International Journal of Research in Medical Sciences
Tiwari S et al. Int J Res Med Sci. 2022 Sep;10(9):1919-1924
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20222265

Original Research Article

Management of post-operative wound in dental surgeries using proteolytic enzyme-flavonoid combination of trypsin, bromelain and rutoside: a single-centre experience

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Received: 10 August 2022
Revised: 25 August 2022
Accepted: 26 August 2022

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ABSTRACT

Background: Appropriate surgical wound management is required to prevent post-operative complications, including delayed wound-healing which may result in increased hospital stay. The present study aimed to evaluate the efficacy and safety of oral administration of a fixed dose combination of trypsin-bromelain-rutoside in the post-operative management after dental surgeries.
Methods: The study was a prospective, observational data collection exercise. Hundred subjects undergoing dental surgeries, who were administered trypsin-bromelain-rutoside combination, were observed over a period of 8 days post-surgery. Verbal rating scales were used for grading the pain intensity and extent of swelling, while a 5-point Likert scale was used to evaluate patient- and investigator-reported global assessment of improvement in pain and swelling. Scores at day 3 and day 8 were analysed using paired t test.
Results: At day 3 and day 8, the mean scores of pain and swelling were significantly reduced from baseline (all $p<0.0001$). By day 8, 100% of the patients achieved complete resolution of pain, while mild swelling was reported in only 2 patients. At day 3, 95% patients reported good/ very good global improvement in pain and swelling; while at day 8, 100% reported good/ very good improvement. No adverse event was reported in any of the patients.
Conclusions: The study results demonstrate that treatment with trypsin-bromelain-rutoside combination led to significant improvement in the post-operative pain and swelling. The use of this combination is useful for wound recovery and reducing the need for other analgesic and anti-inflammatory drugs.

Keywords: Dental surgery, Enzymes, Inflammation, Pain, Swelling

INTRODUCTION

Surgical procedures in the oral cavity are associated with significant pain and swelling in the post-operative period. To minimize these, proteolytic enzymes administered orally are often employed along with other antibiotics, analgesics and/or corticosteroids. These enzymes, including the serine protease trypsin and the cysteine protease bromelain, when given in combination with an antioxidant bioflavonoid like rutoside, are believed to exert anti-kinin, antioxidant, antiplatelet, anti-chemokine, pro-fibrinolytic, and pro-fibrotic activities; with more recent evidence indicating inhibition of pro-inflammatory signal transduction.[1] They are effective in reducing pain, controlling post-operative inflammation and infection, and have higher patient satisfaction compared to other available drugs like steroids and non-steroidal anti-inflammatory drug (NSAID) medications, they are widely accepted as alternate therapy. This is based on evidence, gathered over the decades, from multiple

studies in myriad inflammatory conditions.[2-10] This study was conducted to evaluate the efficacy and safety of an enzyme-bioflavonoid combination of trypsin-bromelain-rutoside in managing the post-operative inflammation in patients undergoing dental surgeries.

METHODS

Study population and design

We conducted a prospective, observational study, evaluating the efficacy of commercially available fixed dose combinations of trypsin, bromelain and rutoside trihydrate in patients undergoing dental procedures at M.V. hospital and research centre, Lucknow, India. This study was reviewed and approved by the institutional ethics committee for MV hospital and research centre, Lucknow, India (registration number: ECR/13/Inst/UP/2013/RR-19). The subjects were enrolled between September 2022 and October 2022. Written informed consent was obtained from all subjects who were ready to comply with study-required visits. Subjects chronically receiving systemic or topical steroidal or non-steroidal anti-inflammatory agents (including study drugs), or analgesics, and immunosuppressive agents, with known history of allergy, hypersensitivity, or intolerance to study drugs and history of use of recreational drugs within 12 months prior to receiving the study drugs were excluded from the study.

Study medication

All enrolled patients, as part of routine hospital practice, were dispensed tablets of either Phlogam® or Disperzyme CD® (Aksigen hospital care limited, Mumbai), containing trypsin 48 mg, bromelain 90 mg and rutoside trihydrate 100 mg [total proteolytic activity not less than 2190 FIP (Fédération Internationale Pharmaceutique) units/tablet by papain method]. The patients were instructed to take the tablets as per the following regimen-1 tablet dissolved in 1 tablespoon of water (15 mL) to be taken thrice daily approximately half an hour to one hour before a meal or at least 2 hours after a meal over the next 8 days.

Outcome measures

Pain was graded by the patient using verbal rating scale-no pain, mild pain, moderate pain, or severe pain, at baseline (pre-dose) and on days 3 and 8. Edema was graded by the investigator using verbal rating scale - none (no swelling), mild (swelling confined to the surgery area), moderate (swelling beyond the surgery area), or intense (swelling spreading beyond the surgery area), at baseline (pre-dose) and on days 3 and 8. Additionally, a 4-point Likert scale (1=poor, 2=fair, 3=good, 4=very good, 5=excellent) was used to measure the global assessment of improvement in pain and swelling reported by the patients and the investigator. Any subjective adverse event or clinically significant laboratory derangement during the course of the study was checked for and noted.

Statistical analysis

Data was collated in a Microsoft® excel® spreadsheet and statistical analysis was performed using SAS® software version 9.4. The mean scores of pain and swelling, reported by the patients and investigator, respectively, at days 3 and 8, were checked for statistical significance using paired t test against the baseline scores. Similarly, the proportions of patients and investigators reporting very good/excellent improvement in pain and swelling at days 3 and 8 were calculated and summarized using descriptive statistics.

RESULTS

Patients

Hundred subjects were enrolled in the study, out of which 64 were males and 36 were females. The mean age of the patients was 40.6 years (range-20-63 years). All 100 subjects completed the 8-day observation period, and their data was analysed. Demographic characteristics is summarized in Table 1. The indications for and types of surgeries is summarized in Table 1. The most common indications were periodontal abscess and gingivitis, while the most common procedures were Incision and drainage, and tooth extraction.

Table 1: Demography and disease summary.

Particular	Values
Age (years) - Mean (Range)	40.6 (20-63)
Gender (Male:Female)	64:36
Indications (n)	
Periodontal abscess	35
Gingivitis/Pericoronitis	22
Mobile tooth	13
Peri-coronal abscess	9
Dental infection	8
Gingival polyp	5
Decayed tooth	4
Gingival hypertrophy	3
Peri-apical granuloma	1
Type of surgery (n)	
Incision and Drainage	47
Tooth extraction	30
Operculectomy	15
Excision	5
Gingivectomy	3

Assessment of pain

At baseline, sixty-four patients reported moderate to severe pain (moderate pain-63, severe pain-1) and 36 patients reported mild/no pain. At day 3, no patient reported moderate/ severe pain; all patients reported

no/mild pain (mild pain-66, no pain-34). At day 8, all hundred patients reported no pain. The mean scores for pain were 1.65, 0.66 and 0 at baseline, day 3 and day 8, respectively. The reduction in pain scores were statistically significant at both day 3 (p<0.0001) and day 8 (p<0001) (Figure 1).

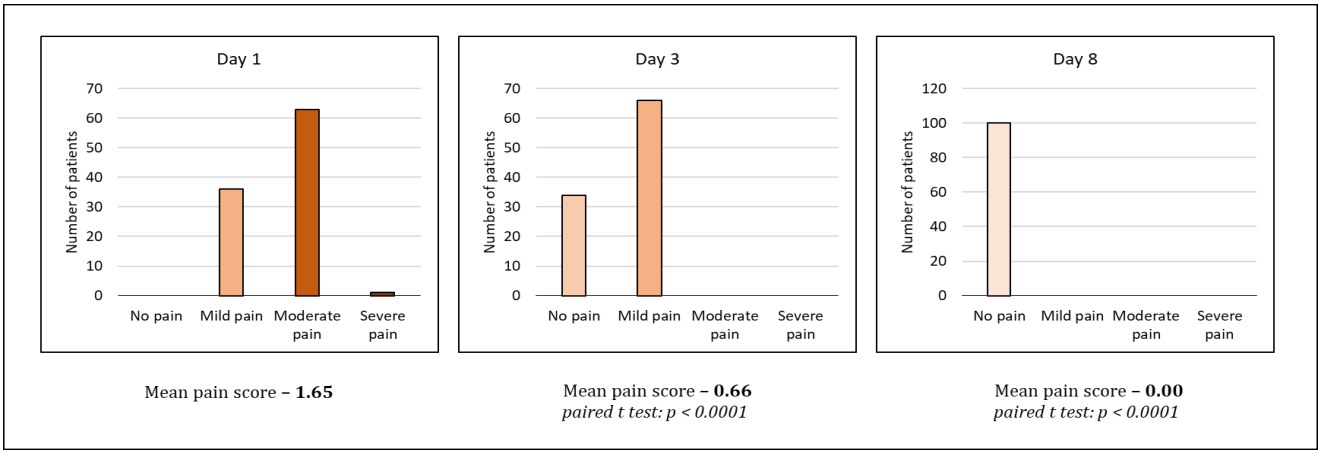


Figure 1: Post-operative pain intensity.

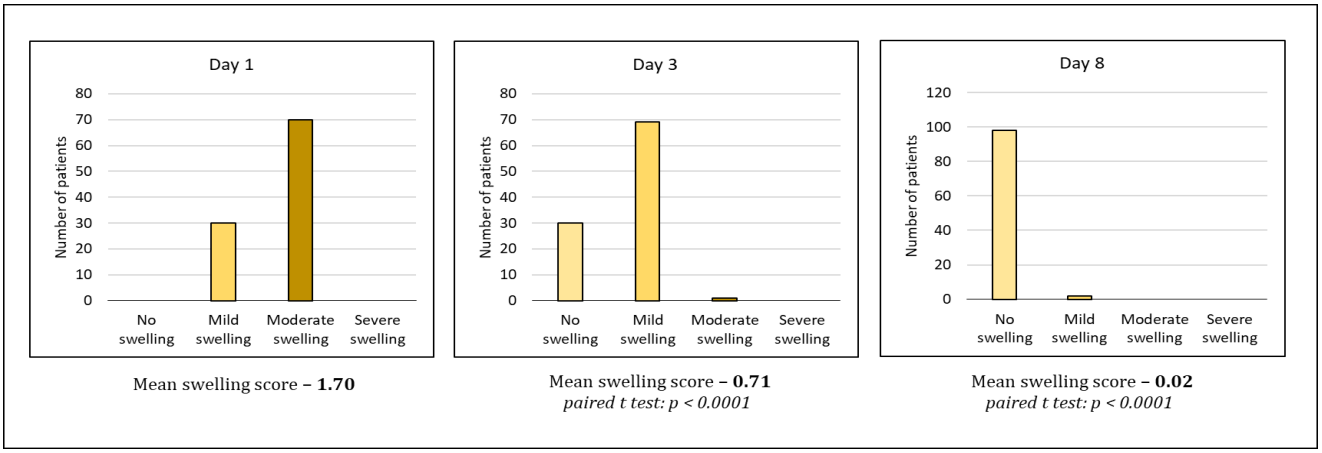


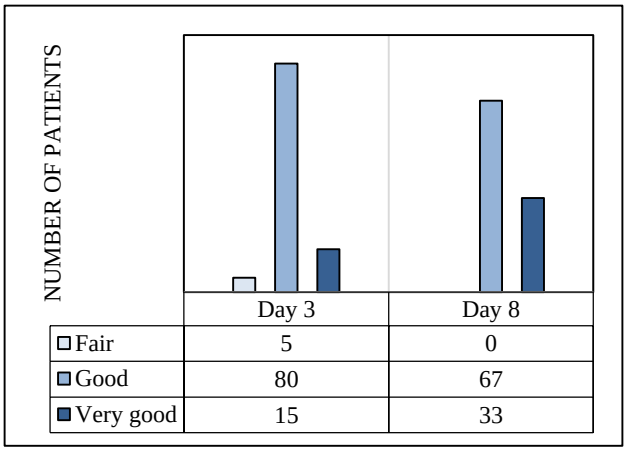
Figure 2: Post-operative swelling intensity.

Assessment of swelling

At baseline, the investigator reported moderate swelling in 70 patients and mild/ no swelling in 30 patients. At day 3, the investigator reported moderate swelling in 1 patient, while the remaining 99 had mild or no swelling (mild swelling-69, no swelling-30). At day 8, complete absence of swelling was reported for 98 patients, while mild swelling was reported in 2 patients. The mean scores for swelling were 1.70, 0.71 and 0.02 at baseline, day 3 and day 8, respectively. The reduction in swelling scores were statistically significant at both day 3 (p<0.0001) and day 8 (p<0001) (Figure 2).

Patient-reported global assessment of improvement

At day 3, 95% patients reported good/ very good improvement in pain and swelling. At day 8, 100% patients reported good/ very good improvement in pain and swelling; of which 33% reported very good improvement (Figure 3).

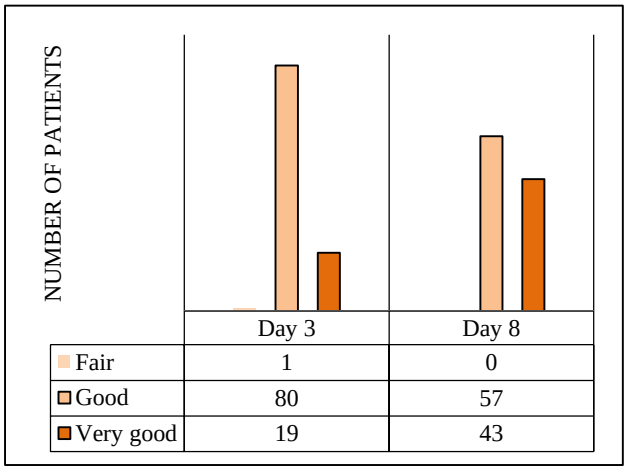


	Day 3	Day 8
Fair	5	0
Good	80	67
Very good	15	33

Figure 3: Patient-reported global assessment of improvement in pain and swelling.

Investigator-reported global assessment of improvement

At day 3, the investigator reported good/ very good improvement in pain and swelling for 99% of patients. Of these 19% were reported to have very good improvement. At day 8, the investigator reported good/ very good improvement in pain and swelling for 100% of the patients, of which 43% reported very good improvement (Figure 4).



	Day 3	Day 8
Fair	1	0
Good	80	57
Very good	19	43

Figure 4: Investigator-reported global assessment of improvement in pain and swelling.

DISCUSSION

The post-operative period is characterised by pain and swelling of the affected tissue, as part of the body's inflammatory and immune processes. There is rapid formation of both localized and generalized oedema in response to surgical wound because of increased microvascular permeability along with vasodilation and increased extravascular osmotic activity.[11,12] Wound healing gets impaired if the edema is excessive and prolonged. This is due to the increase in diffusion distance for oxygen and other nutrients in the tissues, reduced diffusional removal of potentially toxic by-products of cellular metabolism and compression of small vessels leading to reduced blood flow in the swollen tissue. Controlling the edema, thus becomes an important target to ensure proper wound-healing and prevent complications.[11,12] Over the past many decades anti-inflammatory drugs like Rofecoxib, valdecoxib and virtually all NSAIDs are being used very extensively all over the world but their chronic use may lead to side effects such as gastric ulcers, liver- kidney damage and increased risks of heart attack and stroke with their use.[13,14] More importantly, they have been found to impair wound-healing, due to their anti-proliferative effect on blood vessels and skin. This, along with their limited efficacy in controlling edema, limits their utility in ensuring faster recovery of surgical wounds.[15,16]

In the present study, we have demonstrated that the oral administration of trypsin-bromelain-rutoside combination led to significant reduction in pain and swelling associated with surgical wounds in case of dental surgeries by post-operative day 3. By day 8, all patients had complete relief from pain. The improvement was parallelly seen in swelling as well, with resolution of sweeling seen in all patients by day 8. The findings of global assessment of improvement reported by patients and investigator were consistent with these results, where both reported good/ very good improvement in 100% cases by day 8.

These findings are in line with multiple other studies conducted with a variety of dental procedures in literature. These enzymes have been studied in placebo-controlled trials. In one such placebo-controlled double-blind study, 100 patients with impacted and/or dislocated lower third molar tooth received a dose 80 mg bromelain thrice daily for 6 days, starting 1 day prior to surgery. The test group showed swelling to be 7.5% lower than in the placebo group.[17] In another randomized controlled study of 80 patients requiring surgery of impacted third molars, bromelain was started in one group from day 2 of the surgery. Three parameters-pain, edema, and erythema, were evaluated at 3 and 48 hours after surgery, followed by another evaluation 7 days after surgery. All three parameters were significantly lower in the bromelain group than in the control group. Analgesic treatment duration and dose also showed trend towards lower requirement with bromelain. Further, no adverse event was reported with the use of bromelain.[18] In yet another study of 40 patients, the effectiveness of bromelain in reducing swelling and pain after surgical removal of third molars, was evaluated when given at dose of 200 mg twice a day. Facial edema was quantified by measuring the distance between tragus to pogonion, while pain was measured using VAS scale. Bromelain effectively reduced pain and swelling in 70% of the subjects. These patients had less than moderate pain on day 1, mild pain on day 3 and almost no pain by day 7.[19] Another small 34-patient placebo-controlled study of bromelain, given orally at 100-150 mg daily over 7 days after extraction of impacted lower molars, showed trend towards less inflammation, and improved oral aperture.[20] A 30-patient double-blinded randomized, placebo-controlled study was conducted in patients undergoing bimaxillary orthognathic surgery, to evaluate the effectiveness of a 5-day SET. To measure the level of edema, the thickness of the soft tissue at 9 anthropometric points was measured using an ultrasound device on post-operative days 1, 5, and 15. There was a significant difference in soft tissue thickness between the 2 groups, indicating that SET decreases postoperative edema in orthognathic surgery, precluding long-term corticosteroid use.[21]

The enzymes have been compared to other conventional NSAIDs in similar settings. Bromelain was compared to ketoprofen in a single-blind study of 46 patients with dysodontiasis suitable for exodontia. Each one of the 46 patients, after 3.8 teeth exodontia (left mandibular

surgery) was prescribed a cephalosporin with bromelain (oral 40 mg every 6 hours for 6 days). These same patients were subjected to 4.8 teeth exodontia (right mandibular surgery) after a gap of 60 days and were prescribed the same cephalosporin with ketoprofen (oral 100 mg every 12 hours for 6 days). Postoperative pain and oedema were evaluated, at 1, 3, 5, 7 and 30 days in both surgery phases. There similar reduction of the postoperative pain and edema with both drugs, establishing that effectiveness of bromelain was not statistically different from ketoprofen.[22] Bromelain was pitted against diclofenac in a double-blind, placebo-controlled study of 45 patients requiring extraction of single partial bony impacted mandibular third molar. A daily dose of 4 × 250 mg of Bromelain was compared against 4×25 mg of oral diclofenac, started 1 day prior to surgery, and continued for 4 days. Both groups showed a significant reduction in pain compared with the placebo group at 1, 3, and 7 days postoperatively, while being comparable to each other. Both treatment groups also showed a significant difference in the effect on quality-of-life scores.[23]

Combination of enzymes with laser therapy was evaluated in patients requiring acute teeth extraction, planned teeth extraction or anchorage of pin for tooth implantation. The results were compared against laser therapy alone, enzyme therapy alone and control group receiving only ice application. Among a total of 133 patients enrolled in the study, the combination group showed reduced length of pain, edema and healing periods. No patient in the combination or SET alone group used analgesics.[24] In a more recent study, postoperative oral administration of bromelain (40 mg every 6 hours for 6 days) with and without preoperative subcutaneous dexamethasone was compared to a control (no drug) group in 84 patients after mandibular third molar surgery. The combination of bromelain and dexamethasone showed significantly better results in reduction of facial edema by postoperative day 2, reduction in postoperative swelling by postoperative and reduction in the total number of analgesic tablets taken after surgery.[25]

These findings, when compared to serratio-peptidase in the management of post-operative wounds in a randomised, multicentre comparative study conducted across 8 hospitals in India, showed that most of the patients had remarkable improvement in tissue swelling at day 3 and day 8 (no/mild swelling-98.1% and 100%) with similar results in pain reduction.[26]

The study was limited by being an observational study and not having a control arm. But, nevertheless, provides compelling data on the beneficial effect of the study medication, which can further be used to design comparative interventional trials and further studies.

The study results demonstrate that treatment with trypsin-bromelain-rutoside combination led to significant improvement in the post-operative pain and swelling. The use of this combination is useful for wound recovery and reducing the need for other analgesic and anti-inflammatory drugs.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of MV Hospital and Research Centre, Lucknow, India (registration number: ECR/13/Inst/UP/2013/RR-19).

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Cite this article as: Tiwari S, Khemnar BM, John J. Management of post-operative wound in dental surgeries using proteolytic enzyme-flavonoid combination of trypsin, bromelain and rutoside: a single-centre experience. Int J Res Med Sci 2022;10:1919-24.