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A COMPARATIVE STUDY OF THE ANTI - INFLAMMATORY PROPERTIES OF BROMELAIN / SERRATIOPEPTIDASE AS ADD ON THERAPY TO CONVENTIONAL TREATMENT FOLLOWING IMPACTED THIRD MOLAR SURGERY

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ABSTRACT

Objective: To evaluate and compare the anti-inflammatory effects of Bromelain/ Serratiopeptidase as add on therapy to conventional treatment in patients undergoing impacted third molar removal. **Materials and Methods**: A prospective, randomized, comparative, open study was conducted on ninety patients who were undergoing impacted third molar teeth surgery, allocated into three groups each comprising of 30 patients. Group I was treated with caps.Amoxicillin 500mg b.i.d., Tab. Metronidazole 200mg t.i.d., and Tab. Diclofenac sodium 50 mg b.i.d. as conventional treatment for 5 days. Group II and Group III received combination of conventional treatment and Tab.Bromelain 200mg t.i.d. and Tab.Serratiopeptidase 10 mg b.i.d respectively for 5 days. The parameters such as measurement of pain, facial width, trismus and global assessment of functioning were analysed on post – operative days 1, 2 and 7 using one-way analysis of variance followed by Bonferroni test. **Results:** A total of 85 patients were included for the study analysis. The co-administration of Bromelain / Serratiopeptidase and Diclofenac following impacted third molar surgery was significantly superior to diclofenac alone for the relief of pain ($P < 0.05$) and facial swelling ($P < 0.05$) and the global assessment of functioning were greater in group II (71.43%) and group III (65.6%) than group I (46,43%). However there was no significant difference for trismus relief between the three medication protocols ($P > 0.05$). **Conclusions:** The study concludes that Bromelain /

Serratiopeptidase have enhanced the anti-inflammatory effects as add on therapy to conventional therapy following impacted third molar surgery.

KEYWORDS: Bromelain, Serratiopeptidase, Diclofenac, anti-inflammatory effect.

INTRODUCTION

Surgical removal of wisdom teeth under local anaesthesia is widely carried out in general dental practice and it is usually associated with postoperative pain, swelling, and trismus,[1] [2],[3],[4] as direct and immediate consequences of the surgical procedure.[5], [6] The adverse effects of the wisdom tooth surgery on the quality of life has been reported to show a three-fold increase in patients who experience pain, swelling and trismus alone or in combinations; compared to those who were asymptomatic.[5],[6],[7] Many clinicians have, thus, emphasized the necessity for better pain, swelling and trismus control in patients who undergo third molar surgery.[8], [9] The introduction of non-steroidal anti-inflammatory drugs (NSAIDs, e. g. diclofenac and ibuprofen) has significantly altered the management of postoperative pain in dentistry and medicine by limiting the production of prostaglandins and prostacyclins associated with hyperalgesia and edema.[10], [11] The use of oral systemic enzyme therapy (e.g. serratiopeptidase, bromelain, trypsin, and chymotrypsin) is another preventive strategy for limiting postoperative edema and trismus following third molar extractions.[12] Bromelain is the proteolytic enzymes found in tissues of the plant family Bromeliaceae, of which pineapple, Ananas comosus, is the best known. The pineapple tissue as a folk medicine is used for centuries in Central and South America. Bromelain has possess many properties which includes anti-inflammatory, anti-edemic, anti-tumor and immunomodulatory effects. The mechanism of the anti-inflammatory activity is causing inhibition of the generation of bradykinin, proteolytic degradation of circulating immune complexes and interference with the arachidonic acid metabolism.[13], [14] It promotes the absorption of antibiotic drugs topically in the skin debridement of burns.[30] Bromelain has been proposed as additive agents for anticancer therapy.[34] Studies shown that bromalein prevents platelet aggregation and adhestion of platelets to blood vessel endothelial cells.[29], [34] Serratiopeptidase is a powerful proteolytic enzyme obtained from silkworms. The enzyme is produced by the microorganism Serratia E 15 which lives in the gut wall of the silkworm. The enzyme causes proteolysis of all non-vital tissues including blood clots, cysts, tissue plaques and cellular debris and reduces the inflammatory response. The anti-inflammatory activity of serratiopeptidase helps in resolution of postpartum haemotomas, breast engorgements,[23] pregnancy related

thromboplebitis. It reduces internal tissue edema and inflammation caused at post-operative handling.[27] Serratio peptidase does not inhibit prostaglandins and is safe to the gastrointestinal system. The efficacy of Serratiopeptidase in reducing post-operative edema after standardized one stage osteotomy procedure of 4th molar teeth was measured by opto electronic instrument.[28] Co-administration of oral systemic enzyme and NSAID may produce pronounced anti-inflammatory / anti – edemic effect without side effects. Hence the present study is carried out to evaluate and compare the anti-inflammatory effects or Bromelain / Serratiopeptidase as add on therapy to conventional treatment in patients undergoing mandibular impacted third molar removal which includes Post-operative pain, Post-operative Facial swelling, Trismus and Global Assessment of Functioning by Patient and Dental Surgeon.

MATERIALS AND METHODS

A prospective, randomized, comparative, open study was conducted on a total of 130 patients requiring surgical removal of impacted third molar teeth for six months at the Department of Oral and Maxillofacial Surgery, Govt. Dental College and Hospital, Chennai. The study protocol were approved by the Institutional ethics committee and the informed consents were obtained from the patients after explaining about the study protocol in detail.

The inclusion criteria were age between 20-35 years, both genders, patients willing to give informed consent, patients willing to adhere to the study protocol, patients with no history of oral surgical interventions during the past 3 weeks, patients with free of pain and other inflammatory symptoms that included swelling, hyperemia and decreases mouth opening at the time of surgery. Exclusion criteria were pregnant and lactating women, patients with cardiac, renal or hepatic disease, and patients with previous or present gastric ulcers, known hypersensitivities, allergies, or idiosyncratic reactions to any study medications, patients who had taken analgesics or anti-inflammatory drugs within 48 hours before surgery, patients not willing to give informed consent.

Ninety patients who fulfilled inclusion and exclusion criteria were included in the study and they were randomly allocated into three groups in an open fashion and each group comprising 30 patients received the respective study medication orally for 5 days. **Group I** patients were given a combination Caps. Amoxycillin Trihydrate 500mg b.i.d, Tab.Metronidazole 200mg t.i.d and Tab.Diclofenac sodium 50mg b.i.d for 5 days as conventional treatment. **Group II** comprised of patients who were given a combination conventional treatment and

Tab.Bromelain 200mg t.i.d for 5 days. **Group III** comprised of patients who were given a combination conventional treatment and Tab.Serratiopeptidase 10mg b.i.d for 5 days.

All the study medications were provided by the investigator to the respective group of patients. The first dose of the study medication was administered to the respective group of patients 30 minutes before surgery. The proper postoperative care instructions and medication direction were given to all the participant patients by the investigator. The following study parameters were recorded on post-operative days 1st, 2nd and 7th day.

Pain measurement: Preoperative pain was assessed using a Visual Analogue Scale Accordingly, pain was recorded as: "0-no pain" (patient experiences no discomfort), "1-3 mild pain" (almost unnoticeable pain), "3-5 less moderate pain" (noticeable pain, but patient can engage in routine daily activities), "5-7 intense moderate pain" (noticeable pain, but patient can still engage in routine daily activities) and "7-9 severe pain" (very noticeable pain which disturbs the patient's daily routine), "10 worst pain" possible. For each patient, the appropriate score was recorded in the questionnaire by the investigator at pre-operative, post-operative days 1, 2 and 7. Before leaving the clinic, the investigator ensured that all patients were thoroughly instructed how to and when to take medications.

Measurement of facial width: As no published method satisfies all criteria for assessing facial swelling, we decided to use a measuring tape to measure facial width and swelling in one-dimension only. Facial width (swelling) was measured using a measuring tape. The reference points used were the tip of tragus of left and right ears, with the gonium in between and repeating the procedure three times on each patient, made the measurements. The average of measurements was then taken (in cm) and recorded. The measurements were carried out just before the surgery and at post-operative days 1st, 2nd and 7th day.

Measurement of mouth-opening ability: A vernier-calibrated sliding caliper was used to measure maximum interincisal mouth-opening ability of the patient at the commencement of the procedure. The reference point used was incisal edge of the maxillary central incisor and incisal edge of mandibular central incisor at maximum opening available. The measurements were made in triplicate and the average was recorded in millimeters (mm). The measurement was carried out just before the surgery and at post-operative days 1st, 2nd and 7th day.

Global Assessment of Functioning: The Global Assessment of Functioning was used by Dental Surgeon and Patients to rate the symptoms and functioning (social, occupational) up

to day 7. **Very good:** No symptoms. Superior functioning in a wide range of activities (social, occupational).**Good:** Minimal symptoms. Good functioning. **Satisfactory:** Mild symptoms, some difficulty in functioning. **No change:** Symptoms, difficulty in functioning same as day 1.

Operative Procedure: Surgical extraction of the third molars was carried with buccal guttering technique after adequate elevation and reflection of buccal mucoperiosteal flap under local anaesthesia (2 % lignocaine hydrochloride with 1:100,000 adrenaline). Tooth delivery was followed by meticulous irrigation of the surgical site with physiologic saline (0.9%). The three-sided mucoperiosteal flap was repositioned and sutured.

Duration of Operative Procedure: The duration of each operative procedure were recorded. The mean duration of operative procedure was 43.46 ± 1.6 minutes (range, 25 min – 60 min; group I: 42.5 ± 1.7 min., group II: 43.93 ± 1.6 min., and group III: 43.97 ± 1.5 min).

Study Medication: The investigator obtained the medications from the following manufacturers. Tab.Bromelain 200mg, (Bromozyme, Aksigen Hospital Care, KBR5E03), Tab.Serratiopeptidase 10 mg (CIPZEN FORTE, Cipla, AA6016), Tab.Diclofenac Sodium (REACTIN, Cipla AM6158), Caps.Amoxycillin Trihydrate (Cipmox, Cipla DS6034), Metronidazole (Metrogyl, Unique A7032).

STATISTICAL ANALYSIS

Data was analyzed using SPSS for windows (v15, SPSS) statistical software package. One-way analysis of variance followed by Bonferroni test was used for repeated measures for Visual Analogue Scale, interincisal opening and facial swelling. The level of significance was set at $P < 0.05$.

RESULTS

A total of 85 patients (distributed into groups I (N 28), II (N 28) and III (N 29) who completed the study were included in the analysis). Five patients were dropped out from the study. Three patients (one from group I and two from group II) were absent and unavailable at their locations on post-operative day 2. Two patients (One from group I and one from group III) were found to be noncompliant. The anti-inflammatory effect of Bromelain / Serratiopeptidase as an add on therapy with conventional treatment (Diclofenac) following

mandibular impacted third molar removal were compared. The mean age of the participants was 28.13 ± 1.07 years (range 20-35 years) (Table-1).

Table 1. Mean age of the participants

Group	Age (years)
I	28 ± 1.13
II	27.44 ± 0.87
III	28.93 ± 1.20
Mean	28.13 ± 1.07

Types of impactions

The radiographic analysis of the type of impactions showed that mesio-angular impaction constitutes 45.0% of cases, followed by disto-angular impaction 22.0% (Table -2).

Table 2. Types of impactions

Types	Age (years)
Mesioangular	45
Distoangular	22
Horizontal	21
Vertical	12

Measurement of pain

Co-administration of bromelain / serratiopeptidase and diclofenac was significantly superior to diclofenac alone for the relief of pain upto post-operative 48 hour (P<0.05). For group II, the mean pain scores on day 1 was significantly lower than that for group I and group II (p < 0.05).For group II, and group III the mean pain scores on day 3 were significantly lower than that for group I (p <.05).For group II, the mean pain score on day 2 was highly significant than that for group I <p <.05) (Table-3) Fig-1.

Table 3. Measurement of Pain

Post-operative	Group	Pain (VAS)
Day 1	I	4.96 ± 0.22
	II	3.96 ± 0.19*
	III	4.55 ± 0.23
Day 2	I	4.39 ± 0.25
	II	3.00 ± 0.18**
	III	3.34 ± 0.24*
Day 7	I	0.96 ± 0.19
	II	0.79 ± 0.13
	III	0.83 ± 0.19

Each value represents the mean pain score ± SEM. *P < 0.05 **P < 0.01.

Oneway ANOVA followed by Boinferroni Test

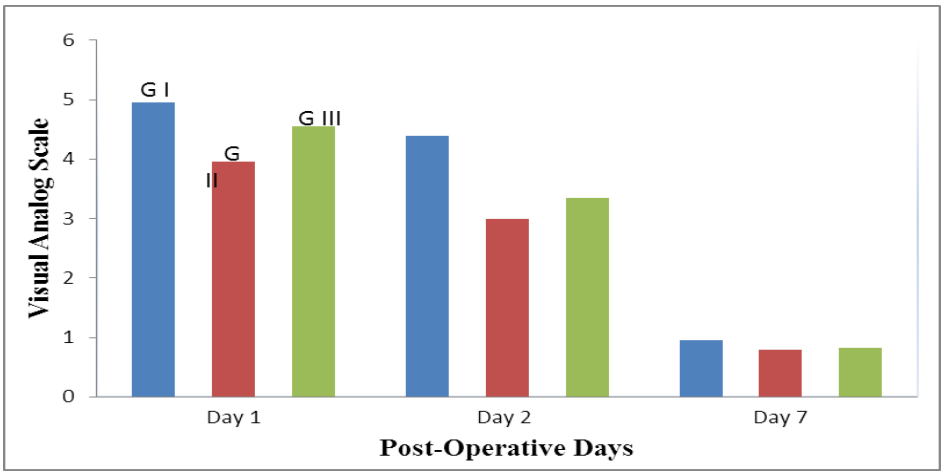

Figure 1. Measurement of Pain

Measurement of facial width

Co-administration of Bromelain/Serratiopeptidase and diclofenac alone for the reduction of post-operative facial swelling up to 48 hour ($P<0.05$) (Table-4) Fig-2.

Table 4. Measurement of Facial width

Post-operative	Group	Pain (VAS)
Day 1	I	29.89 ± 0.31
	II	28.44 ± 0.33*
	III	28.52 ± 0.40*
Day 2	I	29.54 ± 0.30
	II	28.07 ± 0.33*
	III	28.26 ± 0.38*
Day 7	I	27.71± 0.28
	II	27.51± 0.33
	III	27.61 ± 0.38

Each value represents the mean score of facial width ± SEM.* $P < 0.05$.

Oneway ANOVA followed by Bonferroni Test

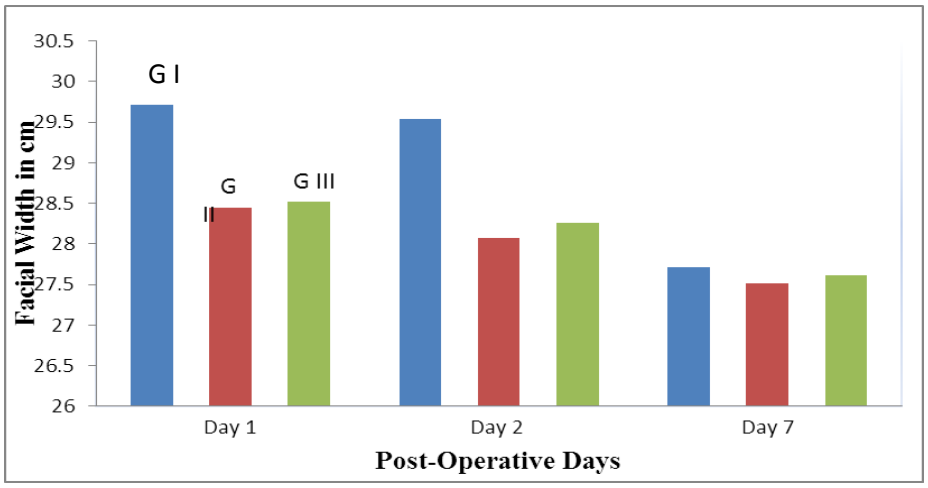

Figure 2. Measurement of Facial Width

Measurement of Trismus

There was no significant difference for trismus relief between the three medication protocols (P>0.05) (Table-5) Fig-3. By the post-operative 7th day, all symptoms had restored to the preoperative level in all the groups. Neither groups demonstrated any adverse reaction, side effect of other complications (e.g., tendency for bleeding) during the follow-up period.

Table 5: Measurement of Trismus

Post-operative	Group	Pain (VAS)
Day 1	I	29.89 ± 0.34
	II	28.44 ± 0.82
	III	28.52 ± 0.83
Day 2	I	29.54 ± 0.52
	II	28.07 ± 0.65
	III	28.26 ± 1.09
Day 7	I	27.71± 1.34
	II	27.51± 0.9
	III	27.61 ± 1.63

Each value represents the mean score of Trismus ± SEM *P < 0.05

Oneway ANOVA followed by Bonferroni Test.

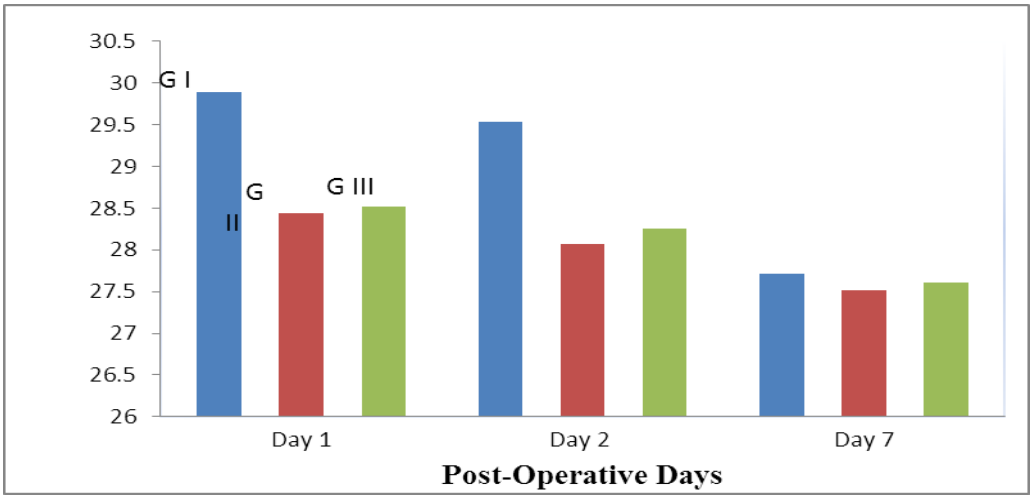

Figure 3. Measurement of Trismus

Global Assessment of Functioning

For group II and group III, the mean percentage of score good in Global Assessment of Functioning were greater than group I by both Patient and Dental surgeon (Table-6).

Table 6. Global Assessment of Functioning by Patients and Dental Surgeon

Mean % score of Global Assessment of Functioning by Patients				
Group	**Very good**	**Good**	**Satisfactory**	**No change**
I	-	42.86	35.6	21.43
II	-	67.86	21.43	10.7
III	-	65.51	24.18	10.34
Mean % score of Global Assessment of Functioning by Dental Surgeon				
I	-	46.43	32.14	17.86
II	-	71.43	25	7.14
III	-	65.6	31	3.4

Each value represents the mean % score of Global Assessment of Functioning.

DISCUSSION

Prostaglandins play a major role in the induction of pain, inflammation, and fever.[3], [11] The reduction of biosynthesis of prostaglandins by inhibition of the cyclo-oxygenase enzyme system in considered an important mechanism of action of NSAIDs. When administered preoperatively, NSAIDs have been shown to be particularly effective in combating postoperative pain.[3],[11] Preventive strategies for postoperative management of pain and inflammation are based on the known ability of NSAIDs to block the arachidonic acid cascade. When NSAIDs are administered preoperatively, absorption and distribution of the medication may occur before the initiation of tissue trauma, the ensuring synthesis of prostaglandins and the subsequent inflammatory response. Prevention of the inflammatory response may decrease the sequelae of tissue trauma; especially the accompanying pain.[3],[11] Diclofenac has been shown to be useful in controlling postoperative pain after removal of third molars. Diclofenac is known to possess both analgesic and anti-inflammatory effect.

It has also been proposed for reduction of postoperative inflammation is the administration of oral systemic enzymes. Bromelain / serratiopeptidase have the capacity to interfere with the physiologic processes of inflammation and, thus, suppress the development of redness, swelling and tenderness by which inflammation is recognized. It has also been reported that administration of bromelain / serratiopeptidase reduces tissue levels of bradykinin.[13], [14] The enhanced anti-inflammatory action of bromelain, possibly the result of difference mechanisms that act simultaneously the depletion of plasma kallikrein system, inhibiting the generation of bradykinin, negative action on the prostaglandin pathway.[13], [14] As known, bradykinin and kallidin are the two kinins that act independently as well as synergistically

with products of the arachidonic acid cascade to produce both pain as well as increased vascular permeability. Due to its anti-inflammatory effects,[21] the administration of oral systemic enzymes may synergize the anti-inflammatory effect and contribute to the reduction of inflammatory exudates as well as edema and pain. Therefore the co-administration of diclofenac and bromelain / serratiopeptidase may be expected to reduce post-operative pain more than that achieved with diclofenac alone.[21]

The present study assessed the clinical effect of bromelain / serratiopeptidase-diclofenac combination and diclofenac alone on pain, facial swelling and trismus. The comparison of pain intensity showed significant difference between the three groups ($P<0.05$), indicating an enhanced analgesic effect of diclofenac when administered in combination with bromelain / serratiopeptidase. Post-surgical facial edema is difficult to quantify accurately, since it requires a three-dimensional measurement with an irregular, convex surface and can manifest itself internally as well as externally. Over the years, numerous researchers have tried various techniques in an effort to objectively measure edema.[24] Most of which is indirect assessments of the altered contours of skin surface. In the present study, a single measurement from the tip of tragus to gonion to the tip of contralateral tragus was taken. It is noteworthy to mention herein that the cheek swelling following third molar surgery is diffuse in different planes and is very difficult to measure accurately. The co-administration of bromelain / serratiopeptidase-diclofenac preoperatively and post operatively, produced a clear reduction in postoperative pain and cheek swelling. The mean increase in facial swelling in days 1 and 2 in group II and group III were significantly less than that of group I. This result shows that add on therapy of bromelain / serratiopeptidase-diclofenac enhances the control of postoperative facial swelling. The mean pain scores in day 2 in group II and group III were significantly lower than that of group I. This results shows that addition of bromelain / serratiopeptidase with diclofenac enhances the control of postoperative pain on day 2. The mean pain score in day 1 in group II was significantly lower than that of group I and group III. The mean pain score in day 2 in group II was highly significant than of group I. This result shows that patient who received bromelain and diclofenac has greater control of postoperative pain than the other groups. Statistical analysis did not show any significant difference in reduction of mouth opening (trismus) between the study groups ($P >0.05$). The time course for pain and facial swelling findings described in the present study are in agreement with those of a recent multicenter triasl indicating similar symptoms that reached a maximum at days 1 or 2 postoperatively and generally resolved at day 7.[25], [26] The results of

Global Assessement of Functioning by patients / dental surgeon analysis showed that the co-administration of bromelain / serratiopeptidase-diclofenac preoperatively and postoperatively, had minimal symptoms and good functioning in social / occupational activities than diclofenac alone.

CONCLUSION

The present study concludes that anti-inflammatory effects of co-administered bromelain/ Serratiopeptidase and diclofenac on post-operative pain, facial swelling were enhanced and good functioning in social / occupational activities was also improved as compared to the conventional treatment following impacted third molar removal. However there was no significant improvement in trismus between conventional and Bromelain / Serratiopeptidase add on therapy. Thus the study helped us to understand the importance of oral proteolytic enzymes in a better manner and proved to have a beneficial role in co-administration with conventional therapy in the management of pain and inflammation.

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