



ORIGINAL ARTICLE

## Effect of Supplementary Administration of Anaheal on Reducing Pain, Swelling and Trismus after Mandibular Third Molar Surgery: A Split-mouth Controlled Randomized Clinical Trial

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### Abstract

**Objective:** To evaluate the effect of supplementary administration of Anaheal capsule in reducing pain, swelling and trismus after surgical removal of impacted mandibular third molars. **Material and Methods:** This single-blind controlled randomized clinical trial was conducted on 36 patients referring to Tabriz University of Medical Sciences. Each of the 36 patients had bilateral surgical removal of mandibular third molars in two sessions, with at least a 4-week interval between sessions. In the same individual, one of the sites randomly received a test medication whereas the other site was used as a control. In the test subgroup (test medication side), the first dose of Anaheal capsule was given as a 200-mg dose of bromelain immediately after surgery according to manufacturer's instructions and the subsequent doses were given at 6-hour intervals after the first dose. The medication was administered for 3 days. In the control subgroup (control side), Anaheal was not administered. The severities of pain, swelling and maximum mouth opening (MMO) were recorded one and three days postoperatively. Paired t-test and t-test for independent samples were used. Statistical significance was defined at  $p < 0.05$ . **Results:** A total of 72 surgical extractions were performed; 36 procedures served as control and 36 cases received Anaheal. Pain, swelling and trismus of the patients were at the highest levels one day after surgery, which decreased on day 3. However, independent t-test showed no significant differences in pain, swelling and trismus after surgery between the study subgroups ( $p > 0.05$ ). **Conclusion:** Supplementary administration of Anaheal (800 mg bromelain daily) had no significant effect on decreasing pain, swelling and trismus at 1- and 3-day intervals after surgical removal of mandibular third molars.

**Keywords:** Postoperative Complications; Tooth, Impacted; Bromelains.

## Introduction

Wisdom teeth remain impacted in the jaw for various reasons, including high density of overlying bone, the position of adjacent teeth, thick mucosa and genetic factors. The prevalence of impacted mandibular wisdom teeth is 20-30% of the population; therefore, surgery of impacted wisdom teeth is one of the most frequent surgeries in dental field [1,2].

This type of surgery inflicts traumas to the highly vascularized region of the impaction, leading to inflammatory complications, also referred to as 'sequelae', because they are common occurrences and include pain, swelling and trismus [3]. Pain, swelling and trismus are frequent complications after impacted third molar surgeries. These complications affect the quality of life [4]. An important principle in dentistry is to reduce the incidence of postoperative complications [5,6].

Different techniques have been suggested to manage immediate inflammatory response associated with impacted third molar surgery, include closing the surgical site with or without the use of a drain, use of physical therapy methods such as cryotherapy and bandage therapy and the use of medications such as analgesics, corticosteroids and antibiotics [7-10].

Nonsteroidal anti-inflammatory drugs (NSAIDs) have often been administered to decrease the incidence of inflammatory complications, especially pain, caused by surgical extraction of third molars. However, the side effects associated with the use of NSAIDs are numerous, including gastrointestinal, hematologic and renal disorders and their propensity to cause skin and mucosal reactions [3,7]. Hence, a natural, effective and safe remedy with no unfavorable side effects would be a good alternative treatment to prevent sequelae after third molar surgery.

Anaheal is a recently introduced pharmacologic product, consisting of bromelain. Bromelain is extracted from the root and fruit of pineapple; it is a combination of proteolytic enzymes, protease, phosphatase, peroxidase, cellulase, glycoproteinase and carbohydrates. The chief pharmacologic effect of bromelain is attributed to its proteolytic properties [11,12]. Studies have shown that oral bromelain decreases bradykinin, plasmakinin, prostaglandin E2 and thromboxane B2 levels in inflamed areas in a dose-dependent manner. Bradykinin might be a factor that is responsible for inducing pain due to tissue injury more than other agents. The advantage of bromelain over other anti-inflammatory agents is the fact that non-steroidal anti-inflammatory agents decrease the levels of proinflammatory and anti-inflammatory prostaglandins by inhibiting cyclooxygenase, while bromelain inhibits proinflammatory thromboxane selectively and changes thromboxane/prostacyclin ratio in favor of anti-inflammatory prostacyclin [12,13].

Various studies have supported the use of Anaheal as a medication to relieve pain, swelling and inflammation in different treatment modalities. Bromelain decreased pain, inflammation and swelling and accelerated wound healing in female subjects undergoing caesarean section [14]. Bromelain decreased acute pain resulting from the strain of ligaments in the ankle of patients effectively [15], and when it was combined with trypsin, it was effective in decreasing pain and the number of analgesics taken in subjects undergoing major abdominal laparotomy procedures [16].

In relation to the use of bromelain to decrease complications after third molar surgery, a limited number of studies are available with contradictory results. Some of these studies have supported the use of bromelain to decrease postoperative complications [3,17]. However, in some other studies, bromelain did not significantly decrease pain, swelling and trismus after surgical removal of third molars compared to placebo and non-steroidal anti-inflammatory agents [11].

Therefore, considering the limited number of studies in this field and the contradictory results of studies that are available and since in previous studies, the combined effect of bromelain and non-steroidal anti-inflammatory agents such as ibuprofen has not been evaluated, the present study was undertaken to evaluate the effect of supplementary administration of Anaheal capsules on decreasing pain, swelling and trismus after surgical removal of hard-tissue impacted mandibular third molars.

## Material and Methods

### Study Design

This single-blind controlled randomized clinical trial was conducted on 36 patients 18-35 years of age, who were systemically healthy and had referred to the Department of Maxillofacial Surgery, Faculty of Dentistry, Tabriz University of Medical Sciences for the bilateral removal of their impacted mandibular third molars in 2016-2017.

### Sampling

The results of a previous study [3] were used to determine the sample size, in which the mean swelling scores in the bromelain and placebo groups were  $4.0 \pm 2.59$  and  $5.8 \pm 5.2$ , respectively. The sample size was calculated at 36 samples by considering  $\alpha=0.05$  and a study power of 80%. The study had a split-mouth design and the left and right sides in the same subject underwent surgery one by one. Patients were selected randomly.

### Data Collection

All the subjects were matched for classification of impaction [18] and inclination of teeth. Subjects with any systemic disease, local infections such as pericoronitis, history of using tobacco and drugs such as oral contraceptives during the previous 4 weeks, poor oral hygiene and pregnant women were excluded from the study. The patients were excluded as study subjects if they reported the use of non-trial drugs during the observation period.

One surgeon who was blinded to the study, performed wisdom tooth surgeries of all the patients in the same manner and condition. All the 36 patients underwent bilateral surgical removals in two sessions, with at least a 4-week interval between the two sessions. In each subject, one of the sites randomly received a test medication and the contralateral site was used as a control. Allocations for treatment were performed by non-clinical staff, using a random block approach, concealed in opaque envelopes, which were opened on the day of surgery.

The surgeries were performed under local anesthesia. Inferior alveolar nerve block and long buccal injections were carried out using 2% lidocaine with 1:80000 epinephrine. A triangular full-thickness flap with a releasing incision on the mesio-buccal aspect of the second molar was designed. After ostectomy, the tooth was sectioned and gently elevated. After all the tooth components were removed, the socket was carefully inspected and the flap sutured with interrupted sutures using 4.0 silk (Sharpoint, Surgical Specialties Corp., Wyomissing, PA, USA). A cold semi-liquid diet was suggested for the first day, with routine oral hygiene procedures being reinstituted after 1 day.

In all the patients, a daily dose of 1.5 gr of amoxicillin (500-mg capsules three times a day) and four 400-mg Gelofen tablets were administered for 5 days. In the test subgroup (test medication side), the first dose of Anaheal capsule (Salamat Parmoon Amin Co., Tehran, Iran) was given at a dose of 200 mg according to manufacturers' instructions immediately after surgery and the subsequent doses were given at 6-hour intervals after surgery. The medication was given for 3 days. In the control subgroup (control side) Anaheal was not administered.

Maximum mouth opening (MMO), pain and swelling were evaluated on the first and third days after surgery. Assessments and measurements were conducted by a person not aware of the group allocations. The main objective variables were measured as follows:

- A) Pain was measured using VAS on the first and third postoperative days. In fact, the absence of pain was given a score of zero, low pain a score of 1, and based on pain intensity, respectively, the patients chose a number from 0 to 10 on the questionnaire given to them after surgery. The patients registered the pain values presented at the beginning of the study (D0), on day 1 (D1) and on day 3 (D3) postoperatively.
- B) Postoperative swelling was determined by measuring the distance from the corner of the mouth to the ear lobe, following the bulge of the cheek. The patients registered the swelling values presented at the beginning of the study (D0), on day 1 (D1) and on day 3 (D3) postoperatively.
- C) The maximum mouth opening (MMO) was assessed by measuring the inter-incisal distances before surgery (D0), on day 1 (D1) and on day 3 (D3) postoperatively, using a ruler. The results were expressed in mm. The patients were asked to open their mouth as much as possible and the distance from the incisal edge of the upper and lower incisors was measured in all the patients.

#### Data Analysis

Data were analyzed with IBM SPSS Statistics for Windows Software, version 16 (IBM Corp., Armonk, NY, USA), using descriptive statistics (means and standard deviations) of the quantitative variables (age, swelling, pain and MMO). Paired t-test was used to test any significant differences at baseline for each treatment subgroup. The differences between the two subgroups for each one of the variables was performed with t-test for independent samples with significant differences at  $p < 0.05$ .

## Ethical Aspects

The study protocol approved by the Ethics Committee of Tabriz University of Medical Sciences. The study was registered in Iranian Registry of Clinical Trials (IRCT) under the code 2017021216246N3. Informed consent was obtained from all the patients.

## Results

Of 36 patients, 20 were male and 16 were female with an age range of 18–35 years (mean:  $25.3 \pm 1.1$ ). A total of 72 surgical extractions were performed; 36 procedures served as control and 36 others were the cases in patients receiving Anaheal.

Swelling, pain and MMO were compared between the two subgroups before surgery (D0), on day 1 (D1) and on day 3 (D3) postoperatively (Table 1).

**Table 1. Preoperative (D0) and postoperative measurements (D1 = day 1; D3 = day 3) in both study subgroups (mean  $\pm$  SD).**

Variables		Control Subgroup	Test Subgroup	p-value
Swelling	D0	$108.4 \pm 11.4$	$109.1 \pm 12.2$	0.8
	D1	$111.02 \pm 13.7$	$114.06 \pm 14.9$	0.37
	D3	$109.8 \pm 10.2$	$110.5 \pm 11.2$	0.78
Pain	D0	0	0	
	D1	$2.6 \pm 1.1$	$2.7 \pm 0.9$	0.67
	D3	$2.1 \pm 0.9$	$2.3 \pm 0.7$	0.29
MMO	D0	$41.3 \pm 4.3$	$41.18 \pm 4.1$	0.9
	D1	$35.04 \pm 9.6$	$34.12 \pm 9.9$	0.69
	D3	$37.04 \pm 6.8$	$36.62 \pm 5.9$	0.78

Comparisons were made with t-test.

Pain, swelling and trismus were at maximum levels one day after surgery, which decreased by day 3 postoperatively. However, no significant differences in pain, swelling and trismus after surgery between the study subgroups was observed ( $p > 0.05$ ).

## Discussion

Surgical removal of impacted third molars is one of the most common procedures. Some of the most common postoperative complications of this surgical procedure include pain, swelling and limitation in the mouth opening. Administration of local and systemic corticosteroids or NSAIDs leads to some complications such as the risk of systemic hemorrhage, gastrointestinal problems and allergic reactions; therefore, attempts are under way to find new alternatives to better control postoperative complications [7,17].

Proteases, such as bromelain, act at specific receptors on the cell surface of the inflammatory component, generating and/or destroying receptor agonists and activating and deactivating them; therefore, they have a significant role in the signal transduction mechanism of inflammation. However, this effect is highly variable, depending on differences in the expression of these receptors in different individuals and in different tissues of the same individual [3,19].

The majority of published studies have suggested different mechanisms by which proteases, including bromelain, can decrease inflammation, the most important of which are the return of the interstitial fluid and inflammatory cells into the bloodstream, resulting in a decrease in swelling in the area [3,20] and they decrease the biosynthesis of plasmakinins and proinflammatory prostaglandins PGE2 and PGF2 [3,21].

In the present study, in the case subgroup, Anaheal capsule was administrated at a daily dose of 800 mg bromelain (200 mg, four times daily) in association with 1.6 g of ibuprofen (400 mg, four times daily); in the control subgroup, ibuprofen was administrated at a dose of 1.6 g/daily (400 mg, four times daily).

Bromelain has exhibited therapeutic effects in doses as small as 160 mg/day; however, it has been reported that for most conditions the best results will be achieved at a dose of 750-1000 mg/day in 4 divided doses [3], which was the regimen used in the present study.

However, the results showed that although pain, swelling and trismus decreased a little in the subgroup receiving bromelain, compared to the control subgroup, there were no significant differences in pain, swelling and maximum mouth opening between the two subgroups during the first 3 days after surgery.

Previous authors evaluated 34 patients on the third and eighth days after third molar surgery in relation to inflammation, pain and mouth opening. One group received bromelain at a dose of 150 mg/daily for three days and 100 mg on days 4 to 7. The other group received placebo in the same dosage. The results showed no significant differences between the groups [11]. The use of bromelain (40 mg every 6 hours for 6 days) was compared to the use of ketoprofen (100 mg every 12 hours for six days) after surgical extraction of third molars and it was verified that bromelain was as effective as an NSAID in the treatment of postoperative inflammation [22].

This is while several studies have supported the usefulness of orally administered bromelain to reduce pain and swelling after surgical procedures due to a decreased levels of certain pain mediators and vascular phenomena associated with acute inflammation [3,23,24].

In a previous study, 80 patients were evaluated 3 hours and 1 and 7 days after mandibular molar surgery in relation to pain, edema and erythema. On the day of surgery, all the patients received 1 gr of paracetamol every 8 hours. On day 1, patients were divided into 2 subgroups. Patients in Group 1 were prescribed bromelain (50 mg every 12 hours for 7 days) together with paracetamol as an analgesic if required. The patients in Group 2 were prescribed only paracetamol if required. Although at the end of the study the dose and interval of use of the analgesic agent were similar in both groups, statistical analysis showed that in the group treated with bromelain the inflammatory response (postoperative pain, edema and swelling) was significantly less than that in the control group. But, clinically, there were no significant differences in pain, swelling and trismus after surgery between the two subgroups [17].

It has been shown that perioperative bromelain prescription, a daily oral dose of bromelain (250 mg every 6 hours) 1 day before surgery, which continued for 4 days, showed a significant



analgesic and anti-edemic effect, a significant improvement in quality of life and a minor decrease in trismus during the early postoperative period in patients undergoing lower third molar surgery. The bromelain effect was comparable to that of diclofenac sodium in all the parameters, making bromelain a good alternative for NSAIDs [3].

Many risk factors for edema, pain and trismus after surgical removal of third molars have been reported by different investigators, including age, gender, operation time and surgical experience [3,25]. The bias of such factors or their dominance in one group or another, which would affect the interpretation of the results, was minimized by randomization of treatment allocation and the strict inclusion criteria. In addition, the surgical phase was made by the same surgeon in all the patients to avoid possible operator variability. Therefore, these differences between studies might be largely attributed to a lack of knowledge of the effective dose of bromelain indicated for postoperative inflammation in the surgical extraction of third molars.

Studies have reported no significant differences between the study groups with the administration of 150 mg [3], 240 mg [23] and 800 mg (the present study) of bromelain daily. It should be pointed out that in one study with daily administration of 100 mg of bromelain there were significant differences between the study groups; but, the difference was not significant clinically [17]. In another study [3], daily administration of 800 mg of bromelain resulted in a significant difference between the study groups. Therefore, it appears high daily doses of bromelain will yield better results.

In addition, the discrepancies in the results of studies might be attributed to the time when the use of Anaheal was initiated. In this context, administration of Anaheal was more successful when it was administrated preoperatively [3]. In addition, in the present study, placebo was not administered in the control subgroup, which might affect the pain reported by the patient (single-blind study). On the other hand, due to the various side effects of non-steroidal anti-inflammatory drugs, attempts are still under way to find an alternative for them.

Although a large number of studies have evaluated the anti-inflammatory and analgesic effects of Anaheal, some of the available studies are poor and limited, with contradictory results, necessitating further studies on the subject because Anaheal is a relatively expensive medication and its administration instead of non-steroidal anti-inflammatory drugs or as a supplement for them requires hard scientific evidence. Therefore, it is suggested that more comprehensive double-blind trials be undertaken with large sample sizes and by administration of various doses of Anaheal at different preoperative and postoperative intervals.

## Conclusion

Supplementary administration of Anaheal capsules (800 mg of bromelain, daily) did not have a significant effect on decreasing postoperative pain, swelling and trismus, one and three days after surgical removal of impacted mandibular third molars.

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