycline would be expected on periodontal bacteria. This can be considered a useful therapeutic approach for periodontal patients. [9]

On the other hand, licorice has been proven to be a suitable medication for prevention and treatment of peptic ulcer, dyspepsia, hepatotoxicity and treatment of sore throat and cough, allergic reactions, periodontal diseases and dental caries. [10] Among the studies focusing on this issue is the one performed by Zhu et al. that detected the falvonoids present in licorice can prevent the activity of osteoclasts and can suppress inflammatory bone resorption. [11]

In a study by Palaska et al. about the effects of licorice on treatment of gingivitis, it was observed that using licorice in toothpastes and mouthwashes has a significant role in treatment of periodontal diseases since it contains licoricidin and licorisoflavan.[12]

In a study by Farhad et al. the side effects of adjunctive treatment with doxycycline and licorice were compared on amount of Matrix Metalloproteinase-8 in the gingival sulcular fluid of patients with chronic periodontitis. The conclusion drawn was that licorice has therapeutic effects on periodontal diseases because it is able to inhibit the production of matrix metalloproteinase by host's cells, although it does not have the side effects caused by doxycycline.[13]

the current study was done to compare the effects of licorice tablet and doxycycline capsules on the clinical indices of PD, CAL and BOP in patients with chronic periodontitis.

Materials and Methods:

Registered at Iranian Registry of Clinical Trials, (registration no. 1N2014041217228), this interventional clinical trial was carried out on 45 patients with mild to moderate chronic periodontitis who were selected from those referred to Department of periodontology at School of Dentistry in Khorasgan Azad University.

Patients with any kind of systemic disease, pregnant and lactating women, individuals who had received any medication or antibiotics over the past six months, those allergic to antibiotics, individuals who had scaling within the past six months or had periodontal surgery in general, as well as smokers were excluded from the study. Physically healthy patients that were selected that , aged 25- 45 with Plaque Index (PI) below 30. [14]

Diagnosing periodontitis was done by a periodontist based on the history, clinical assess-

ment, and attachment loss using a periodontal probe. After the initial screening, the research stages were explained to patients and the candidates who were interested to participate, completed the consent form and were enrolled (the ethical code received from the ethical committee of Isfahan University of Medical Sciences: 493008). Periodontal record was completed for each single patient and PI, PD, CAL and BOP were recorded. The first phase of treatment including scaling and root planning was done.

After hygiene training, patients were assigned to 3 equal groups. The first group received a 20mg doxycycline capsule per day; the second group was given a 490mg licorice tablet daily, and the third group received placebo as control group. After 6 weeks, the patients were examined in identical conditions by a clinician blind to the grouping and all the studied indices were remeasured and recorded for all patients.

O'Leary index was used to evaluate the plaque in patients. The patients were given disclosing solution so that the areas with plaque would be specified. Then the plaque state of the four surfaces of each tooth (labial, lingual, mesial and distal) was recorded in the related table

After evaluating all teeth, the number of surfaces with plaque was divided to the total number of all surfaces of the tooth examined, and was finally calculated in percent. The patients with the index<30% were selected.[14]

The pocket depth (the distance from the free margin of each tooth to the base of pocket) was measured using a probe. To perform the measurement, a periodontal probe was placed into the pocket (or sulcus), parallel to the longitudinal axis of the tooth root. The probe was moved around the surface of each tooth in walking motion and the pocket depth was read from the probe. The mean pocket depth was calculated from the total pocket depth of the 6 areas of each tooth. It was done for all teeth. For each patient, the summation of mean probing depth of each single tooth was divided to the total number of the teeth and was recorded as the index of probing depth. [15]

The clinical attachment surface of gingiva or CAL (the distance between the cemento-enamel junction and the base of the pocket) was measured in six surfaces of each tooth using a Williams probe and the mean value was recorded for each tooth. The summation of the mean values obtained from each tooth was divided to the total number of the teeth and in this way, the value of clinical attachment was specified for each patient. [15]

BOP was assessed based on Muhlemann Index as explained below:

From the most posterior tooth of each quadrant, a blunt end periodontal probe was inserted down to the base of the papilla and was moved in sweeping motion with gentle finger pressure, in the mesial-distal direction. 20-30 seconds after the probing was finished, bleeding was observed, graded and recorded. This was done for all teeth of each quadrant except for wisdom teeth. Based on Muhlemann index. bleeding was graded as follows:

Grade 1: Spot bleeding ; only one spot bleeding was observed 20-30 seconds after probing.

Grade 2: linear bleeding or set of spots; after probing, a thin and delicate streak of some spot bleeding was observed in the gingival margin.

Grade 3: Triangular bleeding; the triangular space between the teeth was filled with blood.

Grade 4: Profuse bleeding; right after probing, blood flowed from the triangular area to some parts of the teeth and might drip towards the gingiva.

The mean value obtained from each quadrant was added to the mean of other quadrants, and the total was divided into four and was recorded as the degree of bleeding for each patient.[15]

Chi-square, paired sample T-test, one-way ANOVA tests were used as appripriated.

Results:

Results of PD, CAL and BOP of patients who received 20mg doxycycline, 490mg licorice tablet and placebo were as follows:

Gender distribution of the studied individuals was 9 men and 6 women within the placebo

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group, 7men and 8 women in doxycycline group, and 7men and 8women in licorice group. According to the Chi-square test, there existed no significant difference in the gender distribution of the three groups and these 3 groups are almost similar in gender distribution (P = 0.70). Frequency distribution of the studied samples within the three groups based on age in placebo group was min=25 and max=44, in doxycycline group minimum was 25 and maximum 45, and in licorice group min=26 and max=45. One-way ANOVA revealed the three groups to have no significant difference in the mean age (P =0.80).

Pocket depth: Kolmogorov-Smirnov test showed that all the values follow normal distribution pattern (P >0.05). According to paired T-test, the mean PD within the three groups had considerable reduction after intervention (P in the three groups<0.05).

However the reduction in placebo group was less than licorice, and licorice group showed reduction less than doxycycline group. One-way ANOVA approved that PD had no significant difference among the three groups before intervention (P: 0.061), while it was found to have significant difference after intervention (P= 0.001). Regarding the same issue, LSD test indicated the difference of PD after intervention to be significant between the doxycycline and placebo groups (P= 0.002), and also between licorice and placebo groups (P= 0.02). But no significant difference was detected between doxycycline and licorice groups (P=0.54) (Table 1).

Table 1- The value of PD before and after intervention within the three therapeutic groups (n=15)

Therapeutic group	Before intervention	After intervention	Reduction		
			Value	%	P
Placebo	3.48±1.14	3.13±1.19	0.35	10	<0.1
Doxycycline	2.86±0.94	1.99±0.49	0.87	30	<0.01
Licorice	2.61±0.89	1.86±0.77	0.75	29	<0.01
P (ANOVA)	0.061	0.001			

Clinical attachment loss: Kolmogorov-Smirnov test represented that all values follow normal distribution pattern (P >0.05). As Paired T-test revealed, CAL significantly decreased in the three groups after intervention (P of all the 3 groups<0.05). However, decrease in placebo group was lower than doxycycline, and doxycycline group had lower decrease than licorice. One-way ANOVA showed that the mean CAL of the three groups had no significant difference before intervention (P =0.064), but intervention made a considerable difference between the groups
(P =0.007). LSD test also indicated the difference of mean CAL to be significant between licorice and Placebo after intervention (P =0.03). But no significant difference was found between doxycycline and licorice (P =0.74), neither between doxycycline and placebo
(P =0.062) (Table 2).

Table 2- Value of CAL before and after intervention within the three therapeutic groups (n=15)

Therapeutic groups	Before intervention	After intervention	Reduction		
			Value	%	P.Value
Placebo	4.97±0.13	4.56±1.12	0.41	8	<0.4
Doxycycline	4.09±1.30	3.55±1.14	0.54	3	<0.2
Licorice	3.94±0.34	3.23±0.29	0.71	18	<0.01
P.value (ANOVA)	0.064	0.007			

Bleeding on probing: according to Kolmogorov-Smirnov test, all values follow normal distribution pattern (P >0.05). Paired T-test showed that BOP of the three groups were reduced significantly after intervention (P Value of the 3 groups<0.05); however, the reduction in placebo group was less than doxycycline and doxycycline was less than licorice. One-way ANOVA proved that BOP was significantly different between the three groups both before and after the intervention (P =0.000). Also LSD test showed that both before and after the intervention, the difference of mean BOP was significant between both doxycycline and placebo and between licorice and placebo (P value of both groups=0.00). But no significant difference

was observed between doxycycline and licorice groups (P =0.64) (Table 3).

Table 3- Value of BOP within the three therapeutic groups based on time of assessment (n=15)

Therapeutic group	Before intervention	After intervention	Reduction		
			Amount	%	P
Placebo	3.02±0.14	2.53±0.20	0.49	16	<0.01
Doxycycline	2.14±0.15	1.53±0.20	0.61	28	<0.01
Licorice	2.24±0.15	1.22±0.19	1.02	45	<0.001
P.value (ANOVA)	0.000	0.000			

Discussion:

This research revealed that licorice decreases the periodontal clinical indices in patients with chronic periodontitis; however it is not superior to doxycycline in this regared.

The results of this study was similar to what Deo et al. found, except for the greater sample size they studied, besides the fact that they evaluated only PD and CAL indices. They studied 60 patients with chronic periodontitis and found that prescribing 10% doxycycline along with periodontal non-surgical treatments can decrease PD and CAL more effectively.[7]

Emingil et al. prescribed SDD for 46 patients with chronic periodontitis and concluded that using SDD in association with periodontal non-surgical treatments can decrease the pro-inflammatory cytokines and increase the anti-inflammatory ones. [8] The results of that study is in agreement with what the current study found; the only difference is the study type (laboratory and clinical).

In a study enrolled by Tavakoli et al., the effects of various concentrations of tetracycline and different washing times on bacterial growth in roots of extracted teeth of patients with chronic periodontitis were studied. They finally detected that presence of tetracycline in this situation would lead to its absorption by the dentin. Following its gradual release over time, antibacterial activity of tetracycline against periodontal bacteria can be expected. This can be a useful method in treatment of patients with periodontitis. [9]

In a study, Zhu et al. found that the falvonoid compounds in licorice can prevent the activity of osteoclasts and can suppress inflammatory bone loss. [11] Also Palaska et al. studied the effects of licorice on treatment of gingival inflammation and reported that using licorice in toothpastes and mouthwashes can play a significant role in treating periodontal diseases since it contains licoricidin and licorisoflavan. [12]

In a different study, Farhad et al. evaluated the effects of doxycycline and licorice as adjunctive treatment on MMP-8 amount of the gingival sulcular fluid in patients with chronic periodontitis. That study concluded that because licorice has the ability to inhibit the generation of metalloproteinase matrix by host's cells, it has therapeutic effects on periodontal diseases, just as doxycycline does. Moreover, licorice does not have side effects of doxycycline. [13]

All the three above mentioned studies affirmed the considerable effects of licorice on treating periodontitis and were all in line with the results of the current study. Nevertheless, contradictory findings have been reported regarding the effects of doxycycline. listgarten, Scopp, ciancio and their colleagues reported in separate studies that there is no significant difference between mechanical treatment per se and associating it with tetracycline or minocycline. They claimed that this difference might probably be due to ethnicity, age range, method and duration of medication consumption adopted in these studies. [16-18]

Needleman et al. conducted a clinical trial about the effects of low-dose doxycycline on patients with chronic periodontitis and observed that this study does not support the prescription of low-dose doxycycline (LDD) associated with periodontal non-surgical treatments in smokers.[19] Also in a review study, Angaji et al. found that the available evidence is not adequate to prove the advantages of using doxycycline for smokers with periodontitis.[20]

The reason for this rejection of hypothesis by

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the two above mentioned studies might be the fact that smoking negatively influences the healing of periodontal tissues; while the smokers were excluded from the present study. Since both doxycycline and licorice are influential on reducing the inflammatory mediators and thereby improve the clinical factors, the lower effectiveness of licorice in the present study might be due to a series of limitations such as the fact that patients were less inclined to use this herbal medication regularly (because the efficacy of herbal medication is not similar to that of the chemical one), the longer time required for more effectiveness of licorice, as well as the small sample size used in this study.

Currently, doxycycline is used as the golden standard in treatment of periodontal diseases, but this medication has some limitations such as development of resistance in bacterial strains, allergic reactions, light sensitivity and sometimes the need for long-term usage to prevent relapse of disease. [21-27]

Conclusion:

The current study revealed that licorice decreases the periodontal clinical indices in patients with chronic periodontitis similar to doxy cycline.

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