Journal of Research in Pharmacy Practice

Original Article

Efficacy of a local-drug delivery gel containing extracts of *Quercus brantii* and *Coriandrum sativum* as an adjunct to scaling and root planing in moderate chronic periodontitis patients

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Received: December 2013
Accepted: March 2014

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ABSTRACT

Objective: Recent advances in the field of alternative medicine introduced various herbal products for the treatment of periodontitis. The purpose of this study was to evaluate the effects of combined extracts from *Quercus brantii* and *Coriandrum sativum* on periodontal indices in adult periodontitis patients.

Methods: In this randomized, double-blinded clinical trial, performed in Isfahan Dental School in 2012, a new herbal medicament containing combined extracts from *Q. brantii* and *C. sativum* was formulated in the gel form for subgingival application. Following scaling and root planing (SRP), both herbal and placebo gels were delivered at the experimental and control sites, respectively. Periodontal pocket depth, clinical attachment level, papilla bleeding index, and plaque index were measured at baseline, 1 month and 3 months later. Both intra-and inter-groups changes were registered. The obtained data were analyzed by SPSS software, using repeated measure analysis of variance, paired *t*-test, Mann-Whitney, Friedman, and Wilcoxon tests. Differences with $P < 0.05$ were considered to be significant.

Findings: Both groups indicated statistically significant improvements in the periodontal indices ($P < 0.05$), but there were no significant differences between two study groups with this regard.

Conclusion: The herbal gel does not have considerable advantages over SRP alone as an adjunct in periodontal treatment.

Keywords: *Coriandrum sativum*; drug delivery systems; periodontitis; *Quercus brantii*

INTRODUCTION

Periodontitis is an infectious inflammatory disease which is widely accepted as being caused by bacteria associates with accumulation of subgingival plaque. Untreated periodontitis results in the inflammation within the supporting tissues of the teeth, resorption of alveolar bone, loss of the periodontal ligament attachment, and is characterized by periodontal pocket formation and/or recession of the gingiva.[1,2]

Access this article online

Website: www.jrpp.net

DOI: 10.4103/2279-042X.137076

Treatment of periodontal disease is routinely based on mechanical debridement of the tooth surface and appropriate maintenance of oral hygiene. Complete removal of plaque is more difficult in deep than in shallow pockets and may result in the failure of periodontal treatment due to the remaining bacterial plaque after therapy.[3-5] Hence, it seems reasonable to combine mechanical periodontal therapy with the use of chemotherapeutic agents.

In 1979, Max Goodson developed the concept of controlled release-local drug delivery. This treatment modality inhibits most of the problems associated with systemic therapy (such as drug toxicity and interactions, and formation of resistant bacteria), limits the drug to its target site and therefore results in higher concentrations.[6,7]

The use of natural products has served as a major source of drugs for centuries and is well-established

as an alternative to health problems in some cultures, especially in Asia, America, and Africa.[8] Phenolic compounds are used in antiseptics, disinfectants, and mouth-rinse preparations because of their low toxicity and anti-bacterial properties.[9] In 2005, Sastravaha *et al*. indicated that adjunctive local delivery of extracts from *Contella asiatica* and *Purina granatum* significantly improved clinical signs of chronic periodontitis.[10] Kushiyama *et al*. demonstrated an inverse association between the intake of green tea and periodontal disease.[11]

There is a growing interest in the use of tannins for the treatment of periodontal disease. Tannins are a family of polyphenols (a plant metabolite) that precipitate proteins. Polyphenols exhibit *in vitro* anti-bacterial activity against periodontal pathogens by increasing the antioxidant ability of oral fluids.[12] Tannins precipitate microbial proteins and prevent the development of microorganisms.[13]

Polyphenols and tannins are the main substances in an oak tree. *Quercus brantii* is abundant specie of this plant and from the Fagacea family which is grown in Western Iran and has been used traditionally for the treatment of gastric ulcers, superficial injuries and local inflammation with hemostatic, anti-bacterial, anti-inflammatory, anti-nociceptive, and anti-oxidant effects.[14-18] *Coriandrum sativum* is from the Umbelliferae family and was used in Iranian folk medicine as a carminative and spasmolytic agent. It has anti-inflammatory, analgesic, anti-bacterial, and anti-oxidant activities. *C. sativum* extract has also tannins.[19,20]

Despite the recognized therapeutic effects of these two agents for a wide range of diseases, they still have not been used for the purpose of periodontitis. The aim of this study was to evaluate the clinical effects of subgingival application of herbal gel (extracts of oak and coriander) in periodontal pockets after full debridement in patients with moderate chronic periodontitis.

METHODS

This was a randomized, double-blinded controlled trial. Our samples were selected randomly from patients with the diagnosis of chronic periodontitis referred to the Department of Periodontology, School of Dentistry, affiliated with Isfahan University of Medical Sciences, Isfahan, Iran, over a 6-month period in 2012. Each volunteer had to fulfill the following criteria: Having moderate chronic periodontitis, a minimum of four periodontal pockets with an average depth of 3-5 mm, not pregnant, having no systemic disease, no antibiotic treatment during the 1-month period prior to the study, no smoking, no periodontal treatment during the previous 3 months, no severe caries or extensive restoration on the objective teeth, no orthodontic treatment during the study, and no history of allergy to the tested drugs.

Totally, 74 pockets (36 sites in experimental and 38 sites in control groups) of single root teeth (to inhibit the effect of confounding factors such as furcation involvement and inaccessibility for instrumentation) of 18 patients (aged 31-52 years old) were selected. An informed consent was obtained from all the volunteers prior to enrollment for the study. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences. All patients received complete scaling and root planing (SRP) using ultrasonic device (Mectron-Carasco GE, Italy) and hand instruments (Hufrieday, Chicago, Illinois, USA) and also oral hygiene instruction that included brushing by modified Bass method and use of dental floss. They were avoided using any mouth-rinses during the experiment.

The following indices were measured for each volunteer: Periodontal pocket depth (PPD), clinical attachment level (CAL), papilla bleeding index (PBI), and plaque index (PI).

Periodontal pocket depth is the distance between the gingival margin and base of the periodontal pocket.[21] Level of attachment is the distance between the base of the pocket and a fixed point on the crown, such as the cementoenamel junction (CEJ).[22] In this study, the distance between CEJ and the bottom of pocket was measured in buccal, lingual, mesial, and distal surfaces of each tooth and was registered in a chart in millimeter. To evaluate the inflammation of gingival, the PBI developed by Saxer and Mühlemann was used.[23] In this index, 0 stands for no bleeding, 1 for a pointed bleeding, 2 for the bleeding shown as a slender bleeding line, 3 represents the condition that the triangular embrasure is filled by blood, and 4 means spontaneous bleeding. For measurement of PI, the teeth (except the third molars) were evaluated by an explorer 17-23 along the gingival margin in four sites: Buccal, lingual, mesial, and distal. If there was no plaque at the gingival margin, the score was recorded as 1, score 2 indicates a thin layer of plaque, score 3 is subject to moderate layer of plaque, and if an excessive accumulation of plaque is at the gingival margin the score is 4.[24] So for each tooth 4 scores existed, and their average was recorded for the whole mouth.

Two weeks later, in the second visit, periodontal pockets were reevaluated and SRP was performed if needed to ensure full debridement of the whole mouth. Then patients were divided randomly (using

the table of random numbers) into two groups; in the experimental group, the tested gel (containing gel-forming agent type 940, ethanol extract of oak hull of the specie *Q. brantii* 20% and ethanol extract of coriander fruit of *C. sativum* specie 1%) and in the control group, the placebo gel (making from gel-forming agent, similar color to test gel without the mentioned extracts) were transferred to a 2-mL syringe, gauge 21 and injected to the pocket.

The percolation method was used for extraction. About 100 g of plant materials (Jaft of *Q. brantii* and the fruits of *C. sativum*) were powdered and soaked in 300 ml of ethanol 70%. After 2 h, the plant materials were extracted with ethanol 70% (700 mL) by percolation method. After 48 h, extracts were concentrated by rotary evaporator (Heidolph VV 2000). Further concentration was done over the boiling water bath.[14]

For this goal, semisolid concentrated extracts of the seed hull (Jaft) of *Q. brantii* and fruits of *C. sativum* were used. Carbopol 940, sodium carboxymethyl cellulose and hydroxypropyl methylcellulose polymers were used as gelling agents.

Local delivery of the gels was repeated 1 week later, so in this manner each formulation was used twice in the pockets. 1 and 3 months after baseline (first visit), patients were recalled, and clinical parameters were recorded again. All measurements were performed by a single masked examiner using a Michigan probe.

Data were analyzed using SPSS version 17 software (SPSS Inc., Chicago, IL, USA), repeated measure analysis of variance (ANOVA), and paired *t*-test, Mann-Whitney, Friedman, and Wilcoxon tests.

Table 1: Mean (SD) of PPD and CAL before and after treatment with herbal or placebo gel

Index	Group	Before treatment	One month after treatment	Three months after treatment
PPD	Herbal gel	4.08 (0.60)	2.58 (0.73)	2.44 (0.87)
	Placebo gel	4.15 (0.54)	2.52 (0.86)	2.57 (1)
CAL	Herbal gel	3.05 (0.47)	1.08 (0.84)	0.8 (0.82)
	Placebo gel	3.1 (0.64)	1.31 (0.77)	1.18 (0.92)

Herbal gel contained extracts of *Quercus brantii* and *Coriandrum sativum*. PPD=Periodontal pocket depth, CAL=Clinical attachment level, SD=Standard deviation

RESULTS

In this study, 74 samples were analyzed (36 sites in the test group and 38 in the control group). Mean of PPD and CAL, before and after treatment in both groups are shown in Table 1. Repeated measure ANOVA showed no significant differences between two groups regarding PPD (P = 0.714) and CAL (P = 0.087). Intra-group differences (using paired *t*-test) were significant in both groups ($P < 0.001$) regarding PPD reduction and gain of attachment level in 1-month and 3-month evaluations compared to the baseline [Table 1].

There were no meaningful differences in PBI and PI values between test and control groups in all three evaluation time points (Mann-Whitney test). Significant reduction was observed regarding PBI and PI in recall appointments compared to the baseline in each studied groups ($P < 0.001$), but this index did not differ significantly (Friedman and Wilcoxon tests) while comparing 1-month and 3-month values in control (P value: 0.103 for PBI, and P value: 0.782 for PI) and test groups (P value: 0.95 for PBI, and P value: 0.285 for PI) [Table 2].

DISCUSSION

Periodontitis has a multifactorial etiology with primary etiologic agents being pathogenic bacteria that reside in the subgingival area.[25] It alone may fail to eliminate the pathogenic microflora due to their location within the gingival dental tissues or in other areas inaccessible to periodontal instruments.[26] The scientific rationale for adding locally applied anti-infective agents to SRP is that certain broad-spectrum antimicrobial agents can theoretically reduce the number of subgingival bacteria left behind after SRP.[27] Irrigation systems have little benefit because of rapid clearance of the drug from the site of application and failure of the irrigator to reach all portions of the subgingival environment.[28]

Table 2: Distribution frequency of PBI and PI before and after treatment with herbal or placebo gel

Index	Group	Before treatment					One month after treatment					Three months after treatment				
		G0	G1	G2	G3	G4	G0	G1	G2	G3	G4	G0	G1	G2	G3	G4
PBI	Herbal gel	0	1	22	13	0	7	10	12	7	0	11	12	10	3	0
	Placebo gel	0	3	22	13	0	6	9	22	1	0	9	15	11	3	0
	P value*	0.661					0.849					0.717				
PI	Herbal gel	0	1	29	4	-	2	29	5	0	-	4	29	3	0	-
	Placebo gel	0	2	31	5	-	0	32	6	0	-	1	31	6	0	-
	P value*	0.617					0.461					0.118				

*Mann-Whitney test. Herbal gel contained extracts of *Quercus brantii* and *Coriandrum sativum*. G=Grade, PBI=papilla bleeding index, PI=plaque index

Local administrations of antimicrobial agents are commonly preferred as they provide a higher dosage of the drug in the periodontal pocket, therefore decreasing its unfavorable systemic side-effects. In the other word, herbal products are safe in comparison with the synthetics for human use.[6,7] To the best of our knowledge, there has been no clinical study to evaluate the effects of extracts of *Q. brantii* and *C. sativum* for the treatment of periodontal diseases. However, other therapeutic aspects of these two plants have been searched as mentioned before.[14-20]

Various herbal remedies have been used for the treatment of periodontal disease. Durre and Muhammad, and Gazi demonstrated the anti-bacterial activity of *Acacia arabica* against strains of *Aggregatibacter actinomycetemcomitans*, *Capnocytophaga*, *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Treponema denticola*. They concluded that the tannin contains of about 24-42% in the bark constituents of *A. arabica* is responsible for this effect.[29,30] In a human clinical trial performed in 2009 to evaluate the effects of pomegranate extract mouth rinsing on saliva measures relevant to gingivitis risk, it was shown that using the pomegranate rinse had reduced total protein associated with the presence of plaque-forming bacteria, reduced activities related to cell injury, and increased the activity of the enzyme ceruloplasmin, which protects against oral oxidative stress.[31] The ellagitannin, punicalagin, was thought to be responsible for pomegranate's anti-bacterial activity.[32] Vasconcelos *et al*. also suggested that pomegranate might be used in the control of adherence of different microorganisms in the oral cavity.[33]

Due to these findings and the tannin contents of *Q. brantii* and *C. sativum*, we decided to evaluate the effects of herbal gel made of oak and coriander extracts compared to placebo gel in clinical variables such as PPD, CAL, PBI, and PI. Means of all studied parameters before the start of the study did not differ significantly between two groups, which indicate their homogeneity and similar conditions. PI was considered an index for oral hygiene to distinguish if differences in this parameter can found our findings or not. This was retrieved from Sastravaha *et al*.'s investigation[10] that compared the effect of two herbal agents *C. asitica* and *P. granatum* in the treatment of periodontal diseases. Since the difference in PI values was not statistically significant before and after treatment in two groups, the amount of plaque cannot be considered as a confounding factor.

Periodontal pocket depth reduction was significant in intra-group comparisons in 1-month and 3-month evaluations, which can be attributed to anti-inflammatory and anti-bacterial effects of the ingredients, but inter-group differences were not meaningful. This finding was not in agreement with previous studies in which herbal compounds were tested, such as Sastravaha *et al*.'s article and Kushiyama *et al*.'s investigation where green tea was demonstrated to reduce PPD, significantly.[10,11]

The pattern of CAL gain changes in and between two groups was like that of PPD reduction, so improvement of CAL can be attributed to the lower penetration of periodontal probe to the epithelium and connective tissue, to the epithelial attachment to the root, or can be as an adaptation of soft tissue portion of pocket with the tooth than do not allow probing through the tissues. Therefore, we cannot determinately relate the gain of CAL to the connective tissue attachment. Histological experiments are needed to exactly evaluate this fact.

When comparisons were made between the control and the test groups at different intervals of time, the PBI was found not to be different between them, but in both the reduction was observed during the 1-month posttreatment period, although this improvement did not continue between 1 month and 3 months after mechanical therapy.

As we know, bleeding in probing (BOP) is not considered as a specific test for diagnosis of inflammation, but due to its high sensitivity, it is an appropriate index for detection of inflammation in early stages. In evaluating the effect of green tea, Kushiyama *et al*. indicated a significant reduction in BO*P* values. This disagreement is somewhat because of the different study agents (although both of them act through host response modulation) and somewhat due to the smaller sample group in our study. Of course, durability of the drug is an important parameter that must be attended. In the present research, missing some of the participants during the study was of the limitations. However, evaluating the sustained releasing effect of the tested drug and its comparison with other herbal agents with a larger sample of subjects is suggested in further studies.

Although the use of herbal gel containing extracts of oak and coriander resulted in more clinical improvements than placebo gel totally, but it was not considered as a significant benefit. This fact again emphasizes the major role of SRP as the main method of periodontal treatment. It may be possible that by increasing the gel concentration, its sustainability or consumption repetition, significant effects be observed.

AUTHORS' CONTRIBUTION

Dr Jaber Yaghini: Measurement of clinical parameters.

Dr Mohammad Shahabooei: Proposal preparation and literature review.

Dr Abolfazl Aslani: Prepartion of herbal gels, detection of their dosage and method of usage.

Mozhhgan Reza zadeh, Sima Kiani: Sample collection.

Dr Narges Naghsh: Writing and preparation of final article.

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How to cite this article: Yaghini J, Shahabooei M, Aslani A, Zadeh MR, Kiani S, Naghsh N. Efficacy of a local-drug delivery gel containing extracts of *Quercus brantii* and *Coriandrum sativum* as an adjunct to scaling and root planing in moderate chronic periodontitis patients. J Res Pharm Pract 2014;3:67-71.

Source of Support: Nil, **Conflict of Interest:** None declared.