

SYSTEMIC ENZYME THERAPY WITH TRYPSIN- BROMELAIN-RUTOSIDE IN THE MANAGEMENT OF POST-OPERATIVE WOUND: A SINGLE-CENTRE EXPERIENCE

Surgery

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ABSTRACT

Management of post-operative wounds is an important component of surgical care. Inflammation, and the attending edema, in the post-operative period can lead to delayed wound-healing among other complications and may result in increased hospital stay. We conducted a study to evaluate the efficacy and safety of an enzyme-bioflavonoid combination of trypsin-bromelain-rutoside in managing the post-operative inflammation in patients undergoing different surgeries. The study was a prospective, observational data collection exercise, conducted at a medical college located in central India. Hundred patients undergoing different 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 analyzed using paired t test. All patients had moderate to severe pain and moderate to intense swelling at baseline. 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 swelling, while 72% patients had mild pain. At day 3, 96% patients reported very good global improvement in pain & swelling; while at day 8, 55% reported excellent improvement. The investigators reported excellent improvement in 99% patients at day 8; the corresponding figure at day 3 was 44%. No adverse event was reported in any of the patients. Treatment with trypsin-bromelain-rutoside combination led to significant reduction in the post-operative pain and swelling. The improvement was more notable in swelling, where all patients had complete resolution of swelling by day 8. This can potentially help in faster wound recovery and reduce the need for other analgesic and anti-inflammatory drugs.

KEYWORDS

Inflammation, Enzymes, Wound, Edema, Surgery

INTRODUCTION

It is estimated that more than 300 million surgeries are conducted worldwide every year.[1] Based on the peri-operative adverse event rate, it is estimated that around 7 million patients develop major complications in the post-operative period. [2] Care of the wound created during these surgeries forms an integral part of surgical care and can help prevent many of these complications.

Inflammation, in response to surgical wound, leads to rapid formation of both localized and generalized oedema, because of increased microvascular permeability along with vasodilation and increased extravascular osmotic activity. [3,4] Excessive and prolonged local edema significantly impairs wound-healing by increasing the diffusion distance for oxygen and other nutrients in the tissues, limiting the 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. [3,4]

Non-steroidal anti-inflammatory drugs (NSAIDs) are the drugs most commonly used to counter inflammation and pain. However, they come with their own set of risks. NSAIDs are known to be associated with gastro-intestinal irritation, renal (glomerular perfusion) disturbances and increased risk of serious vascular events. 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. [5,6]

Systemic enzyme therapy (SET) involves the oral administration of combinations of proteolytic enzymes and bioflavonoids. These naturally occurring substances have been used since decades to for the management of various inflammatory conditions including musculoskeletal disorders, arthritis and in the post-surgery setting. [7,8] With improvement in the bioanalytical techniques, we are now discovering the various mechanisms by which these ingredients help control inflammation and edema and assist in wound healing.

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 different surgeries

MATERIALS AND METHODS

Study center and design

This was a prospective, observational data collection study, conducted at Chirayu Medical College and Hospital, a multispecialty tertiary care hospital, located at Bhopal in central India. The study was reviewed and approved by the Institutional ethics committee, Chirayu medical college and hospital, Bhopal, Madhya Pradesh, India (Registration number - ECR/502/Inst/MP/2013/RR-22). Written informed consent was obtained from each subject prior to observation and collection of relevant data.

Study population

One hundred consecutive patients, irrespective of age and gender, posted for various surgeries, 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 September and November 2021. The major criteria for exclusion were chronic use of systemic or topical steroid or non-steroidal anti-inflammatory agents, analgesics, and/or immunosuppressive agents; known history of hypersensitivity or intolerance to study drugs; recent use of recreational drugs; pregnant or lactation.

Study medication

All enrolled patients, as part of routine hospital practice, were dispensed tablets of Disperzyme* (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 investigators 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 5-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

The mean scores of pain and swelling, reported by the patients and investigators, respectively, at days 3 and 8, were checked for statistical significance using paired t test. Similarly, the proportions of patients with patient-reported and investigator-reported very good/ excellent improvement in pain and swelling at days 3 and 8 were calculated and presented.

RESULTS

Patients

Seventy-eight females and 22 males were enrolled in the study. The mean age of the patients was 46 years (range – 20 – 76 years). All 100 subjects completed the 8-day observation period, and their data was analyzed. The types of surgeries performed on different patients is summarized in Table 1. Arthroscopy was the most common procedure, followed by cataract and abdominal surgeries.

Table - 1 Demographic Characteristics

Particular	Value
Age (years) (Mean $\pm$ SD)	46 $\pm$ 12
Gender (Male:Female)	22:78
Type of surgery (n)	
Arthroscopy	37
Cataract surgery	26
Abdominal surgery	20
Septoplasty	9
Dental surgery	5
Others	3

Assessment of pain

At baseline, all 100 patients reported moderate to severe pain (moderate pain – 26, severe pain – 74). At day 3, no patient reported severe pain, while 60 patients reported moderate pain. The remaining 40 patients reported no/mild pain (mild pain – 39, no pain – 1). At day 8, none of the patients reported moderate or severe pain. All 100 patients reported no/mild pain (mild pain – 72, no pain – 28). The mean scores for pain were 3.74, 2.59 and 1.72 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 ($p < 0.0001$). (Figure 1)

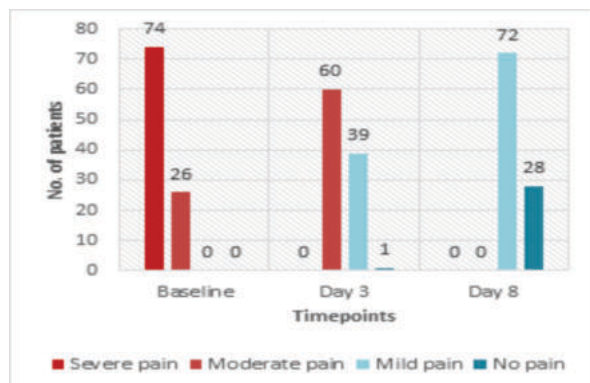


Figure 1: Post-operative pain intensity

Assessment Of Swelling

At baseline, for all 100 patients, the investigators reported moderate to intense swelling (moderate swelling – 43, intense swelling – 57). At day 3, the investigators did not report intense swelling in any patient, while moderate swelling was reported in 20 patients and mild swelling was reported in 80 patients. At day 8, complete absence of swelling was reported for all 100 patients. The mean scores for swelling were 3.57, 2.20 and 1.00 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 ($p < 0.0001$). (Figure 2)

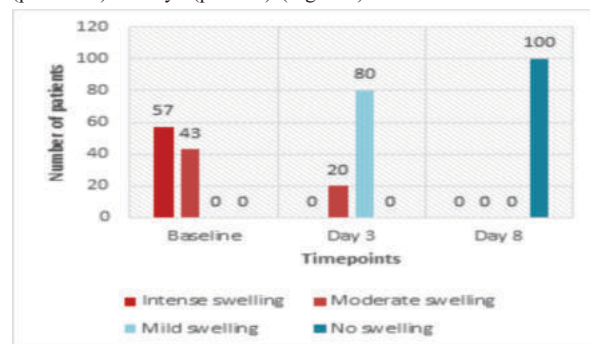


Figure 2: Post-operative Swelling Intensity

Patient-reported global assessment of improvement

At day 3, 96% patients reported very good improvement in pain and swelling. At day 8, 99% patients reported very good / excellent improvement in pain and swelling; of which 55% reported excellent improvement (Figure 3). No patient reported poor or fair improvement at day 3 or 8.

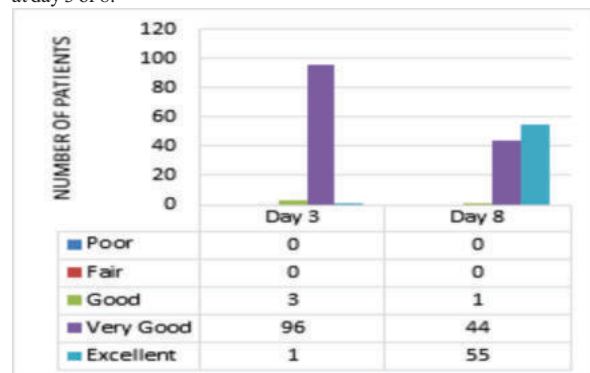


Figure 3: Patient-reported global assessment of improvement in pain and swelling

Investigator-reported global assessment of improvement

At day 3, the investigators reported very good / excellent improvement in pain and swelling for 100% of patients. Of these 44% were reported to have excellent improvement. At day 8, the investigators reported excellent improvement in pain and swelling for 99% of the patients (Figure 4). No patient reported poor or fair improvement at day 3 or 8.



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

DISCUSSION

Interstitial edema at the wound site is known to disrupt the blood supply to the capillary network, thereby reducing the blood flow to the surrounding tissue. The resultant increased oncotic pressure in postcapillary venules impairs antegrade delivery of vital nutrients to the area, thus prolonging or even reversing the normal wound-healing process. [4] Aggressive reduction of edema would benefit wound healing.

NSAIDs, although effective in providing pain relief in majority of the patients, do not demonstrate any significant reduction in tissue edema. [6] More importantly, studies indicate towards a deleterious effect of NSAIDs on mesenchymal stem cell response, thus impacting wound-healing. [6]

In the present study, it was demonstrated that the oral administration of trypsin-bromelain-rutoside combination was able to show significant reduction in pain and swelling associated with surgical wounds, as early as post-operative day 3. By day 8, almost all had no/mild pain and swelling. The improvement was more prominent in swelling, with complete resolution, reported by the investigators, in 100% of the patients by day 8. The findings of global assessment of improvement reported by patients and investigators were consistent with these results, with the investigators reporting much better improvement than the patients – the investigators reported excellent improvement in 99% cases, compared to 55% by the patients. A likely explanation to this difference is the fact that patient assessment is driven mainly by the pain component, while the investigator assessment is driven mainly by the extent of swelling observed.

These findings corroborate well with the findings of a randomized, multicenter comparative study, in which two different formulations of the same combination were compared against serratiopeptidase in the management of post-operative wounds, across 8 hospitals in India. In that study too, with both formulations of the combination, most of the patients had remarkable improvement in tissue swelling at day 3 (no/mild swelling – 84.4% and 91%) and day 8 (no/mild swelling – 98.1% and 100%). Pain reduction also had similar results. [9]

Multiple other studies have reported impressive results with the use of the combination or its individual ingredient in various post-surgical settings including oral surgeries [10-18], orthopedic surgeries [19], cosmetic surgeries [20,21], septoplasty [22] and onco-surgeries [23]. In some of these studies, the enzymes were compared with NSAIDs [14,15,19,23] and laser therapy [16], with favorable results.

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

CONCLUSION

Treatment with trypsin-bromelain-rutoside combination led to significant improvement in the post-operative mean pain and swelling scores at day 3 and day 8. The improvement was more notable in swelling, where all patients had complete resolution of swelling by day 8, and the investigators reported excellent improvement for nearly all patients. This can potentially help in faster wound recovery and reduce the need for other analgesic and anti-inflammatory drugs.

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