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ORIGINAL ARTICLE

Efect of Anaheal (Bromelain) Drug on the Periodontal Clinical Indices in Nonsurgical Periodontal Treatment of Patients with Chronic Periodontitis

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Abstract

Objective: To evaluate the effect of Anaheal (Bromelain) drug on the periodontal clinical indices in nonsurgical periodontal treatment of patients with chronic periodontitis. **Material and Methods:** In this double blind clinical trial, 80 patients with chronic moderate periodontitis and a healthy systemic status were chosen, and divided into two 40-subject groups. Thereafter, the standard treatment of periodontitis including scaling and root planning in one session by the unit operator was performed for all patients. Eventually, one group of the patients was administered Bromelain medication (500-mg capsule twice a day) one hour before food, while the other group was given placebo. Four and eight weeks after the treatment, the clinical periodontal indicators were measured and recorded in both groups. The data were assessed using descriptive statistics and analytical test methods (Mann-U-Whitney and Chi-square). P value less than 0.05 was considered statistically significant. **Results:** Gingival index, probing depth and plaque index before the treatment were similar in both groups (Anaheal and placebo). However, four and eight weeks after the treatment, the three studied indices were significantly lower in the Anaheal group as compared to the placebo ($p<0.05$). The index of bleeding on probing was also similar before the treatment and four weeks after the treatment in both groups. However, eight weeks after the treatment, this index was significantly lower in the Anaheal group as compared to the placebo group ($p<0.05$). **Conclusion:** Administration of oral Anaheal medication after nonsurgical periodontal treatments reduced all the clinical periodontal indices among patients with chronic periodontitis as compared to the control group. Therefore, it can be a suitable substitute for the common oral industrial antibiotics.

Keywords: Bromelains; Chronic Periodontitis; Periodontal Index; Root Planing.

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Introduction

Periodontal diseases are inflammatory diseases affecting the periodontium, causing progressive loss of the bone around the teeth. If left untreated, it can result in loose teeth and eventually teeth loss. Periodontitis is majorly responsible for loss of teeth after the age of 35 years [1]. Nonsurgical treatments including scaling and root planning with or without supplementary treatment such as prescription of antibiotics and mouthwash are among the treatments recommended for this purpose [2].

Studies have shown that removing all the microbial and bacterial plaque from the surface of infected root of teeth is not possible. Furthermore, complete removal of the subgingival microbial plaque needs an antimicrobial material with a suitable concentration and enough time [3,4]. Therefore, it seems that the use of a supplementary treatment in addition to the standard treatments of scaling and root planning is required for a successful treatment [5].

In different studies, to investigate the effect of these supplementary treatments, clinical indices were used. Sulcus Bleeding Index is an index designed for investigating gingival bleeding [6]. The extent of plaque, scales, inflammation and bleeding of gingival, depth of periodontal pockets, and the extent of alveolar bone loss have also been examined in such studies [7].

As mentioned earlier, one of the supplementary treatments after nonsurgical periodontal treatments is pharmacological treatment. Anaheal is an herbal medicine, with major compound being Bromelain. Bromelain is a compound extract consisting of proteolytic enzymes extracted from Ananas comasus plant. The commercial form of Bromelain has no chemical analog, because if the enzyme is purified extremely, it loses its characteristics and natural properties. The main ingredient of Bromelain consists of proteolytic enzymes, though trace amounts of phosphatase acid, peroxidase, and several types of protein inhibitors are also found [8,9]. Among the effects of Bromelain are, anti-inflammatory effect, and reduction of swelling and pain [10]. Further, Bromelain has a very low toxicity [11].

Studies have shown that oral Bromelain causes reduced levels of bradykinin, thromboxane and prostaglandin E2 in inflamed tissues in a dose-dependent manner [12-14]. In addition, it has been shown that by stimulating leukocytes, bromelain causes increased level of interleukin-1, -6, and -8 (IL-1, IL-6, IL-8) and tumor necrosis factor alpha (TNFα) in the inflamed region [15]. Elevation of cytokines, especially IL-8, results in absorption of granulocytes and monocytes to the inflamed region, causing their enhanced phagocytic and chemotactic activities. The anti-edema properties of bromelain are due to increased vascular permeability following fibrinolysis and enhanced resorption of edema liquid to the bloodstream [15].

The results of investigating the effect of oral bromelain on improving wound healing also suggested that oral Bromelain is effective in accelerating the wound healing process. Thus, it was suggested to accelerate wound healing after surgery [16]. In addition to anti-inflammatory properties and wound healing acceleration mentioned for Bromelain, this substance also has anti-bacterial properties. The antibacterial effect of Bromelain on periodontal pathogens was evaluated

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and the authors concluded that this substance is effective in all isolated aerobic and anaerobic strains under study (Streptococcus mutans, Escherichia coli, Porphyromonas gingivalis and actinomycose) [17].

Based on the studies mentioned with regards to Anaheal (Bromelain) properties and absence of investigations on the effects of Anaheal (Bromelain) regarding periodontal patients, this study was conducted with the aim to determine the effect of Anaheal (Bromelain) on improving clinical periodontal indices in nonsurgical periodontal treatment of patients with moderate chronic periodontitis. It is hoped that the results of this research will be useful for selecting a suitable drug to improve clinical periodontal indices in nonsurgical treatment of periodontitis.

Material and Methods

Sampling

Eighty patients with moderate chronic periodontitis, 3-4 mm clinical attachment level (CAL) and a healthy systemic state, were chosen from among the visitors of the periodontics ward of Tabriz Dentistry Faculty. Random allocation was performed using random list software as random estimation.

Data Collection

The patients were divided into two groups randomly (n=40). The demographic data of the patients as well as the clinical indices were recorded before the intervention. The pocket depth was measured and recorded in six regions including mesial buccal, midbuccal, distobuccal, mesiolingual, midlingual and distolingual regions. Furthermore, bleeding on probing, plaque index and gingival index were also measured and recorded in the studied patients [18]. The standard treatment of periodontitis including scaling and root planning was performed by the unit operator in one session for all the patients. To operator calibration (the person who performed the scaling and root planning), the operator performed the scaling and root planning procedure for five patients. The calibration was accepted when Kapa agreement is over 90%. Together with the standard treatment, it was stated that one group of patients received Bromelain drug (500 mg capsule twice a day) [19] orally one hour before meal, while the other patients group received placebo. Four weeks and eight weeks after performing the periodontal nonsurgical treatments and prescribing Anaheal drug in the placebo, the clinical indices were measured and recorded again [20].

To examiner calibration (the person measuring the clinical indices), the examiner measured probing depths of over 3 mm on at least five teeth within 48 h before the treatment and two weeks after it on five patients. Calibration is accepted when the agreement between the two temporal stages is more than 90%. In addition, the examiner did not know which patient received Anaheal (bromelain) drug and which patient did not (double blind study).

Methods for Measuring the Studied Clinical Indices

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- Plaque Index: This index measures the plaque thickness in gingival one third (Table 1). Method for calculating the plaque index [18]: PI = Total scores / No of surfaces examined.

Table 1. The plaque index criterion score.

Score	Criteria
0	Absence of plaque
1	Plaque attached to the free edge of the gum or adjacent to the dental region which cannot be seen by naked eye. However, it is observable using detector solutions or probe
2	Moderate aggregation of dental plaque in the gingival pocket, in the gum margin, or surface of the adjacent tooth which can be seen by naked eye.
3	Large amounts of soft materials in the gingival pocket or in the teeth and gum margin [21,22].

- Gingival Index: The probe was dragged on the external surface of the gingival (Table 2). Incompletely grown teeth, remaining roots, teeth with periapical lesions and the third molars were excluded from the investigation and had no substitute. Calculation of the gingival index [18]: GI = Total scores / No of surfaces examined.

Table 2. The gingival index score.

Score	Criteria
0	Absence of inflammation
1	Mild inflammation, mild color change, mild edema, without bleeding in probing
2	Moderate inflammation, moderate blaze, redness, bleeding on probing
3	Severe inflammation, evident redness and hypertrophy, wound, tendency for spontaneous bleeding [18].

- Bleeding on Probing: The probe was moved slowly in the margin of the pocket wall laterally. The examiner investigated the bleeding again 30-60 second after probing.

- Probing Depth: To measure this index, periodontal probe was used. The first clinical observable sign in the pocket is the pocket depth. On average, normal sulcus depth was considered to be about 3 mm without any bleeding after probing. A depth of over 3 mm can be associated with gingival attachments loss, which is a characteristic of periodontitis. Furthermore, pockets with a depth higher than 3 mm can be a sign of gingival hyperplasia [21].

Inclusion and Exclusion Criteria

Patients with moderate chronic periodontitis, clinical attachment level of 3-4 mm and who were healthy systemically were included. Patients with any of the following conditions were excluded from the study [20]: a) People with sensitivity to this medication (those who are sensitive to pineapple, celery, carrot, and fennel may be sensitive to bromelain); b) People with history of heart disease; c) Pregnant women; d) People with digestive system diseases such as peptic ulcer; e) Those with renal or hepatic diseases; f) People with coagulation disorders such as hemophilia; g) Those with systemic lupus erythematosus; h) Patients with any history of periodontal treatment (route

planning and scaling or surgery) in the past six months; i) Patients younger than 15 years and older than 60 years, alcohol consumers, smokers, drug abusers, and those who consume anticoagulant and thrombolytic medication.

Statistical Analysis

The data were statistically analyzed by descriptive statistics (mean and standard deviation) as well as Mann-Whitney and Chi-square test by IBM SPSS Statistics for Windows Software, version 17 (IBM Corp., Armonk, NY, USA). In this study, $p<0.05$ was considered statistically significant.

Ethical Aspects

The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences. A written informed consent was obtained from all the participants prior to the inclusion in the study.

Results

In this research, 80 patients were examined in Anaheal and placebo groups. In the Anaheal group, 60% were female (24 patients) and 40% were male (16 patients). However, in the non-surgical treatment group, 40% were female and 60% were male. The mean age of the Anaheal and placebo groups was 40.75 and 43.9 years, respectively. According to t-test, no significant difference was observed in the mean age of the groups ($p = 0.16$).

The mean and standard deviation related to the studied indices before the treatment, four and eight weeks after the treatment in the studied groups are shown in Table 3.

Table 3. Comparison of the periodontal indices in the two studied groups before, four weeks and eight weeks after the treatment.

Periodontal Indices	Groups	Treatment		
		Before	Four weeks After	Eight weeks After
		Mean ± SD	Mean ± SD	Mean ± SD
Probing Depth (PD)	Placebo	4.35 ± 0.86	3.77 ± 0.73	3.75± .74
	Anaheal Drug	4.42 ± 0.93	3.35 ± 0.66	3.02± .15
	p-value	0.710	0.008	0.000
Plaque Index (PI)	Placebo	68.5 ± 5.07	66.67 ± 4.97	64.97 ± 4.59
	Anaheal Drug	67.8 ± 4.6	61.87 ± 4.3	59.12 ± 3.9
	p-value	0.520	0.000	0.000
Gingival Index (GI)	Placebo	1.92 ± 0.99	1.50 ± 0.93	1.35 ± 0.89
	Anaheal Drug	2.07 ± 0.91	1.10 ± 0.77	0.65 ± 0.48
	p-value	0.480	0.041	0.000
Bleeding on Probing (BOP)		N (%)	N (%)	N (%)
	Placebo	31 (77.5)	20 (50.0)	15 (37.5)
	Anaheal Drug	28 (70.0)	16 (40.0)	7 (17.5)
	p-value*	0.446	0.369	0.045

p-value: Mann-Whitney test; *p-value: Chi-square test.

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Probing depth before the treatment was similar in the groups (p = 0.71). Four and eight weeks after the treatment, the probing depth significantly reduced in the Anaheal group, as compared to the placebo group (p<0.05). Plaque index before the treatment was similar in both groups (p = 0.52). Four and eight weeks after the treatment, this index significantly reduced in the Anaheal group, as compared to the placebo group (p<0.05). The gingival index before the treatment was similar in both groups (p = 0.48). However, after four and weight weeks of treatment, the GI significantly reduced in the Anaheal group than in the placebo group (p<0.05). Bleeding during probing was similar in both groups before the treatment (p = 0.44) and four weeks after the treatment (p = 0.36). However, eight weeks after the treatment, it significantly reduced in the Anaheal group than in the placebo group (p<0.05).

Discussion

Chronic periodontitis is one of the most common periodontal diseases whose prevalence in third-world countries is far higher due to economic and cultural problems. Currently, it is controlled by surgical and non-surgical treatments [1,23,24]. It was proposed scaling and root planning as the golden standard treatment for chronic periodontitis [25].

Like under edema and infection conditions, the collagenases secreted by host cells (such as PMN leukocytes, macrophages, fibroblast, bone cells, etc.) and bacteria directly cause degradation of the soft periodontal tissue, affecting pathological loss of alveolar bone. In many periodontal diseases, mechanical treatment only in the long-term is inefficient, and auxiliary chemical methods such as antibiotic therapy are also required. For this reason, researchers have tried to study the treatment of this disease in a non-surgical manner using medication and by controlling these enzymes and bacteria [26,27].

In the present study, 80 patients with chronic periodontitis and a healthy systemic state were chosen and divided into two 40-subject groups. Next, the standard periodontitis treatment including scaling and root planning was performed by a unit operator in one session for all patients. Eventually, one group of patients was given Bromelain (500 mg capsule twice a day) orally one hour before meal, while the other group was given placebo.

The reason for choosing bromelain as supplementary pharmacological treatment in this study is because of the intrinsic characteristics stated for this material in different studies [28]. On the other hand, although synthetic drugs have a high efficiency, they have numerous adverse effects. For this reason, revisiting the use of herbs such as bromelain has been of interest to many scientists [16].

According to experimental and clinical studies, bromelain has numerous advantages including reduction of pain, wound healing, and debridement of burns, as well as anti-inflammatory, anti-edema, anti-coagulant and platelet aggregation inhibition properties [12,15,29]. The major pharmacological effects of bromelain are related to its proteolytic properties. Studies have shown that oral bromelain causes reduction of bradykinin, plasmakinin, prostaglandin E2 and thromboxane

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B2 levels in people affected by inflammation in a dose-dependent way. Indeed, bromelain inhibits thromboxane selectively, and alters the ratio of thromboxane to prostacyclin in favor of anti-inflammatory prostacyclin [12,16].

In the present research, in evaluating and comparing the clinical indices, which was performed four and eight weeks after the non-surgical periodontal treatments and prescription of Anaheal and placebo drugs, it was found that the gingival index (representing intensity of inflammation in periodontal disease), probing depth and plaque index were the same before the treatment in both groups (Anaheal and placebo). However, four and eight weeks after the treatment, the three studied indices were significantly lower in the Anaheal group, as compared to the placebo group. The bleeding on probing index was also similar before treatment and four weeks after the treatment. However, in the eighth week after the treatment, it was significantly lower in the Anaheal group as compared to the placebo group.

In a clinical trial on the anti-inflammatory and anti-gingivitis effects of toothpaste containing bromelain and some other compounds, it was observed that the GI and plaque index were significantly reduced in the studied group, as compared to the control [30]. A previous study has shown that bromelain alone has moderate anti-inflammatory effects and reduces post-surgical swelling [31]. Another study showed that the prescription of oral bromelain caused a significant reduction in pain, and thus had moderate anti-swelling effects [19].

In a study on biological and anti-inflammatory activities of bromelain, the authors attributed the effects to two important inflammatory mediators including cyclooxygenase (Cox) Types I and II. Cox-1 is synthesized in different tissues and supports biosynthesis of prostaglandin required for preserving homeostasis [32]. Cox-2 is also induced in response to stimulation by pro-inflammatory molecules such as IFNγ, TNF-α and GMCSF. This situation during inflammation grows as positive self-regulatory. Cox-2 is involved in the synthesis of prostaglandin E2. PGE-2 is widely found in the gingival crevicular fluid (GCF) of periodontal patients as compared to healthy individuals [21]. In various studies, treatment with bromelain has shown significant negative self-regulation in relation with Cox-2 expression [33-35].

In addition, a study indicated that treatment with bromelain causes removal of the superficial molecules of cells involved in attachment of leukocytes and activation by proteolytic activity. These cells are abundantly found in inflamed periodontal sites [36,37]. Various clinical trials have shown the effects of bromelain on the treatment of inflammatory diseases. These anti-inflammatory effects have also been proven in osteoarthritis of hip bone, knee and nasal sinusitis [32].

It is noteworthy that bromelain inhibits the growth of microorganisms in periodontal diseases such as *Streptococcus mutans*, *Enterococcus faecalis*, *Porphyromonas* gingivalis (P.g), and *Aggregatibacter actinomycetemcomitans* (A.a) [17]. Bromelain has a wide range of therapeutic properties, but its mechanism of activity has not been understood properly. It has been proven that after oral administration, it is well absorbed and has no significant adverse effect in long-term use.

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All the studies provided in this research as well as the results of the present study suggest that bromelain can be used as an effective drug supplement after non-surgical periodontal treatments.

Conclusion

The probing depth, plaque index and gingival index were similar in both groups before the treatment. However, four and eight weeks after the treatment, they significantly reduced in the Anaheal group as compared to the placebo group. Bleeding during probing before the treatment and four weeks after treatment was similar in both groups. However, eight weeks after the treatment, it was significantly lower in the Anaheal group as compared to the placebo group.

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