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ORIGINAL PAPER

Comparison of Anaheal Plus and Ibuprofen's Analgesic Effect after Root Canal Treatment in Patients Referred to Amol Private Clinic: a Clinical Trial Study

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ABSTRACT

Background and purpose: *Since pain control in dental treatments, including root canal treatment, is challenging, and no study has measured the appropriate pattern of Anaheal Plus drug consumption in reducing pain after root canal treatment, in this study the appropriate pattern of taking Anaheal Plus drug in reducing pain after root canal treatment was evaluated.*

Materials and methods: *The present study examined maxillary and mandibular molar teeth with irreversible pulpitis. Patients were divided into three groups: A) Anaheal Plus capsule; B) control; and*

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C) ibuprofen. Teeth were treated in two sessions, pulpectomy treatment was performed and drugs were used between sessions. A visual analog scale questionnaire was used to assess pain. Patients were asked to record the pain score before the root canal treatment as well as eight hours, 48 hours and five days after root canal treatment. All procedures were done in Amol's private clinic, where root canal treatment was administered by a dentist, and the teeth were obturated after a week.

Findings: *This study examined 90 patients with an average age of 33.94 years. Rescue doses were reported only in the control group, and there was a significant difference between groups (p-value < 0.001). In all groups, pain had decreased significantly (p-value<0.001), but the average pain in groups A and C was lower than that of group B at all times, and there was no difference between them.*

Conclusion: *Anaheal Plus significantly reduced pain after root canal treatment compared to the control group.*

Keywords: painkiller, bromelain, curcumin, root canal treatment.

INTRODUCTION

Pain after root canal treatment may be the result of an inflammatory reaction in the peri-apical tissues. The intensity of the inflammatory response is different and depends on local and systemic factors (1). Although the cause of pain and swelling after root treatment is not always clear, researchers have identified several determinants of that type of pain. Current studies have provided various solutions to control pain after root canal treatment, one of which is using different painkillers, including narcotics and non-narcotics. Among non-narcotics, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are included in this category. After root canal treatment, acetaminophen and ibuprofen are the most important analgesic drugs for pain control. These drugs can have various side effects such as liver damage and platelet inhibition (5). In recent years, research has been conducted on the effect of herbal painkillers (e.g., bromelain) on pain caused by various diseases. Bromelain is a complex of proteolytic enzymes extracted from the pineapple fruit (*Ananas cosmosus*). This substance is a phytochemical product (a plant chemical with medicinal properties) that has various characteristics, including inhibition of platelet aggregation and anti-inflammatory due to its proteolytic properties. Also, decreasing the amount of bradykinin in the blood reduces the permeability of the vessels and, consequently, the pain and swelling (6). Turmeric is also a phytochemical extracted from turmeric and ginger, which has inhibitory action against COX-2 (7). Anaheal Plus capsule is one of the drugs introduced based on the active ingredients of bromelain and turmeric. This capsule is mostly used to reduce pain and inflammation in arthritis (8). Of course, recent research has been conducted to investigate the analgesic effects of bromelain in dental surgery treatments, but clinical research is still needed in the field of endo pain (9). Since there has been no research in finding the appropriate pattern of taking Anaheal Plus to control pain after root canal treatment, the present study aims to determine the appropriate pattern of Anaheal Plus for its analgesic effect after root canal treatment. ❑

MATERIALS AND METHODS

This study registered under the ethics code IR.MAZUMS.REC.1402.153 is a clinical trial with the IRCT code 20220517054898N1. It was done to compare the analgesic effect of Anaheal Plus and ibuprofen during drug use after endodontic treatment on pain after root canal treatment.

Study participants aged between 20-60 years old were randomly selected from patients referred to Amol dental treatment center. All subjects were healthy in terms of systemic diseases and had low to moderate stress according to the anxiety questionnaire which was administered to them. The HAD (Hospital Anxiety & Depression) evaluation questionnaire (10, 11) was chosen to include normal patients in the study. The effect of stress on pain after root canal treatment was minimal and equalization was done. Maxillary and mandibular teeth with three canals were included in the study. For these teeth, irreversible periapical pulpitis was diagnosed, and they did not have periapical peri-

odontitis. Also, patients with pain before endodontic treatment in the range of moderate pain (VAS 4-7) were selected. Selected teeth were radiographically normal without any lesion, sinus tract, or acute periapical abscess and had a long response to the electrical pulp test (EPT) and cold test (ice-Endo).

Patients younger than 20 years (due to the possibility of the open apex) and older than 60 (due to calcification, which complicates the treatment process and affects the pain after root canal treatment), users of any analgesic drug in the last 12 hours, pregnant patients (8), patients with allergies to pineapple, celery, carrot, fennel, saffron, and ginger (12 and 13), and those who were not healthy in terms of systemic diseases were all excluded from the present study. Also, patients who could not complete the treatment protocol, those who did not fill out and sign the informed consent form, people with severe stress level according to the anxiety questionnaire, patients with invasive periodontal disease or those with pain in more than one tooth have been also excluded from the study.

A two-stage sampling method was used in the current study. In the first stage, samples which met the inclusion criteria were selected using a simple random sampling method. The block sampling method was used for random allocation in the second step. Samples were assigned to three groups using block classification. The blocking process was done with Random Allocation software. Samples were placed in three blocks of 30 subjects each using the mentioned method. The present study was registered and implemented in Mazandaran University of Medical Sciences, Iran. Patients were examined at Amol Dental Center. The teeth underwent endodontic treatment in two stages. During the first session, teeth were treated with pulpectomy and cleaning and shapping were done. During the next session, obturation of the dental canals was performed. Each patient had to use medicine between sessions. Infra alveolar block anesthesia was performed using 1.8 mL of 2% lidocaine with 1/80000 epinephrine (Darupakhsh, Iran). The tooth was isolated and prepared with a rubber dam. The length was determined with the help of an apex locator and periapical radiography. Then, cleaning and shaping were done with the down crown technique and rotary system (M3, Progold, China) (14). Saline and 2% hypochlorite were used as washing agents. Then, the canals were dried with paper points and calcium hydroxide, and dressings were applied. Study participants were randomly divided into three groups (A, B and C) of 30 people each.

Intervention group A received Anaheal Plus capsules containing 200 mg of bromelain and 300 mg of tromeric (Permon Amin Health Company, Tehran, Iran) every eight hours for five days (one dose was taken one hour before treatment and after treatment every eight hours for five days). Control group B received placebo medicine containing starch or carboxymethyl cellulose (CMC) every eight hours to five days (one dose was taken one hour before treatment and every eight hours for five days after treatment). Intervention group C received ibuprofen tablets (every eight hours to five days) (15, 16).

Standard treatment is using ibuprofen as an analgesic and pain reliever; for this reason, a rescue dose (ibuprofen) was considered for the control group. If patients had pain, they could take ibuprofen and note the number of doses taken. The method of using the Visual Anxiety Scale or pain questionnaire was taught to each patient. Before starting the work, patients were asked to record their pain score before endo treatment as well as eight hours, 48 hours and the fifth day after endo treatment. A dentist performed all procedures in Amol's private clinic, and the teeth were extracted after one week. Due to the nature of the drugs, double-blinding was not possible, so only the person recording the pain intensity was blinded, and the study was single-blinded. The placebo group helped to compare the analgesic effect with Anaheal Plus. Since the nature of root treatment reduces pain, the analgesic effect of Anaheal Plus was also compared with placebo.

Descriptive and inferential statistical methods were used to analyze the findings. The data were reported using descriptive frequency, mean, percentage and standard deviation (SD) indicators. Kolmgrove-Smirnov test and graphic method were used to check the hypothesis of normality. Analysis of variance and Kruskal-Wallis tests were used to compare the mean in groups, Friedman's test was used to compare pain scores over time and the chi-square test was used to compare frequencies in groups. The GEE test was used to control the effect of confounding variables on pain scores over time. The resulting data were ana-

lyzed by SPSS software version 23, and the significance level was considered 0.05. ❑

RESULTS

According to our findings, there was no significant difference in participants' average age between the three groups, as shown by Table 1.

In Table 2, the frequency of gender in the three groups was reported and compared using the chi-square test. There was no significant difference in the gender frequency of participants in the three groups (p-value 0.67).

Table 3 summarises the frequency of tooth position in the three groups. In groups A and B, most teeth were in the mandible position, while in group C in the maxilla position.

The frequency of molar position in the three groups was compared using the chi-square test, and the results showed that it did not have a significant difference (p-value 0.271) and most of the teeth were first molars in all groups.

In Table 5, the frequency of the number of rescue doses in each group was reported and compared using the chi-square test, with a significant difference being found (p-value <0.001).

In Table 6 and Figure 1, the average pain score at different times was reported by groups. There was no significant difference in the pain scores of the three groups at zero time (p-value 0.918). In the following times, no significant difference was observed in the pain scores of the three groups.

In group A, the average pain score decreased from 6.17 at zero time to 0.93 after five days, and Friedman's test showed that these changes in pain score were significant (p-value <0.001). Similar significant changes in the pain score were also observed in groups B and C.

Based on the initial comparisons, there were significant differences in terms of tooth position and number of rescue doses, so it was useful to investigate the effect of group and time on the pain score; therefore, the two variables of tooth position and number of doses were also controlled using the GEE test. The average pain score in group B was 0.46 lower than group A, which was significant (p-value <0.001). The average pain score in group C was 0.18 higher than group A, but their difference was insignificant (p-value 0.304). In general (all samples of the three groups), the average pain score decreased by 2.19, 3.66

TABLE 1. Comparison of study participants' average age between groups

Group A	Group B	Group C	P-value
10.88±35.13	9.37±35.37	8.73±31.33	0.201

TABLE 2. Comparison of gender frequency between groups

Sex	Group A	Group B	Group C	P-value
Female	14 (46.7)	17 (56.7)	14 (46.7)	0.670
Male	16 (53.3)	13 (43.3)	16 (53.3)	

TABLE 3. Comparison of the frequency of molar positions between groups

Molar	Group A	Group B	Group C	P-value
First molar	25 (83.3)	20 (66.7)	24 (80.0)	0.271
Second molar	5 (16.7)	10 (33.3)	6 (20.0)	

TABLE 4. Comparison of molar frequency between groups

Molar	Group A	Group B	Group C	P-value
Frist molar	25 (83.3)	20 (66.7)	24 (80.0)	0.271
Second molar	5 (16.7)	10 (33.3)	6 (20.0)	

TABLE 5. Comparison of the frequency of rescue doses in groups

Dose number	Group A	Group B	Group C	P-value
0	30 (100)	18 (60.0)	30 (100)	<0.001
2	0	1 (3.3)	0	
3	0	4 (13.3)	0	
4	0	2 (6.7)	0	
5	0	3 (10.0)	0	
6	0	2 (6.7)	0	

TABLE 6. Average pain score at different times by groups and their comparison

Time Group	Zero□	Eight hours	Two days	Five days	P-value+
A	6.17± 0.65	3.70±1.15	2.23±1.07	0.93±0.78	<0.001
B	6.07±0.83	4.10±1.47	2.67±1.49	1.23±1.16	<0.001
C	6.10±0.66	3.977±0.77	2.47±0.86	1.10±0.80	<0.001
P-value*	0.918	0.396	0.446	0.654	-

*Kruskal-Wallis test
+Friedman test
□zero before root treatment

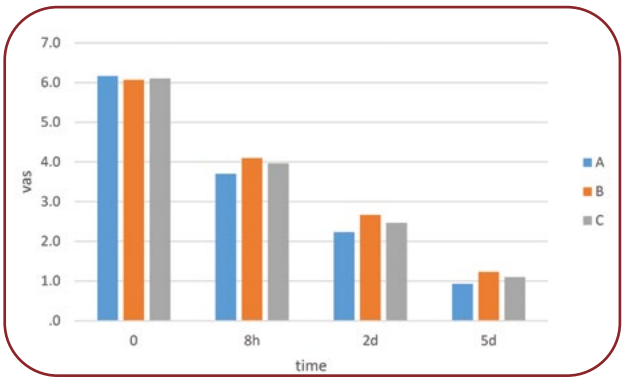

FIGURE 1. Average pain score at different times by groups

TABLE 7. Regression coefficients of the effect of time and group on pain score with GEE test

Variable		Regression coefficient	Standard deviation	Confidence interval 95%	P-value
Group	A				
	B	-0.46	0.18	-0.11 , -0.82	**0.011**
	C	0.18	0.17	-0.16 , 0.51	0.304
Time	Zero				
	Eight hours	-2.19	0.10	-2.39, -1.99	**<0.001**
	Two days	-3.66	0.11	-3.87, -3.44	**<0.001**
	Five days	-5.02	0.10	-5.22, -4.82	**<0.001**
Position	Mandible				
	Maxilla	-0.09	0.12	-0.33, 0.16	0.485
Dose number		0.44	0.05	0.36, 0.54	**<0.001**

and 5.02 units after eight hours, two days and five days, respectively, compared to time zero. Patients who took each higher dose had a 0.44 higher pain score. No significant relationship with pain score was observed regarding tooth position.

The results summarised in Table 7 were related to all patients. Next, the GEE test was performed separately for the groups to answer the question of how the pain score changes varied by group, and the results were reported in Table 8. In all three groups, changes in pain scores were significant and decreased over time, while tooth position had no significant effect on the pain score. In group B, patients who took more rescue doses reported higher pain scores, but this could not be calculated in groups A and C because no patient used rescue doses. ❑

DISCUSSIONS

Pain after root canal treatment is one of the problems and complications that mainly brings an unpleasant experience for patients and may lead to patient dissatisfaction with medical services, creating fear of dental treatments and avoiding continuing treatment (17). Therefore, effective pain control is very important in root canal treatment. The visual analog scale (VAS) has been used in different studies to measure pain, and its efficiency has been confirmed in previous studies (18). In our study, this method was also used to measure pain. Using VAS scale to evaluate pain intensity is easy for patients to understand, and the implementation of this method is simple, reliable and valid (18).

Bromelain is an enzyme compound extracted from pineapple root and fruit, which has a known proteolytic effect. Bromelain compounds are a group of sulfhydryl proteolytic enzymes that can contain acid phosphate, peroxidase and protease inhibitors (19). This extract is obtained by centrifuging, ultrafiltration and lyophilization of pineapple juice (20). The oral use of bromelain increases pain mediators such as bradykinin, reduces the production of pro-inflammatory factors such as prostaglandins, especially PGE2, and has fibrinolytic effects that lead to reduced edema and swelling. This combination leads to reduced pain, swelling, and tissue recovery time. Howe-

TABLE 8. Regression coefficients of the effect of time on pain score by groups using the GEE test

Group	Variable		Regression coefficient	Standard deviation	Confidence interval 95%	p-value
A	Time	Zero				
		Eight hours	-2.47	0.19	-2.84 , -2.09	**<0.001**
		Two days	-3.93	0.18	-4.28 , -3.59	**<0.001**
		Five days	-5.23	0.15	-5.53,-4.93	**<0.001**
	Position	Mandible				
		Maxilla	-0.10	0.26	-0.61 , 0.42	0.714
	Dose number					
B	Time	Zero				
		Eight hours	-1.97	0.18	-2.33 , -1.60	**<0.001**
		Two days	-3.40	0.19	-3.78 , -3.02	**<0.001**
		Five days	-4.83	0.17	-5.17 , -4.50	**<0.001**
	Position	Mandible				
		Maxilla	0.04	0.18	-0.30, 0.39	0.809
	Dose number		0.45	0.04	0.36 , 0.54	**<0.001**
C	Time	Zero				
		Eight hours	-2.13	0.14	-2.41 ,-1.86	**<0.001**
		Two days	-3.63	0.18	-3.98, -3.28	**<0.001**
		Five days	-5.00	0.19	-5.37 ,-4.63	**<0.001**
	Position	Mandible				
		Maxilla	-0.20	0.21	-0.60 , 0.21	0.344
	Dose number					

ver, its effects may differ slightly in different people and treatments (21).

Curcumin is a natural yellow pigment obtained from turmeric (*Curcuma longa*), a flowering plant in the ginger family and it has been used for a long time in Indian and Chinese traditional medicine as an anti-inflammatory agent in the treatment of digestive disorders to heal wounds and in the treatment of cystic fibrosis due to its anti-inflammatory effect (22). It has been proven that curcumin is useful in the prevention and treatment of a number of inflammatory diseases. At the cellular and molecular levels, curcumin has been shown to regulate a number of signaling pathways, including the eicosanoid pathway involving COX-2. The regulation of COX and LOX enzymes by curcumin may be the main mechanism of its beneficial effects in the prevention of various inflammatory diseases (22).

Almanza-Arande *et al* (23) investigated the anti-inflammatory and cytotoxic effects of turmeric and aloe vera in the gingivitis model. They observed the anti-inflammatory effects of turmeric on the gingivitis model. Also, Zuhir Alasfar *et al* (24) explored the effect of 10% turmeric gel on wound healing in free gingival grafts. The authors reported that 10% turmeric gel showed positive effects in relieving pain after surgery and speeding up the healing process compared to Coe-pack dressing. These two studies were conducted in research fields related to gums, and turmeric showed positive effects, but so far, there was no study on the effects of turmeric in root treatment. In our study, considering the dose of 300 mg of turmeric in Anaheal Plus capsules, we discussed the analgesic effects of turmeric in root treatment.

The effects of bromelain are dose dependent. So, its therapeutic effects start from low doses of 160 mg per day. However, the highest and best results are related to doses of 750 to 1000 mg daily (in four equal doses) (25). Although the bromelain drug has very little cytotoxicity and is generally considered a very low-complication drug, it can potentially cause IgE-mediated sensitization; therefore, it should not be prescribed beyond the recommended dose (19). The present study used 200 mg bromelain capsules every eight hours (600 mg per day). In Singh *et al*'s study (26), a dose of 200 mg/twice a day of bromelain was prescribed to patients. In the study of Majid and Al-Mashhadani (25), the drugs were given to each patient in the morning before surgery and continued for four days at a dose of 250 mg every six hours. Hozt *et al* (27) prescribed a dose of 80 mg three times a day for six days in their study. Ramasubbu and Wahab (28) administered a dose of 200 mg bromelain three times a day for five days to their patients. In similar studies, the anti-inflammatory and pain-relieving effects of bromelain have been investigated in patients who were candidates for impacted wisdom teeth surgery. It has been recommended to prescribe doses higher than 200 mg three times a day to ensure the anti-inflammatory and swelling effectiveness of the given drug (25, 27). However, in the current study, the effects of this drug in root treatment were investigated. Side effects have not been reported in previous studies, and they were not investigated in our study, but in the study of Bhoobalakrishnan *et al* (29), no side effects were reported in the bromelain group. However, in Bormann *et al*'s study (30), side effects such as diarrhea, nausea, allergic reactions and digestive system were reported in patients who received higher doses of this drug.

In the current study, the greatest reduction in pain was seen in the bromelain group at all investigated times (numerical pain reduction in Anaheal 5.24 *vs* 5 for ibuprofen), and statistically, ibuprofen and Anaheal did not have a statistically significant difference. A similar study in the field of root canal treatment has not investigated the effectiveness of this drug. All studies conducted in the field of dentistry were related to wisdom tooth surgery. In line with the present study, in Singh *et al*'s study (26), which examined the analgesic, anti-inflammatory and swelling effects of bromelain after wisdom tooth surgery, it was observed that bromelain medication led to a reduction in pain and swelling after surgery in 70% of cases. Majid and Al-Mashhadani (25) investigated the effect of bromelain administered before wisdom tooth surgery and observed a significant reduction in patients' postoperative pain in both groups with bromelain and diclofenac sodium. Also, the swelling caused after surgery in the bromelain group was less than in other groups. In their study, patients' quality of life after surgery was examined. In the bromelain and diclofenac sodium treatment groups, patients' quality of life was higher than in the control group. Ordesi *et al* (31) also reported a significant reduction in pain after wisdom tooth surgery. Ramasubbu and Wahab (32) investigated the effectiveness of bromelain and serratiopeptidase in reducing inflammation and

pain after impacted wisdom tooth surgery. Their study observed that pain, swelling and trismus in the bromelain group were significantly less than in the control and serratiopeptidase groups. Also, in the Anaheal group, pain reduction was significantly higher than in the placebo group. Bhoobalakrishnan *et al* (29) conducted a study of the effectiveness of bromelain after mandibular wisdom tooth surgery and found that its effectiveness was equal to that of diclofenac sodium.

In the present study, patients in the two groups with ibuprofen and bromelain did not use rescue doses. However, in the study of Bhoobalakrishnan *et al* (29), patients generally used an average of 1.6 rescue drugs during the entire treatment period and two drugs in the diclofenac sodium group, but there was no difference between the two groups. In the study of Majid and Al-Mashhadani (25), the rescue dose in the bromelain and diclofenac groups was 4.4 and 2.8, respectively. The results of the two mentioned studies differ from those reported by the present study; one of the reasons for this could be due to the examination of patients after third molar surgery, but in the present study, they were examined after root canal treatment. The amount of postoperative pain, swelling, inflammation and discomfort is much higher than those caused by root canal treatment.

One of the limitations of the current study was that the side effects of the drug were not investigated by us, which was partly explained by the short-term use of the drug. In the case of long-term drug use, it is necessary to check its side effects. ❑

CONCLUSION

The two explored drugs, Anaheal Plus and ibuprofen, had a similar effectiveness and lead to more pain reduction than that found in the control group. Although the pain in all stages was less in the Anaheal Plus group, there was no significant difference when compared to the ibuprofen group. No rescue dose was used in the Anaheal Plus and ibuprofen groups. ❑

Conflicts of interest: none declared.

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