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The effect of bromelain–acetaminophen combination on the intensity of endodontic postoperative pain: A randomized clinical trial

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ABSTRACT

Background: Despite significant advances in dentistry, postendodontic pain is one of the problems that patients still suffer from. This study aimed to evaluate the effect of bromelain–acetaminophen combination on the reduction of postendodontic pain in teeth with symptomatic irreversible pulpitis.
Materials and Methods: In this randomized double-blind clinical trial, 60 patients with mandibular first molars with irreversible pulpitis were evaluated. To homogenize the samples, patients who needed endodontic treatment of mandibular first molars with moderate severity were selected according to the American Association of Endodontists case difficulty assessment form. After endodontic treatment, half of the patients were given a placebo and 500 mg acetaminophen every 6 h, and the other half were given 500 mg Anahil capsule and 500 mg acetaminophen every 6 h until the patients' pain was ameliorated. If the patient did not feel pain, they didn't take medication, also we excluded the patients who felt pain for more than 2 days. The Visual Analog Scale (VAS) was used to measure pain before and 6, 12, 24, and 48 h after endodontic treatment. Data were analyzed by SPSS (version 22) software using *t*-test, Mann–Whitney, and Kaplan–Meyer tests at a 5% error level.
Results: The amount of pain decreased more in the experimental group than in the placebo group 6 and 12 h after endodontic treatment, but by controlling the effect of initial pain ($P = 0.627$), no significant difference was observed between the two groups in the amount of pain ($P = 0.875$).
Conclusion: The bromelain–acetaminophen combination did not have an added value when it comes to controlling postendodontic pain.

Key Words: Acetaminophen, bromelain, endodontic treatment, pain

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INTRODUCTION

After endodontic treatment patients vary widely in their perception of pain, hence, the occasional need for analgesics.[1]

To eliminate these side effects, various techniques such as drug therapy are used to prevent the release or formation of inflammatory mediators. Among these drugs, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) have shown anti-inflammatory, immunosuppressive, and analgesic effects.[2] However, the use of corticosteroids and

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NSAIDs has side effects such as gastrointestinal bleeding, renal dysfunction, decreased platelet activity, shortness of breath, and hypertension.[3] The most commonly used painkillers in this group are acetaminophen and ibuprofen. Acetaminophen is a derivative of para-aminophenol and is used in cases not requiring anti-inflammatory effects. It is one of the most important drugs used for the treatment of mild-to-moderate pain.[4]

Natural products have always been used with corticosteroid drugs to reduce inflammation, pain, and fever.[5] Anahil, a newly introduced drug, contains bromelain. Bromelain, obtained from the roots and fruits of the pineapple tree, contains proteolytic enzymes, proteases, phosphatases, peroxidases, cellulases, glycoproteins, and carbohydrates.[6,7] Research has shown that oral bromelain dose-dependently reduces bradykinin, plasmocin, prostaglandin E2, and thromboxane B2 at the site of inflammation. Bradykinin may be a factor that causes pain due to tissue damage. The advantage of bromelain over anti-inflammatory agents is that NSAIDs reduce the levels of proinflammatory and anti-inflammatory prostaglandins by inhibiting cyclooxygenase activity, whereas bromelain selectively inhibits the activity of proinflammatory thromboxane and alters the thromboxane–prostacyclin ratio in favor of anti-inflammatory prostacyclin.[7-9]

A study on the effect of three analgesics, including novafen, naproxen, and tramadol, on postendodontic pain showed that novafen has the same analgesic effect as naproxen.[10] Another study conducted in Tabriz on the effect of a prodrug with novafen before crown lengthening surgery showed that a prodrug with novafen reduced pain and swelling after crown lengthening surgery.[11]

Several studies have used Anahil as a medicine to treat pain, swelling, and inflammation. In a study, bromelain reduced pain, swelling, and inflammation in women who underwent cesarean section.[12] Soheilifar *et al*. stated that oral bromelain (500 mg per day) could effectively reduce pain at the donor site after gingival transplantation and might also lead to wound healing.[13] Bormann *et al*. evaluated the effect of bromelain on 75 patients after placebo treatment and showed that the use of bromelain had a positive effect on the reduction of inflammation and surgical pain.[14] A review of 117 published articles on the effectiveness of bromelain in reducing inflammation and pain due to mandibular third molar surgery showed that bromelain reduced pain, swelling, and trismus caused by third molar surgery, although this study recommended further studies in this regard.[15]

Ghensi *et al*. compared the effects of bromelain and anti-inflammatory drugs and reported that bromelain alone had a moderate effect on the reduction of inflammation and pain compared to the group that did not take any drugs. However, this substance was found to have an optimal effect in combination with an anti-inflammatory drug.[16] Contraindication is the administration of bromelain in patients with severe liver, kidney, and coagulation disorders and a history of allergy to various drugs and pineapple. Bromelain also increases the absorption of some antibiotics such as tetracycline and amoxicillin, so it is prescribed for patients in whom the dose of these antibiotics is far from toxic.[17]

To the knowledge of the authors, there are no studies that evaluate, etc., to evaluate if bromelain can have an added value in controlling postoperative endodontic pain.

In this study, pain was measured before and 6, 12, 24, and 48 h after endodontic treatment using the Visual Analog Scale (VAS),[18,19] and the difficulty of endodontic treatment was measured according to the American Association of Endodontists (AAE) case difficulty assessment form.[20]

Given that bromelain reduces pain and inflammation, in this study, we want to investigate whether bromelain can improve pain after root canal treatment?

MATERIALS AND METHODS

In this double-blind Clinical trial Study (approved ethically, IRCT:20210802052051N1) double-blind study, two groups of AA and AB pills were designed by a pharmacist, one of which was acetaminophen (Hakim Company, Iran) placebo and the other was acetaminophen–bromelain.

Inclusion criteria

Patients who needed endodontic treatment of mandibular first molars with moderate severity were selected according to the AAE case difficulty assessment form. For example, the selected tooth had moderate inclination and rotation (10°–30°) and moderate root curvature (10°–30°) and three canals.

Excluded criteria

People under 20 and over 50 years of age. Most

studies have demonstrated that elderly people over 50 experience reduced discomfort following root canal therapy.[21] Those who did not meet the requirements of the Aee form as well as those who did not want to continue cooperation.

The patient's tooth was treated in one session (free treatment). For temporary tooth dressing, eugenol-free, and analgesic Coltene Coltosol F filling material and AH26 (Dentsply Company) sealer were used. The canal was filled by lateral compaction technique. The percussion and palpation tests were also negative and without periapical inflammation. The first molar is the most common tooth with irreversible pulpitis, so this tooth was selected for evaluation.

All teeth were treated by an endodontics who is an assistant professor using one method. Three heat, cold, and electrical pulp tests were performed to ensure the vitality of the teeth and that the pulp was irreversible. Further, the percussion and palpation tests should be negative.

Pain measurement

VAS was used to measure pain before and 6, 12, 24, and 48 h after endodontic treatment.[18,19] The absence of pain was given a score of zero, and maximum pain was given a score of 10. Finally, Table 1 was designed for each patient as follows.

Sixty patients with mandibular first molar teeth with irreversible pulp were selected. According to Table 2, the mean age of patients was 35 years. There were 23 (38.4%) male and 37 (61.6. %) female patients among them. In this study, 500 mg of Anahil capsules (Parmoon Health Company) were used. After endodontic treatment, half of the patients were given a placebo and 500 mg acetaminophen every 6 h, and the other half were given 500 mg Anahil capsules and 500 mg acetaminophen every 6 h until the patients' pain was improved. Medications were prescribed 1 h before or 2 h after meals.

A formula was used to determine the required sample size:

$R = 10 - 0 = 10 = \sigma = 1.67$

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 (\sigma_1^2 + \sigma_2^2)}{d^2}$$

P value $\alpha = 0.05$

Table 1: Mean and standard deviation of pain score (out of 10 points) in the two groups before, 6, and 12 h after treatment

Drug	Pain before treatment	Pain 6 h after treatment	Pain 12 h after treatment
Bromelain- acetaminophen			
Mean	36.6	86.1	40.0
n	30	30	30
SD	62.1	16.2	83.1
Placebo-acetaminophen			
Mean	83.5	93.1	56.0
n	30	30	30
SD	46.1	43.2	19.2
Total			
Mean	10.6	90.1	48.0
n	60	60	60
SD	55.1	28.2	00.2

SD: Standard deviation

Table 2: Descriptive statistics and frequency percentage of demographic characteristics

Characteristics	Frequency (%)
Age/year	
Minimum	20
Maximum	50
Mean	35
Gender	
Male	23 (38.4)
Female	37 (61.6)

$Z_{1-\frac{\alpha}{2}} = 1.96$

Power of a test = 0.8

$Z_{1-\beta} = 0.84$

$\sigma_1 = \sigma_2 \approx 1.67$

d = 1.2

$N = 60$

Data analysis is done at two levels: descriptive and inferential. At the descriptive level, the status of the studied population was examined using mean, frequency, and drawing relevant graphs, and at the inferential level, the research questions were answered using covariance and Kaplan–Meier. All analyses were performed at a 5% error level and using SPSS version 22 software (IBM, Illinois, US).

In this study, the researcher considered the following to comply with ethical considerations.

1. The researcher registered his research title with the university before starting the research and obtained

the necessary permission in this regard
2. The researcher introduced himself fully to the participants and provided them with sufficient information about the research. The researcher tries to protect the rights of the participants in this research in the field of research participation and strives to obtain informed consent. In this way, after providing the necessary explanations about the importance, goals, and benefits of the research, the participants' consent was obtained, and it was explained to them that they were free to withdraw from the research
3. The participants in the research were assured that the information obtained would remain confidential. To maintain the confidentiality of the information, a number or code was used instead of the participants' names, and writing their first and last names was not required
4. By providing the participants with their contact numbers and addresses, they were able to learn about the research results if they wished
5. It was explained to the participants that their response and participation in the research would not affect their treatment process
6. At the end of the research, verbal thanks and appreciation were given to the participants and the authorities
7. The principle of confidentiality was observed in presenting research sources
8. The code of ethics in research has been registered with the Isfahan Medical Sciences Ethics and Research Committee under number IR.MUI.RESEARCH.REC.1400.106 for this thesis.

RESULTS

Analysis of covariance for repeated data showed no significant difference between the pain levels of the two groups by controlling the effect of initial pain ($P = 0.627$) [Figure 1]. Moreover, for more accurate assessment, survival analysis was performed using the Kaplan–Meier method, which showed no significant difference between the two groups [Figure 2] ($P = 0.665$).

DISCUSSION

Pain is an unpleasant sensation that originates from a specific area of the body and is usually caused by processes that can cause injury.[22] Potentially, stimulating periapical tissues during treatment causes inflammation and the release of a group of chemicals that initiate

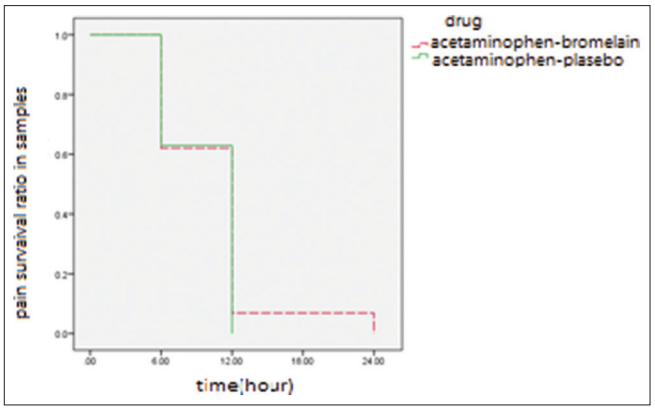

Figure 1: Percentage of patients with residual pain 6, 12, and 24 h after treatment.

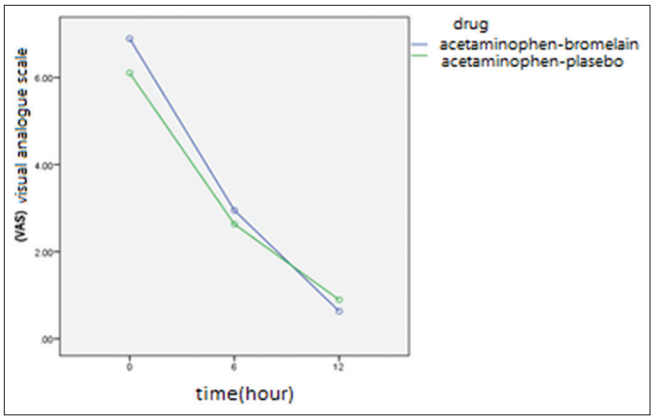

Figure 2: Mean pain score by time and group.

inflammatory responses, and inflammation is initiated by histamine, bradykinin, and prostaglandins.[23]

In the present study, two groups of bromelain–acetaminophen and acetaminophen alone were used to evaluate the reduction of postendodontic pain in teeth with symptomatic irreversible pulpitis. It was assumed that the concomitant use of bromelain and acetaminophen can have a better effect on pain reduction because bromelain contains different compounds that have proteolytic properties.[24-26] Some studies have investigated the effect of bromelain on pain reduction and have shown higher pain relief for bromelain than placebo.[12,27-29] Yet, an important point about most of these studies is that the effect of bromelain has been compared to that of a placebo. The present study was performed to determine the effect of bromelain and acetaminophen on pain reduction after endodontic treatment of teeth with symptomatic irreversible pulpitis in comparison with placebo and acetaminophen.

The results indicated the amount of pain before treatment was higher in the bromelain–acetaminophen group than

the placebo-acetaminophen group, but 6 and 12 h after treatment, the bromelain–acetaminophen group underwent a greater pain reduction than the placebo-acetaminophen group. However, since pain reduction was similar in both groups, no significant difference was observed between the study groups. In other words, bromelain–acetaminophen and placebo-acetaminophen had the same effect on pain reduction after endodontic treatment of the teeth with symptomatic irreversible pulpitis.

Soheilifar *et al*. stated that oral bromelain (500 mg per day) could effectively reduce pain at the donor site after gingival transplantation and might also lead to wound healing.[13] Oral bromelain was evaluated in comparison with the placebo group, so their results cannot be generalized to the present study, but in terms of the effect of bromelain on pain reduction in endodontically treated patients, the results are in line with those of the present study. Studies have confirmed the effect of drugs such as tramadol, novafen, and acetaminophen on pain reduction in patients undergoing endodontic treatment and have reported good results for pain reduction in patients, but each of these drugs has long-term side effects.[10] Therefore, the introduction of a drug with minimal side effects can be effective.

Bormann *et al*. examined 1000, 2000, and 3000 doses of bromelain in comparison with the placebo group and found no significant difference between the two groups in terms of the side effects of the drug. Further, 1000, 2000, and 3000 doses were not significantly different from each other, but the amount of pain was much lower in the bromelain group than in the placebo group.[14] In the present study, bromelain–acetaminophen had a better effect on pain reduction than acetaminophen alone, but no significant difference was observed between the two groups. In other words, in the present study, the main effect on pain reduction was related to acetaminophen, and bromelain did not have a significant effect on pain reduction.

de Souza *et al*. stated that bromelain is effective in controlling pain, edema, and trismus after mandibular third molar surgery. However, more clinical studies are needed to provide more accurate results.[15] Inchingolo *et al*. also found that bromelain alone had a moderate effect on the reduction of inflammation and pain compared to the group that did not take any medication, while the best effect was reported for bromelain in combination with an anti-inflammatory drug. The results clearly show the effectiveness of bromelain in the treatment of edema after third molar surgery.[16]

The use of herbal medicine as an efficient and strategic method is on the agenda of most countries in the world, including Iran. This approach is used owing to factors such as fewer side effects, lower economic costs, a variety of effective compounds in plants, and, in particular, the recommendation of the World Health Organization on the use of medicinal plants. Numerous studies have supported the usefulness of oral bromelain in reducing pain, swelling, inflammation, and wound healing in humans due to reduced levels of pain mediators and vascular phenomena associated with acute inflammation.[30,31]

In all studies, bromelain has been compared with the placebo group (nondrug). Moreover, few studies have compared the simultaneous effect of bromelain and other drugs with analgesics and anti-inflammatory drugs. Therefore, it can be argued that bromelain as an herbal medicine without reported serious side effects can be effective in reducing postendodontic pain in teeth with symptomatic irreversible pulpitis, but this effect is far less than that of acetaminophen and other analgesics, and bromelain is recommended to be used with other analgesics.

CONCLUSION

The amount of pain before the start of the treatment in the bromelain and acetaminophen group was higher than the placebo and acetaminophen group, but 6 h and 0 h after the treatment, the bromelain and acetaminophen group had a greater reduction than the placebo and acetaminophen group, but because the amount of pain reduction in the two studied groups was close to each other, this decrease in the studied groups did not lead to significant differences, in other words, the effect of bromelain and acetaminophen and placebo and acetaminophen in reducing pain after root canal treatment with symptomatic irreversible pulpitis is the same.

Limitations

One of the limitations of the study is the lack of full cooperation of the patients in taking the drugs and also the lack of participation in the follow-up sessions.

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Conflicts of interest

The authors of this manuscript declare that they have

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