Original Article

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Dentistry Section

Comparison of Clinical Efficacy of Bromelain with Paracetamol on Postoperative Sequelae after Surgical Removal of Impacted Mandibular Third Molar: A Split-mouth Randomised Clinical Study

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ABSTRACT

Introduction: The most frequent oral and maxillofacial surgical operation carried out in an outpatient setting is the surgical extraction of impacted mandibular third molars. The removal of impacted mandibular third molars involves surgical trauma in a highly vascularised area, which causes inflammatory changes referred to as "sequelae," including pain, swelling, and trismus. These symptoms gradually appear, peaking two days after the extraction. To limit these postsurgical inflammatory complications, surgeons have advised the patients to use proteolytic enzymes, such as bromelain, along with routine antibiotics, analgesics, and corticosteroids.

Aim: To compare the clinical efficacy of bromelain with that of paracetamol on pain, swelling, and trismus after the surgical removal of bilateral impacted mandibular third molars with similar difficulty indices.

Materials and Methods: The present study was a split-mouth randomised clinical trial conducted at the Department of Oral and Maxillofacial Surgery, Bharati Vidyapeeth DU Dental College and Hospital, Pune, Maharashtra, India, over a period of six months from August 2022 to January 2023. Twenty subjects requiring surgical extraction of an impacted mandibular third molar were selected for the study. All subjects were randomly assigned to receive one of the following treatments for five days after surgery: Cap. bromelain 500 mg-BD 24 hours preoperatively and continued until the 4th day postoperatively (n=10, Group A) or Tab. paracetamol 500 mg-TDS (n=10, Group B). Pain scores were evaluated using the Visual Analog Scale (VAS) on postoperative days 1, 2, and 3. Swelling and mouth opening were assessed on postoperative days 2 and 7. Intergroup comparison was done using Student's t-test.

Results: The mean VAS scores for pain evaluation were 6.60, 5.80, and 5.20 for bromelain on days 1 (p=0.001), 2 (p=0.001), and 3 (p=0.001), respectively. The difference between the swelling values for the bromelain group was significant, while there were no significant differences in the values of trismus.

Conclusion: It was concluded that bromelain is a better analgesic and anti-inflammatory drug compared to paracetamol. There were no significant differences in the values of trismus.

Keywords: Pain, Proteolytic enzyme, Swelling, Trismus, Wisdom tooth surgery

INTRODUCTION

In an outpatient setting, the most frequent oral and maxillofacial surgical operation is the surgical extraction of impacted mandibular third molars [1]. Mandibular third molars remain impacted due to various reasons such as high bone density, the status of adjacent teeth, and genetic factors [2]. Nowadays, the third molar has less room to grow in the majority of people, and anatomical conditions are commonly unfavourable for eruption. In these situations, the third molar is still partially or completely impacted within the retromolar trigone's soft and hard tissues [3]. Impaction increases the likelihood of various pathologies such as pericoronitis, bone lesions, and damage to the second molar [4], which are indications for extraction.

The removal of impacted mandibular third molars involves surgical trauma in a highly vascularised area, which causes inflammatory changes, also termed "sequelae," including pain, swelling, and trismus [5]. These symptoms are not observed immediately but begin gradually, peaking two days after extraction [6]. Thus, reducing postoperative complications is important as it increases the quality of life for the patient. To limit these postsurgical inflammatory complications, surgeons have improvised surgical techniques such as using lasers and cryotherapy [7] or advised patients to use proteolytic enzymes along with routine antibiotics, analgesics, and corticosteroids [8,9].

Non steroidal Anti-Inflammatory Drugs (NSAIDs) are often prescribed to reduce the postsurgical inflammatory sequelae of impacted mandibular third molar surgery [7]. NSAIDs act directly by inhibiting the enzyme Cyclo-oxygenase (COX). They have a wide range of adverse effects, especially those related to gastrointestinal, haematologic, and renal diseases, as well as the potential for skin and mucosal reactions [10]. A natural, potent, and risk-free therapy that does not have the aforementioned side-effects would be a welcome alternative for overcoming these restrictions and treating the after-effects of third molar surgery [11].

Recent years have seen the emergence of data demonstrating the effectiveness of proteolytic enzymes in a number of medical problems [12]. With high quantities of proteolytic enzymes and a composition that varies depending on the source and technique of purification, bromelain is a crude, aqueous extract made from the stem and immature fruit of pineapple (Ananas comosus) [13,14].

Bromelain directly influences pain mediators such as bradykinin [15]. The analgesic properties of bromelain are closely related to its anti-inflammatory properties [16,17]. It is a fibrinolytic agent

that promotes the reabsorption of oedema in the blood circulation [18]. It decreases postoperative discomfort, bruising, oedema, and healing time. In addition, bromelain also inhibits the synthesis of Proinflammatory Prostaglandins (PGE), particularly [19].

Since bromelain is thought to be non toxic, it can be taken daily in doses ranging from 200 to 2,000 mg/kg for extended periods of time [18]. Various studies have suggested that bromelain remains biologically active with a half-life of approximately 6-9 hours, and plasma concentration may reach as much as 5,000 pg/mL by 48 hours after oral multidosing of 3 g/day [20]. Compared to other anti-inflammatory drugs, bromelain derives its safety from the difference in its action mechanism: it diverts COX synthesis by increasing the production of anti-inflammatory prostaglandins despite the proinflammatory ones. In this way, the typical gastrointestinal damage caused by NSAIDs is avoided, and renal pharmacological activity is assured [21].

Recent studies have assessed the clinical implications of bromelain in the reduction of postoperative inflammatory complications after third molar surgery [1,3,7], but the results are inconsistent. There is a paucity of research contrasting bromelain and paracetamol used alone after third molar surgery. The aim of the present study was to compare the clinical efficacy of bromelain with that of paracetamol on pain, swelling, and trismus after the surgical removal of bilateral impacted mandibular third molars with similar difficulty indices.

MATERIALS AND METHODS

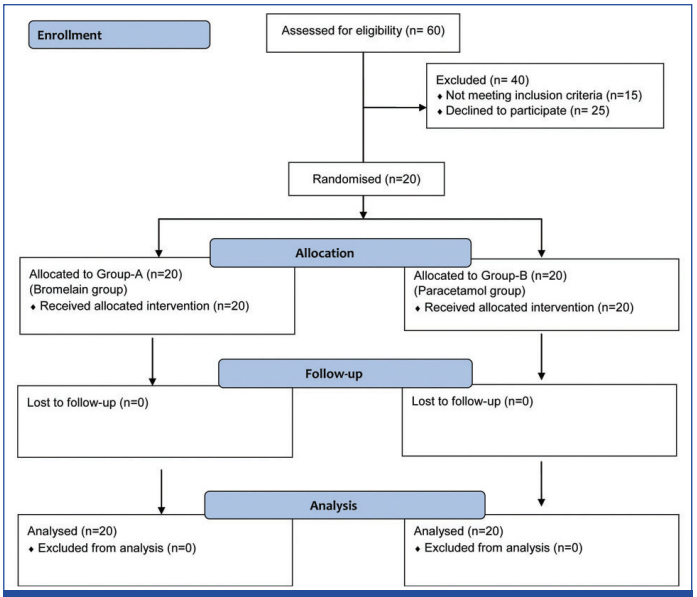
A split-mouth randomised controlled trial was conducted at the Department of Oral and Maxillofacial Surgery, Bharati Vidyapeeth DU Dental College and Hospital, Pune, Maharashtra, India, for a period of six months from August 2022 to January 2023. The study was approved by the Institutional Ethics Committee (Registration File number-EC/NEW/INST/2019/329), and written informed consent was obtained from all the patients included in the study.

Sample size calculation: The sample size was determined to be 20 patients. The calculation was performed considering two groups, with an alpha of 0.050 and a power level of 0.80 for pain, which was the primary variable for analysis [22]. The primary variable 'pain' showed a difference between groups of 0.60 (mean) and a SD of 0.75. Based on these values, it was determined that a minimum of 20 patients in each group was required.

Using a computer-generated table of random numbers and sealed opaque envelopes, subjects were randomly assigned and divided evenly between two groups, irrespective of their age or sex. Group A served as the study group, and group B was designated as the control group. Patients in group A (n=20) received bromelain 500 mg twice a day for five days, while patients in group B received paracetamol 500 mg three times a day for five days. The study design was triple-blind, as the chemist decoded and administered the medications to the patients in each group from a sealed opaque envelope that was hidden from the patient, operating surgeon, and researcher. The Consolidated Standards of Reporting Trials (CONSORT) flowchart of the study participants is shown in [Table/Fig-1].

Inclusion criteria:

- Patients above 18 years of age who were willing to participate in the study.
- Bilateral impacted mandibular third molars without active infection, with similar difficulty indices (according to the Pederson scale [22], the difficulty index was 5-8).
- Patients belonging to American Society of Anaesthesiologists (ASA)-1 classification.
- Patients should be free of drug reactions or allergies to the drugs used in the present study.



[Table/Fig-1]: CONSORT 2010 flowchart.

Exclusion criteria:

1. Patients who were mentally challenged or unable to communicate.
2. Patients who were pregnant or nursing.

Study Procedure

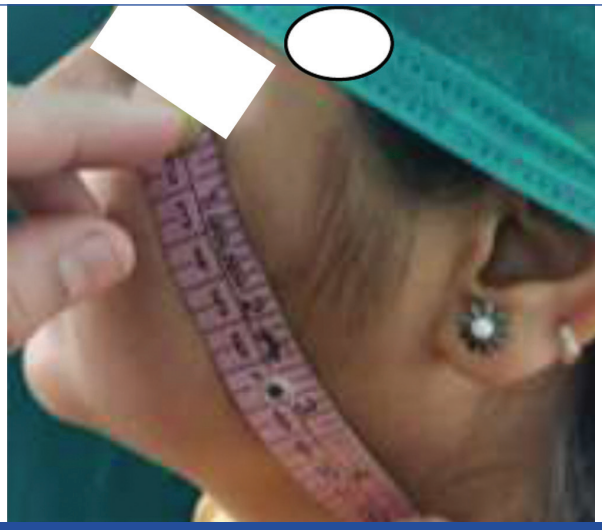
Prior to undertaking the procedure, a detailed medical and dental history of the patient was recorded.

Treatment details: Inferior alveolar, lingual, and long buccal nerve blocks were administered using local anaesthesia with adrenaline in a 1:200,000 ratio. All impacted teeth were surgically removed followed by incision and flap reflection in a similar fashion. The flap was sutured with a 22 mm 3/8 circle needle using resorbable (3-0) Vicryl sutures (manufactured in India by Johnson and Johnson Private Limited). Each patient underwent two surgical extractions separated by 21 days to allow sufficient healing time at the first operated site. During the first surgical removal of the impacted lower third molar, the patient was started on the medications as mentioned for group A. During the contralateral surgical procedure after 21 days, the patient was given medications as mentioned for group B.

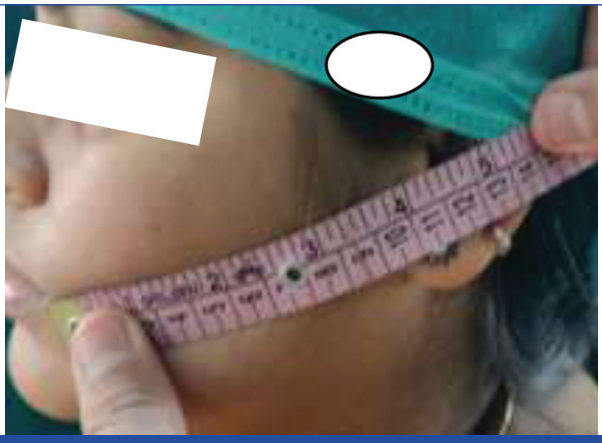
Medication details: The study group belonging to group A was started on Cap. bromelain 500 mg-BD 24 hours preoperatively and continued until the 4th day postoperatively. Other medicines, including Tab. Augmentin 625 mg (Amoxicillin 500 mg+Potassium clavulanate 125 mg)-BD and Tab. Pan 40 (Pantoprazole 40 mg)-OD, were given for five days postoperatively. The time interval between performing surgery on each side was 21 days. The study group belonging to group B was given the following medications postoperatively for five days: Tab. Augmentin 625 mg (Amoxicillin 500 mg+Potassium clavulanate 125 mg)-BD, Tab. Paracetamol 500 mg-DS, and Tab. Pan 40 (Pantoprazole 40 mg)-OD.

The parameters assessed for the present study were pain, swelling, and trismus. All parameters were assessed by a single examiner. Postoperative average pain was assessed over the next 1st, 2nd, and 3rd postoperative days using a 10-point VAS. Patients were asked to rate their current level of pain using a numeric rating scale that ranged from 0 (no pain) to 10 (the greatest conceivable pain). Swelling was measured (cm) using an inch tape based on the Matsumara and Gabka technique [23]. Three different measurements were taken: from the lateral canthus of the eye to the soft tissue gonion (LCG) (Line 1), from the tragus to the corner of the mouth (TM) (Line 2), and from the tragus to the soft Tissue Pogonion (TP) (Line 3) [Table/Fig-2,3]. These measurements were taken on the 2nd and 7th postoperative days in both groups [Table/Fig-4]. The preoperative

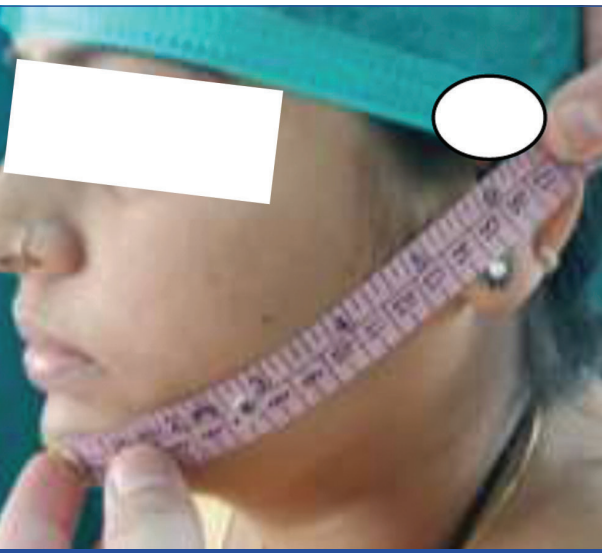
measurement served as the baseline value, and the swelling for each day was determined by comparing it to the baseline. Only one observer measured the patients' swelling to minimise observer bias.



[Table/Fig-2]: Measurement of Line 1 at POD 2 for a patient (Bromelain group).



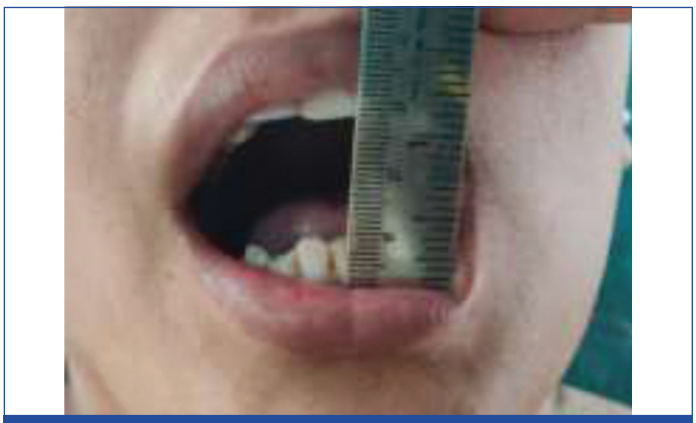
[Table/Fig-3]: Measurement of Line 2 at POD 2 for a patient (Bromelain group).



[Table/Fig-4]: Measurement of Line 3 at POD 2 for a patient (Bromelain group).

As illustrated in [Table/Fig-5], trismus was assessed by measuring the interincisal distance at maximal mouth opening (mm) between the maxillary and mandibular incisal edges, as shown in [Table/Fig-5]. This measurement was taken on the day of the surgery (preoperative) and on the second and seventh postoperative days. Trismus was determined by comparing the interincisal opening before and after surgery.

Specification of safety parameters: All safety parameters for surgery to prevent postoperative infection at the surgical site were followed.



[Table/Fig-5]: Measurement of mouth opening at POD 2 (Bromelain group).

STATISTICAL ANALYSIS

Means and Standard Deviations (SDs) were used to present descriptive statistics for each group. Student t-tests were conducted to compare pain, swelling, and trismus between the groups. A repeated measures Analysis of Variance (ANOVA) was performed to compare the mean VAS scores for pain associated with bromelain at three different time points. In the mentioned tests, a p-value of 0.05 or below ($p<0.05$) was considered statistically significant. All analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 21.0.

RESULTS

1. Pain: On day 1, the mean VAS score used to assess pain for group A taking bromelain was 6.60, while the mean score for group B taking paracetamol was 7.95. The difference between the two was found to be statistically significant. For day 2, group A's mean VAS score was 5.80, while group B's was 7.30. The student t-test revealed a statistically significant difference between them. Similar findings were observed on day 7, where the mean VAS score for group A was 5.20 and for group B was 6.80, with a statistically significant difference between the two groups [Table/Fig-6].

Postoperative evaluation times	Group A		Group B		p-value
	Mean	Standard deviation	Mean	Standard deviation	
1st day	6.60	0.68	7.95	0.76	p<0.001
2nd day	5.80	0.77	7.30	0.80	p<0.001
3rd day	5.20	0.53	6.80	0.70	p<0.001

[Table/Fig-6]: Comparison of pain using mean VAS score between group A taking bromelain and group B taking paracetamol on 1st, 2nd and 3rd day postoperatively using student t-test.
*p<0.05=statistically significant

A repeated measures ANOVA test was conducted to compare the mean VAS score for pain associated with group A at three different time points (Day 1 vs Day 2 vs Day 3). The difference in VAS scores between postoperative days 1, 2, and 3 was found to be statistically significant. On posthoc analysis of two individual time points, the differences between postoperative Day 1 to Day 2, Day 2 to Day 3, and Day 1 to Day 3 were all found to be statistically significant [Table/Fig-7].

Postoperative evaluation times	Wilk's Lambda value		p-value
Day 1 vs Day 2 vs Day 3	0.100		<0.001
	Mean difference	Standard error	p-value
Day 1 vs Day 2	0.800	0.092	<0.001
Day 2 vs Day 3	0.600	0.112	<0.001
Day 1 vs Day 3	1.400	0.122	<0.001

[Table/Fig-7]: Comparison of pain using Mean VAS scores at three different time points (1st, 2nd and 3rd postoperative days) for group A using repeated measures ANOVA test.
*p<0.05=statistically significant

A repeated measures ANOVA test was also conducted to compare the mean VAS score for pain associated with paracetamol at three different time points (Day 1 vs Day 2 vs Day 3). The difference in VAS scores between day 1, 2, and 3 was found to be statistically significant. On posthoc analysis of two individual time points, the differences between day 1 to day 2, day 2 to day 3, and day 1 to day 3 were all found to be statistically significant as well [Table/Fig-8].

Postoperative evaluation times	Wilk's Lambda value		p-value
Day 1 vs Day 2 vs Day 3	0.087		<0.001
	Mean difference	Standard error	p-value
Day 1 vs Day 2	0.650	0.109	<0.001
Day 2 vs Day 3	0.500	0.115	<0.001
Day 1 vs Day 3	1.150	0.082	<0.001

[Table/Fig-8]: Comparison of pain using Mean VAS scores at three different time points (1st, 2nd and 3rd day) for group B using repeated measures ANOVA test.
*p<0.05=statistically significant

2. Swelling: The mean value of facial swelling for Line-1 in group A taking bromelain at postoperative day 2 was 9.62 cm [Table/Fig-9], while for group B taking paracetamol it was 11.57 cm. The difference between them was statistically significant. Similarly, on postoperative day 7, the means for group A and group B were 9.08 cm and 11.13 cm, respectively. The student t-test revealed that this difference was also statistically significant.

Postoperative evaluation times	Group A		Group B		p-value
	Mean	Standard deviation	Mean	Standard deviation	
2nd day	11.78	0.66	13.70	0.59	<0.001
7th day	11.13	0.79	13.38	0.58	<0.001

[Table/Fig-9]: Comparison of facial swelling (in cm) for Line 1 between group A taking bromelain and group B taking paracetamol on 2nd and 7th postoperative days using student t-test.

At postoperative day 2, the mean value of facial swelling for Line-2 in group A [Table/Fig-10] was 11.78 cm, whereas it was 13.70 cm in group B. A comparison between them using a student t-test showed that the difference was statistically significant. Similarly, on postoperative day 7, the means for group A and B were 11.13 cm and 13.38 cm, respectively, with a statistically significant difference between them.

Postoperative evaluation times	Group A		Group B		p-value
	Mean	Standard deviation	Mean	Standard deviation	
2nd day	13.71	0.96	15.56	0.80	<0.001
7th day	13.18	1.06	15.21	0.82	<0.001

[Table/Fig-10]: Comparison of facial swelling (in cm) for line-3 between group A taking bromelain and group B taking paracetamol on 2nd and 7th postoperative days using student t-test.
*p<0.05=statistically significant

On the second postoperative day, the mean value of facial swelling for Line-3 in group A was 13.71 cm [Table/Fig-8], while it was 15.56 cm in group B. This difference was also found to be statistically significant. Likewise, on postoperative day 7, the means for group A and group B were 13.18 cm and 15.21 cm, respectively, with a statistically significant difference between them.

3. Trismus (Mouth opening): The mean value of mouth opening for group A taking bromelain at postoperative day 2 was 33.90 mm [Table/Fig-11], while it was 33.30 mm for group B taking paracetamol. However, the difference between them using a student t-test was not found to be statistically significant. However, on postoperative day 7, the means for group A and group B were 40.06 mm and 39.40 mm, respectively, and the student t-test revealed a statistically significant difference between them.

Postoperative evaluation times	Group A		Group B		p-value
	Mean	Standard deviation	Mean	Standard deviation	
2nd day	33.90	1.55	33.30	1.45	0.215
7th day	40.06	0.99	39.40	0.94	0.041*

[Table/Fig-11]: Comparison of mouth opening (in mm) between between group A taking bromelain and group B taking paracetamol on 2nd and 7th postoperative days using student t-test.
*p<0.05=statistically significant

It was observed that the facial swelling elicited in patients taking paracetamol was more as compared to the facial swelling seen in patients taking bromelain. A statistically highly significant difference was evaluated on the 2nd postoperative day, which was less appreciated on the 7th postoperative day. The pain experienced by patients in both groups on the first, second, and third postoperative days was statistically significant and was lesser in patients taking bromelain. The trismus observed in both groups was statistically insignificant on the second postoperative day, while it was statistically significant on the 7th postoperative day. No signs of any systemic toxicity were clinically observed in both groups.

DISCUSSION

Bromelain is a proteolytic enzyme obtained from pineapple stems, although it is found in all parts of the pineapple [24]. In dentistry, bromelain has been used for comparison or in combination with other anti-inflammatory drugs, especially after the extraction of third molars [25].

The key finding of the current study was that bromelain demonstrated superior analgesic and anti-inflammatory effects compared to paracetamol. This supports the use of bromelain as a viable alternative to frequently prescribed NSAIDs for treating postoperative complications following the surgical removal of impacted mandibular third molars. The clinical efficacy of both drugs on postoperative trismus was statistically insignificant on the second postoperative day but became statistically significant on the seventh postoperative day. The present study revealed that bromelain effectively reduced pain and swelling following the surgical removal of impacted mandibular third molars, which is consistent with other studies [26].

Ordesi P et al., found a significant reduction in pain and swelling in patients who had taken bromelain after the extraction of mandibular third molars, compared to the control group [3], which aligns with the results of the present study. Hozt G et al., conducted a double-blind study to estimate swelling after administration of placebo and bromelain following the removal of third molars [27]. They observed a decrease in swelling, which is consistent with our research.

In a study conducted by Majid OW and Al-Mashhadani BA, the efficacy of bromelain and diclofenac sodium following surgical removal of lower third molars was compared. They observed that bromelain effectively reduced postoperative pain and swelling, consistent with the present study [1].

Inchingolo F et al., and de la Barrera-Nunez MC et al., also concluded that bromelain effectively reduced postoperative swelling in patients undergoing third molar surgery [28,29], which is in line with the results of the present study.

Bromelain did not have a significant effect on reducing postoperative trismus after mandibular third molar surgery on the second postoperative day in the present study. This is consistent with the studies conducted by Majid OW and Al-Mashhadani BA, and de la Barrera-Nunez MC et al., [1,28]. However, on the seventh postoperative day, there was a significant reduction in postoperative trismus after mandibular third molar surgery. This result contradicts the studies conducted by Majid OW and Al-Mashhadani BA and de la Barrera-Nunez MC et al., [1,28]. Studies by Maurer HR and Bormann KH et al., have reported very few adverse effects

associated with bromelain [18,30]. No patients in the present study reported any adverse effects.

In a study conducted in 2021 by Bhoobalakrishnan MS et al., oral bromelain and oral diclofenac sodium were compared for their effectiveness and safety in treating pain, swelling, and trismus following mandibular third molar surgery [31]. They did not find any significant difference between the two drugs, which contradicts the present study. No severe or serious side-effects were reported by patients in either group. In 2019, Liu S et al., conducted a study to evaluate whether bromelain can reduce trismus, pain, and facial swelling in patients undergoing surgical removal of impacted mandibular third molars [32]. They concluded that bromelain proved to be useful in reducing facial swelling and pain in the early and late stages of recovery from surgery, although it had a negligible effect on trismus. The findings of our study were comparable to those of this study.

Gupta AA et al., conducted a study in 2022 to compare the effectiveness of bromelain and aceclofenac in preventing postoperative inflammatory sequelae following surgical removal of mandibular impacted third molars [7]. On both the 2nd and 7th postoperative days, the bromelain group showed a substantial reduction in the severity of oedema and trismus compared to the aceclofenac group. No significant difference was found in the analgesic efficacy of bromelain and aceclofenac. Thus, it was shown that bromelain can be utilised as a reliable and effective substitute for aceclofenac in treating inflammatory sequelae following surgery. A systematic review was conducted by de AC Almeida R et al., in 2018 to investigate the efficacy of bromelain in reducing pain and inflammation following third molar surgery [33]. They found that bromelain was successful in reducing postoperative discomfort 48 to 72 hours after surgery, but it had no discernible impact on oedema or trismus compared to the control group. This finding contradicted the findings of the present research.

A randomised, comparative clinical study was conducted by Ramasubbu S et al., in 2021 to evaluate and compare the effectiveness of oral bromelain and serratiopeptidase for the treatment of postoperative sequelae following third molar surgery [34]. They concluded that bromelain's anti-inflammatory effects on postoperative pain and facial swelling were superior to the serratiopeptidase group after the surgical removal of an impacted third molar tooth. However, the difference in trismus between the two groups was not significantly different. These outcomes were consistent with the findings of the present research. Thus, the results of the present study showed significant advantages of prescribing bromelain compared to paracetamol for the prevention of pain, swelling, and trismus after surgical removal of impacted mandibular third molars. Further studies with larger study groups and more parameters are required to study in detail the effect of bromelain compared to NSAIDs after impacted mandibular third molar surgery.

Limitation(s)

The duration of bromelain given was five days, which is insufficient to fully understand the side-effects associated with the drug. A longer time period of bromelain administration would be necessary to assess the broader effects of the drug, especially in chronic inflammatory conditions.

CONCLUSION(S)

In conclusion, administering bromelain daily at a dose of 1000 mg after the surgical removal of an impacted mandibular third molar may reduce postoperative pain, swelling, and trismus. For individuals who cannot tolerate NSAIDs or for whom they are contraindicated, bromelain serves as a good alternative due to its superior effects compared to paracetamol. Further research with a larger sample size is warranted to assess the analgesic and anti-inflammatory effects of bromelain in surgical procedures.

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