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Original Research Article

Post-operative management of inflammation after orthopaedic surgeries using trypsin, bromelain and rutoside combination: a single-centre prospective observational study

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ABSTRACT

Background: Post-operative management of inflammation plays an important role in orthopaedic surgeries, as delay in wound healing may lead to extended hospital stay. Proteases like trypsin and bromelain combined with the bioflavonoid rutoside are often used to reduce post-operative pain and swelling. 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 orthopaedic surgeries.
Methods: The study was a prospective, observational data collection exercise. Hundred subjects undergoing orthopaedic 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, 74% of the patients achieved complete resolution of pain, while 50% reported complete resolution of swelling. By day 8, 54% patients reported excellent/ very good global improvement in pain and swelling, while the investigator reported excellent/ very good global improvement in 81% of the patients. No adverse event was reported in any of the patients.
Conclusions: The combination of trypsin-bromelain-rutoside was safe and effective in reducing the post-operative pain and swelling after orthopaedic surgeries. An 8-day treatment led to complete resolution of pain in three-fourths of the patients and complete resolution of swelling in half the patients. The use of this combination has the potential to reduce hospital stay and pill burden.

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

INTRODUCTION

Post-operative management of inflammation plays an important role in orthopaedic surgeries, since, delay in wound healing may lead to extended hospital stay. Inflammation is a natural, protective and restorative response of the body, which facilitates the disposal of cellular debris, ensuring protection and repair of injured tissues. Pain and swelling occur mainly as an inflammatory response. Non-steroidal anti-inflammatory drugs (NSAIDs) and steroids are widely used in the management of inflammation. However, they also come with many side effects and risks. Proteases trypsin and bromelain combined with bioflavonoid rutoside have

shown their effectiveness for reducing pain and swelling. This orally administered enzyme combination shows pro-fibrinolytic, anti-chemokine, antiplatelet, pro-inflammatory signal transduction and anti-oxidant activities. [1] This oral enzyme therapy has been used since many decades in management of multiple inflammatory conditions and various studies demonstrated the effectiveness of this therapy.[2-10] This study was conducted at a single centre to evaluate the efficacy and safety of an enzyme-bioflavonoid combination of trypsin-bromelain-rutoside in management of post-operative inflammation in patients undergoing orthopaedic 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 orthopaedic surgeries at Vishwaraj hospital, Pune, India. This study was reviewed and approved by the institutional ethics committee (IEC, Maeers Vishwaraj hospital, Pune, India (registration number: ECR/1138/Inst/MH/2018/RR-21). One hundred consecutive patients, irrespective of age and gender, posted for various orthopaedic procedures, with potential to benefit from anti-inflammatory treatment in the post-operative period, and willing to give informed consent, were enrolled in the study between December 2021 and March 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)/ 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 Phlogam® (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-2 tablets 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

A pragmatic sample size of 100 consecutive patients was planned for the study. 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 60 were males and 40 were females. The mean age of the patients was 33.2 years (range-19-78 years). All 100 subjects completed the 8-day observation period, and their data was analysed. Demographic characteristics is summarized in Table 1. The most common indications were fractures of the leg and forearm, majority of which required open reduction and internal fixation.

Table 1: Demography and disease summary.

Particular	Value
Age (years)-Mean (Range)	33.2 (19-78)
Gender (Male:Female)	60:40
Indications (n)	
Tibia and/or fibula fracture	21
Radius ± Ulna fracture	18
Anterior cruciate ligament tear	10
Femur ± tibia fracture	09
Total knee replacement	09
Shoulder dislocation	07
Zygomatic arch fracture	06
Polytrauma	03
Femur neck fracture	02
Foot fracture	02
Hand fracture	02
Hip replacement	02
Humerus fracture	02
Tendon repair	02
Others*	05

*Including localized trauma, ganglion excision.

Assessment of pain

At baseline, 57 patients reported moderate to severe pain (moderate pain-55, severe pain-2) and 43 patients reported mild pain. At day 3, only 1 patient reported moderate pain; all other patients reported no/mild pain (mild pain-84, no pain-15). At day 8, no patient had moderate/severe pain; 26 patients reported mild pain and 74 patients reported no pain. The mean scores for pain were 1.59, 0.87 and 0.26 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).

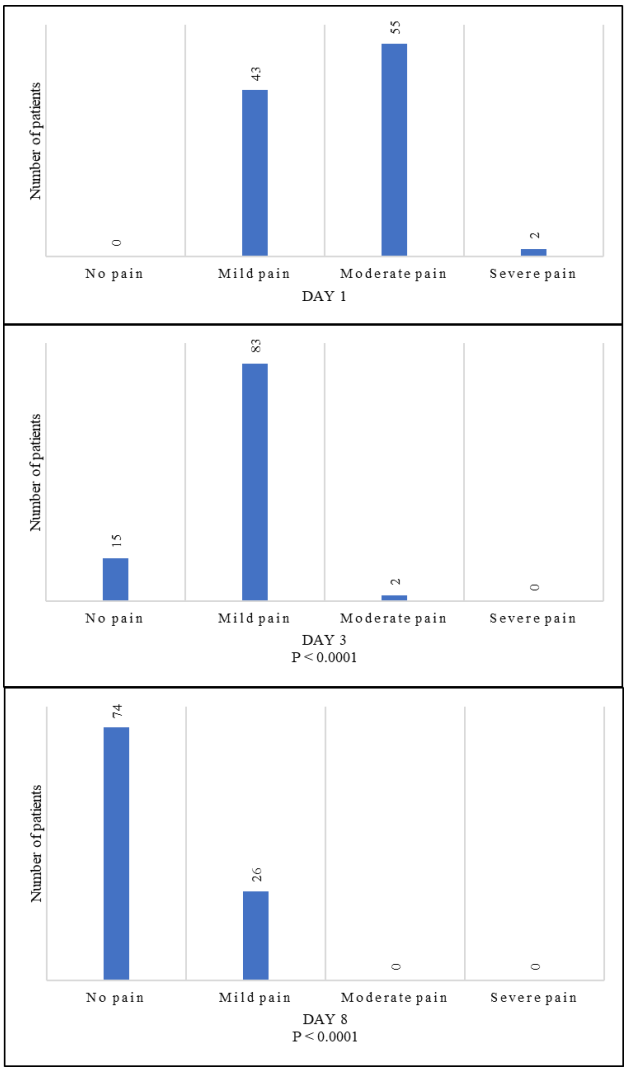


Figure 1: Post-operative pain intensity.

Assessment of swelling

At baseline, the investigator reported moderate swelling in 68 patients and mild swelling in 32 patients. At day 3, the investigator reported moderate swelling in 20 patients, while the remaining 80 had mild swelling. At day 8, only 1 patient had moderate swelling, 49 had mild sweeling, while complete absence of swelling was reported in the remaining 50 patients. Mean scores for swelling were 1.68, 1.20 and 0.51 at baseline, day 3 and 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, 84% patients reported good/very good improvement in pain and swelling (good-80, very good-4); the other 16% reported poor/fair improvement. At day 8, 3% patients reported excellent improvement in pain and swelling, while 51% reported very good improvement and 43% reported good improvement. Only 3% reported fair improvement (Figure 3).

Investigator-reported global assessment of improvement

At day 3, the investigator reported good/ very good improvement in pain and swelling for 90% of patients, while fair improvement was reported in the remaining 10%. At day 8, the investigator reported excellent improvement in 35% patients, very good improvement in 46% and good improvement in 17%. Fair improvement was reported in the remaining 2% patients (Figure 4).

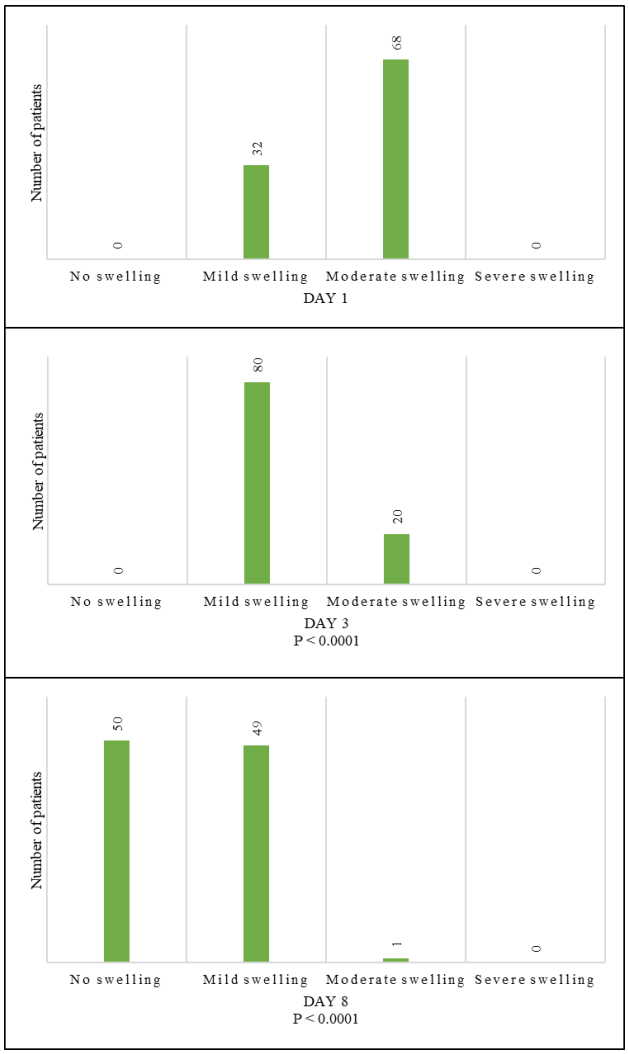
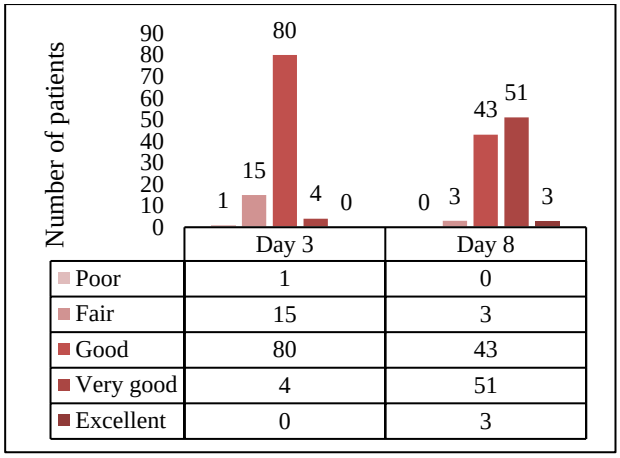
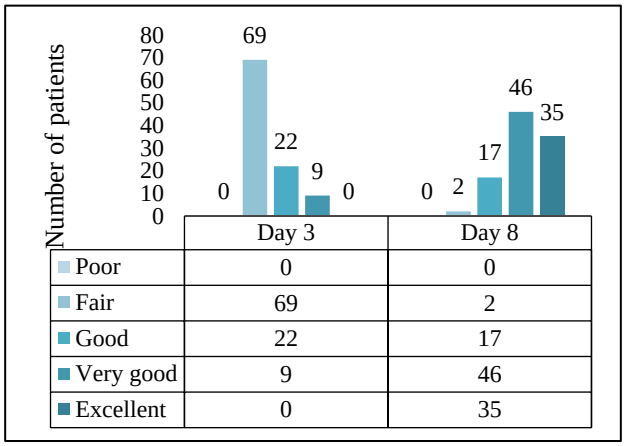


Figure 2: Post-operative swelling intensity.



	Day 3	Day 8
Poor	1	0
Fair	15	3
Good	80	43
Very good	4	51
Excellent	0	3

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



	Day 3	Day 8
Poor	0	0
Fair	69	2
Good	22	17
Very good	9	46
Excellent	0	35

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

DISCUSSION

Pain and swelling, that occur as part of the inflammatory response of the body to tissue injury, is a characteristic feature of the post-operative period. In various orthopaedic procedures this may be a result of both the primary pathology/injury and subsequent invasive interventions. The swelling results from increased microvascular permeability along with vasodilation and increased extravascular osmotic activity.[11,12] Swelling impairs wound healing as result of 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 swollen tissue. Controlling this swelling, thus becomes important target to ensure proper wound healing and prevent complications.[11,12] Steroidal and NSAIDs have been the mainstay to manage pain and swelling in these situations. But their use may lead to side effects such as gastric ulcers, liver- kidney damage, hypertension, increased risks of heart attack and stroke with their use.[13-15] More importantly, drugs such as NSAIDs 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.[16,17]

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 various orthopaedic conditions and their surgical corrections, as early as post-operative day 3. By day 8, almost three-fourths of the patients had complete relief from pain, while the remaining had only complaints of mild pain. The improvement was parallelly seen in swelling as well, with half the patients showing complete resolution of swelling. The findings of global assessment of improvement reported by patients and investigator were consistent with these results, where both reported good/ very good/excellent improvement in 97% and 98% cases, respectively, by day 8.

Similar findings have been reported by others who studies such enzyme combinations in various orthopaedic surgeries. In one such study, 60 patients requiring internal fixation of fractures of long bones were divided into two groups-one half received enzyme therapy in addition to routine analgesics in the postoperative period, while the other half received only the routine analgesics. The outcome measures included change in the volume of operated limb on postoperative days 1, 3, 5, 7, 10 and 14. The group which received enzyme therapy showed a continuous and significantly faster reduction of the post-traumatic and postoperative swelling. The average volume of limb reduced by 12% at the end of first week in the enzyme therapy group, compared to only 1.45% in the control group. By the end of second week, the corresponding values were 17% and 9%. Patients in the enzyme therapy group required significantly lower amount of analgesics. All patients tolerated the enzyme therapy well, with only one reported case of indigestion.[18] More recently, in a randomised, comparative, three-arm, multicentre 2 different formulations of trypsin-bromelain rutoside combination-enteric-coated and dispersible, were compared to serratiopeptidase in patients undergoing minor surgical/ dental procedures. A total of 307 patients, including those requiring general surgical, orthopaedic/ dental surgeries were included. Both enteric coated and dispersible formulations of the enzyme-flavonoid combination showed significantly better control and resolution of both wound swelling and pain throughout the post-operative week. Around 98% subjects reported mild/no pain by day 8. Similarly, 98-100% patients reported mild/no swelling by day 8. A greater part of the pain relief was evident within the first 8 hours, with 93-100% subjects achieving at least half of the maximum total pain relief, indicating a potentially faster induction of pain relief. Also, significantly fewer of these subjects required rescue analgesic medication. Mild and transient nausea and flatulence were the only reported events, in two subjects.[19] The beneficial effect of such enzymes and their combinations with flavonoids have also been demonstrated in other types of surgeries, including many studies in oral, dental and cosmetic surgeries.[20]

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.

The study results demonstrate that patients who undergo orthopaedic surgeries, when treated with trypsin-bromelain-rutoside combination, show significant improvement in the post-operative pain and swelling. This can result in faster wound recovery and reduce the need for other analgesic and anti-inflammatory drugs.

CONCLUSION

The combination of trypsin-bromelain-rutoside was found to be safe and effective in reducing the post-operative pain and swelling after orthopaedic surgeries. An 8-day treatment led to complete resolution of pain in three-fourths of the patients and complete resolution of swelling in half the patients. The use of this combination has the potential to reduce hospital stay and pill burden.

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Ethical approval: The study was approved by the Institutional Ethics Committee of Maeers Vishwaraj Hospital, Pune, India (registration number: ECR/1138/Inst/MH/2018/RR-21

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