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COMPARATIVE EVALUATION OF CLINICAL EFFICACY OF ORAL ADMINISTRATION OF TABLET BROMELAIN VERSUS TABLET IBUPROFEN ON SWELLING, PAIN AND TRISMUS AFTER SURGICAL EXTRACTION OF IMPACTED MANDIBULAR THIRD MOLAR – A PROSPECTIVE DOUBLE-BLIND RANDOMIZED CONTROLLED SPLIT MOUTH STUDY.

Oral Pathology

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ABSTRACT

Aim and objective: The aim of this study was to compare and evaluate the efficacies of tablet bromelain and ibuprofen administered orally for reducing swelling, pain, and trismus after the extraction of impacted mandibular third molars.

Materials and method: Thirty consecutive patients requiring surgical removal of a bilateral mandibular impacted third molar under local anesthesia were randomly assigned to receive postoperatively tablet bromelain 500mg (Group A), and tablet ibuprofen 400mg (Group B) every 8 hours for 7 days. Standardized surgical and analgesic protocols were adopted. Swelling was evaluated using a tape measure method, pain with a visual analogue scale (VAS), and trismus by measuring the maximum interincisal distance (MID). Assessments were made on the day of surgery and on day two, five and seven after surgery.

Result: Statistically significant differences were seen in the scores for swelling and trismus determined by tape measure method and MID respectively in the two treatment groups (A and B) on postoperative day two; however, no statistically significant difference was seen in the pain determined by VAS score between the two groups.

The swelling seemed to be reduced significantly with bromelain group A (P=0.003) as compared to the ibuprofen group B (P=0.024) on second post operative day; but after seven days of surgery, there was no difference in the degree of edema between both the groups. On post-operative day two and seven, mouth opening was significantly more reduced in the bromelain group than in the ibuprofen group (P < .05). At the first six hours, ibuprofen group B had more effective pain relief (p<0.05), but after this time point, both groups reported similar degrees of relief to pain. Hence, the oral administration of tablet bromelain was found to be more effective than tablet ibuprofen in reduction of swelling and trismus post surgical extraction of third molar.

Conclusion: The present study demonstrates an important anti-inflammatory and anti-edematous effect of bromelain. Statistical analysis shows that bromelain appears to offer a beneficial effect in the management of swelling and trismus during the postoperative period following impacted third molar surgery. So further studies are necessary to analyze different modes of administration and dosage of bromelain for its use after surgical extraction of impacted mandibular third molar.

KEYWORDS

bromelain, ibuprofen, swelling, trismus, impacted, mandibular third molar.

INTRODUCTION:

The surgical extraction of impacted third molars is one of the most common procedure in oral and maxillofacial surgery. Patients often complain of postoperative swelling, pain, and trismus associated with the inflammatory response to surgical trauma.[1-3]In order to prevent these post-operative complications, adequate anti-inflammatory therapy is required.

Corticosteroids are widely used to decrease the edema and trismus related to third molar surgery[4];however,the potential side effects of corticosteroid use are delayed wound healing, increased susceptibility to infection and adrenal suppression [6]. In addition to the steroids, non steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the rapid relief of moderate pain[5,6], which acts by inhibition of the release of cyclooxygenase (COX), an enzyme that is responsible for the production of prostaglandins[7].

Ibuprofen is an NSAID; belongs to the class of derivatives of propionic acid, which reduces the biosynthesis of PGs and inhibits the migration of leukocytes, in addition to other functions[9] .Within the classification of anti-inflammatory drugs, ibuprofen belongs to the group of non-selective inhibitors of COX-1, an enzyme that confers protection to the gastric mucosa and renal tissues, and COX-2, an enzyme that contributes to the inflammatory process[6,8].It is widely used in clinical practice because of its well-documented efficacy and safety when compared with similar group of drugs[8,9].

On the other hand, bromelain is the name given to a family of proteolytic enzymes obtained from Ananas comosus, the pineapple plant. It is considered to have a potent anti-inflammatory and anti-edematous properties.

It directly influences pain mediators such as bradykinin [10]; although, its analgesic properties are closely linked to its anti-inflammatory properties [11]. In addition, it inhibits the synthesis of pro-inflammatory prostaglandins, particularly PGE2. Evidences show that it digests fibrin and thus promotes reabsorption of edema in the blood circulation[12]; it also indirectly increases the time required for the conversion of prothrombin into thrombin, and thus activation of plasminogen into plasmin; by these means, it prevents fibrin formation [12]. All these causes a reduction in vascular permeability. Thus it reduces pain, swelling, bruising and healing time after trauma and surgical procedures[11].

Thus the study was planned to evaluate and compare the clinical efficacy of oral administration of tablet bromelain 500mg and tablet ibuprofen 400mg on pain, swelling and trismus after surgical extraction of impacted mandibular third molars.

MATERIALS AND METHODS

Patient selection:

This study was a prospective double-blind, randomized, crossover clinical trial. The study received approval from the institutional ethics committee. Thirty patients were enrolled in the study and provided a signed statement of informed consent. All patients had bilateral symmetrically impacted mandibular third molars. Out of thirty patients 15 male, 15 female; mean age 23.35_ 3.89 years completed the study.

The following patients were included in the study : patients with no history of allergies, any systemic diseases, or bleeding problems; bilateral symmetrically impacted mandibular third molars with total or partial bone cover; no complain of pain, trismus and swelling at the time of extraction; with comparable surgical difficulty; and cooperates well with the treatment procedures and post operative follow up.

The following patients were excluded from the study: those with signs of pericoronitis and/or pain before surgery; pregnant women or nursing mothers; underwent antibiotic or other medication therapies during the pre-ceding two weeks; has an active carious lesions and/or periodontal diseases ;and contraindications to the drugs or anesthetic agent used in the surgical protocol.

Study Design

All of the patients included in the study were operated on by the same experienced oral and maxillofacial surgeon and assistant in order to

minimize differences due to operator variability. Each patient underwent two surgical procedures at 2-4 weeks interval. A signed statement of informed consent was taken.

At the time of first procedure, the site of third molar extraction was decided. The patients were divided randomly into two groups "A" and "B". The randomization was performed through a randomized list generated on a computer, and the coin was used to prepare the pharmacological choice of medication (tablet ibuprofen or tablet bromelain), with a blind design that did not allow the identification of any of them without access to the list; this access was only at the end of the study to analyze the data. After the completion of first procedure, the patients were given either tablet bromelain 500 mg -brand name Bromelain 500,manufactured by Nova Nutrition's (Group A), or tablet ibuprofen 400mg- brand name Brufen and manufactured by Abbot India Ltd (Group B); and were instructed to take every eight hourly for seven days.

In the second procedure, the remaining third molar was extracted and the appropriate ibuprofen/bromelain was given accordingly. Both the surgeons and the patients were blinded to the tablets given.

Instructions on postoperative precautions were given to all the patients who underwent the procedure and postoperative follow up dates were given. They were also provided with a chart and asked to tick on the chart whenever they took the medicine and were asked to bring the chart and the bottle which contained the tablet, whenever they come for follow-ups.

Surgical protocol

All patients underwent the procedure under inferior alveolar, lingual and buccal nerve blocks using lignocaine with 1:2,00,000 epinephrine. A three-cornered flap was raised to gain access to the third molar and buccal osteotomy and sectioning was carried out whenever necessary. Once the tooth was extracted, the alveolus was irrigated with sterile saline solution at room temperature to eliminate debris and the bone edges were smoothened. The flap was then repositioned and the closure was done with 3–0 silk. All patients received postoperative prophylactic antimicrobial drug and the test group drugs with the postoperative instructions. The postoperative medication for both groups were capsule amoxicillin 500mg three times a day for five days. The degrees of surgical difficulty were rated before the extractions by a single investigator, who performed the preoperative patient selection. The Pederson scales were used for this purpose. The extractions were classified as easy, moderate, or difficult.

Assessment of postoperative pain:

Pain intensity was assessed using a 10-point visual analogue scale (VAS), with the patient placing a mark on the scale to indicate an intensity range from no pain '0' to severe/unbearable pain '10'. The severity of the pain was evaluated on the day of the procedure and on postoperative day two , five and seven.

Assessment of postoperative facial swelling:

The degree of facial swelling was determined by a modification[11,13] of the tape measure method described by Gabkaand Matsumara. Three measurements was made between five reference points: the distance between the lateral corner of the eye and angle of the mandible; the distance between the tragus and soft tissue pogonion; and the distance between the tragus and outer corner of the mouth. The mean of the three measurements were calculated[13]. Measurements were taken pre-operatively and on postoperative day two , five and seven.

Assessment of postoperative trismus:

Trismus was evaluated by measuring the maximum interincisal distance (MID) i.e. measuring the distance between the edges of the upper and the lower right central incisors at maximum opening of the jaws, using Vernier caliper preoperatively and on postoperative day two , five and seven.

Statistical analysis:

All of the data obtained were evaluated using SPSS 14.0 package program. Data were analyzed as the frequency and percentage rate, and as the mean and standard deviation. The Student t-test and repeated measures tests were performed for parametric continuous data. A significance level of $P < 0.05$ for the 95% confidence interval was chosen to define statistical significance.

RESULTS

- Thirty patients 15 male and 15 female; the mean age of the patients was 25.80±4.708 years with a median age of 25.0 years, completed the present study. The impacted mandibular third molars on the left and right sides of the patients were comparable with respect to the degree of surgical difficulty. There was no significant difference in the difficulty score for mandibular third molar impaction between the sides and their mean difficulty score for the ibuprofen group (4.72_ 0.22)and for the bromelain group(4.83_ 0.21). The test showed that there was no significant statistical difference in the difficulty level for both groups (p=0.658). All patients underwent close follow-up during the postoperative period to obtain measurements of trismus and edema. There were no cases of postoperative complications or adverse reactions to the study drugs.
- With both bromelain and ibuprofen, it was noted that pain was highest on the day of the procedure and decreased gradually on postoperative day two and seven. Mean VAS score and p-values for each time interval was noted. At the first six hours, the ibuprofen group had more effective pain relief ($P < .05$), but after this time point, both groups reported similar degrees of relief to pain.The immediate operative pain noted in bromelain group was 8.433.There was no significant difference in pain between bromelain and ibuprofen on postoperative day two ($p = 1.000$), postoperative day five ($p = 1.000$) and postoperative day seven ($p = 0.726$)(graph 1).
- With both bromelain and ibuprofen, edema peaked at 48 hours postoperatively, when compared to preoperative measurements; however, the facial swelling in the group A (121.2±1.56) was lower than that in the group B (123.4±1.32); with facial contours returning closer to normal by postoperative day seven. Statistically significant differences between the two protocols (p=0.003) were found on subsequent postoperative follow up on day five and seven (graph 2).
- Maximal mouth opening levels were similar preoperatively in the two groups. The means of mouth opening at each time interval were compared and the results were as follows, there was no significant statistical difference in mouth opening between bromelain group and ibuprofen group B in the preoperative period ($p = 1.000$). There was a significant statistical difference in mouth opening between bromelain group(28.83±3.17) and ibuprofen group(26.6±3.19) on the postoperative day two (p=0.011).There was a significant statistical difference in mouth opening between bromelain group(34.8±2.72) and ibuprofen group(32.6±2.86) on postoperative day five($p = 0.024$) (graph 3).There was no significant statistical difference in the mouth opening between bromelain group and ibuprofen on postoperative day seven($p = 0.577$).

DISCUSSION

This study was done to evaluate and compare the efficacy of oral administration of tablet bromelain and tablet ibuprofen for relief of pain, swelling and trismus following impacted mandibular third molar surgery.

Nonsteroidal anti-inflammatory drugs (NSAIDs) especially ibuprofen is widely prescribed for effective postoperative pain relief following third molar surgery. It was found to be as effective as other NSAIDs such as indomethacin, paracetamol and diclofenac sodium. Hence ibuprofen was used in the present study as a reference drug to represent the NSAID[14]. It is to be noted that though NSAIDs are effective postoperative analgesic, gastrointestinal consequences are significant with its use and needs to be considered, which has resulted in the development of alternative therapeutic options like bromelain[15,16,17].

Bromelain is an aqueous extract obtained from the stem and fruit of the pineapple plant[15,18]. It contains high level of proteolytic enzymes and acts at the specific points on the cell surface of the inflammatory component, specifically where their receptors are found, generating and / or destroying receptor agonists and activating and deactivating them, contributing significantly in the signal transduction mechanism of the inflammation1[8]. Most of the published studies suggest various types of mechanisms by which proteases like bromelain, can decrease inflammation. Among them the most prominent are favoring the return of the interstitial fluid and inflammatory component cells into the bloodstream, and thus decreasing the swelling of the area and decreasing the biosynthesis of plasmacinins and proinflammatory prostaglandins PGE2, PGF2[15,18].

In the present study, as expected, ibuprofen group showed significant analgesic effect in the immediate postoperative period when compared to bromelain group; but on postoperative day five and seven, both groups reported similar degrees of relief to pain; however, it had no significant effect was on trismus, a sequel that is usually related to the magnitude of swelling. There are several studies stating the advantage of oral administration of tablet bromelain helps in reduction of pain and swelling after certain surgical procedures by decreasing the level of certain pain mediators and vascular phenomenon associated with acute inflammation [15,18].In the present study bromelain was found to have significant effect on trismus and edema during the first post operative week with facial contours returning closer to normal by postoperative day seven when compared to ibuprofen group.

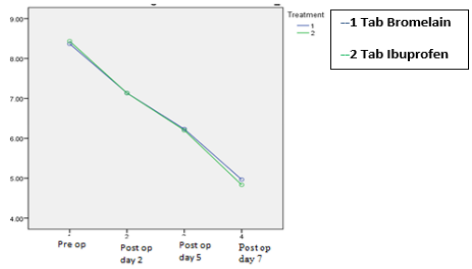
Thus in present study where patients underwent surgical procedure for extraction of lower third molar, bromelain 500 mg when given eight hourly for seven days showed effective postoperative analgesic as well as anti-inflammatory property with significant improvement in the mouth opening, and limited reduction in the incidences of trismus when compared to ibuprofen group; thus making it a suitable alternative options for patient with gastrointestinal difficulties in whom NSAIDs are contraindicated.

Though no side effects were seen with bromelain in the present study with the sample size of thirty; however, more studies and research is warranted with larger samples to conclude this findings as well as to consider its various other modes of administration and dosage for its use as an analgesic and anti inflammatory following surgical procedures.

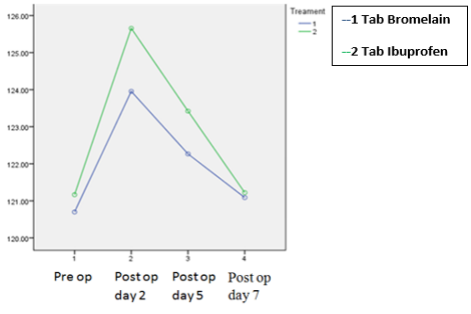
CONCLUSION

In summary and based on the results obtained, we can conclude that:

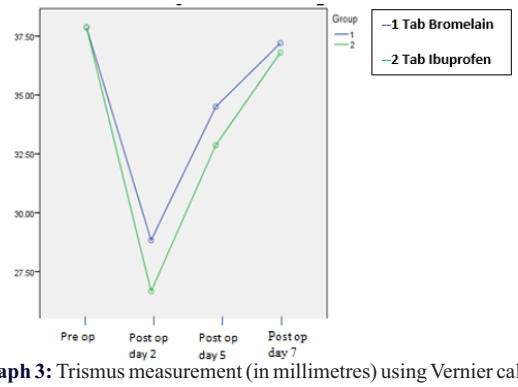
- Ibuprofen and bromelain showed same effective analgesic properties.
- Bromelain tablet appears to offer a beneficial effect on the management of swelling and trismus in the postoperative period and can be recommended for the patient's postoperative comfort.
- Further studies are needed to investigate the hypothesis that different dosing regimens of bromelain may be associated with a greater anti-inflammatory effect in the postoperative management of impacted third molars.
- Further studies are needed to investigate the hypothesis that difference in pre-operative regimens of bromelain may be associated with a greater anti-inflammatory effect in the postoperative management of impacted third molars then giving it postoperatively.
- Further randomized placebo-controlled trials are needed to confirm the efficacy of Bromelain in larger tertiary clinical setting.



Graph 1: Pain scale assessed by visual analog scale (VAS) during pre op and day 2,5 & 7 postoperatively with bromelain and ibuprofen.



Graph 2: Swelling measurement (in centimeters) using Gabkaand Matsumara method during pre op and day 2,5 & 7 postoperatively with bromelain and ibuprofen.



Graph 3: Trismus measurement (in millimetres) using Vernier caliper, during pre op and day 2,5 & 7 postoperatively with bromelain and ibuprofen group.

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