International Journal of Research in Orthopaedics
Dhadiwal RK et al. Int J Res Orthop. 2022 Sep;8(5):532-536
http://www.ijoro.org

DOI: https://dx.doi.org/10.18203/issn.2455-4510.IntJResOrthop20222058

Original Research Article

Oral enzyme therapy using trypsin-bromelain-rutoside combination to counter pain and swelling in orthopaedic conditions: a single-centre experience

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Received: 08 July 2022
Revised: 25 July 2022
Accepted: 27 July 2022

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ABSTRACT

Background: Various orthopaedic conditions end up being painful, chronic and progressive, and are associated with persistent inflammation. The present study aimed to evaluate the efficacy and safety of an enzyme-bioflavonoid combination of trypsin-bromelain-rutoside in managing the chronic pain and swelling in out-patients with various orthopaedic conditions.
Methods: The study was a prospective, observational study, conducted in 100 patients attending the orthopaedics department at a multi-speciality hospital located in Nashik, Maharashtra, India. Verbal rating scales were used for grading the pain intensity and extent of swelling at baseline and on days 3 and 8, after being prescribed oral tablets of trypsin-bromelain-rutoside combination. Scores were analysed using paired t test. A 5-point Likert scale was used to evaluate patient- and investigator-reported global assessment of improvement in pain and swelling at days 3 and 8.
Results: At baseline, 68 patients reported moderate-severe pain, while 74 patients had moderate swelling. The mean scores for pain and swelling showed statistically significant reduction at both day 3 ($p<0.0001$) and day 8 ($p<0001$). By day 8, 98 patients reported good-excellent improvement and the investigator reported good-excellent improvement in 97 patients. No adverse event was reported by any patient.
Conclusions: The results indicate that this therapy led to significant improvement in the pain and swelling as early as day 3 and further improvement with continued therapy, and can, thus, provide a safe alternative in patients with various orthopaedic conditions and reduce the need for other analgesic and anti-inflammatory drugs.

Keywords: Inflammation, Antioxidant, Arthralgia, Flavonoid

INTRODUCTION

Unabated inflammation is at the core of many orthopaedic conditions affecting the joints tendons, ligaments, bones, and muscles. These often end up end up being painful, chronic and progressive and are associated with persistent inflammation.[1] The persistent inflammation in these conditions is a result of the imbalance in the pro-inflammatory and anti-inflammatory processes in the body. Drugs like non-steroidal anti-inflammatory drugs (NSAIDs), which are currently the most used drugs in these conditions, often target certain pathways in the inflammatory cascade, with analgesia being the primary goal. However, these are attended by limitations in their efficacy and certain safety concerns, including renal toxicity, hypertension, fluid retention, gut-related complications, and cardiovascular events.[2,3]

Proteolytic enzymes, often combined with flavonoids, have been used since decades, in various forms and combinations, to alleviate symptoms and aid physiological recovery in various inflammatory conditions. They have been found to act in a multi-pronged manner due to the mechanisms exhibited by the individual ingredients. These include anti-inflammatory, anti-oedematous, anti-kinin, pro-fibrinolytic, anti-platelet and antioxidant actions.[4]

The present study was conducted at a single centre to evaluate the efficacy and safety of an enzyme-bioflavonoid combination of trypsin-bromelain-rutoside in managing the chronic pain and swelling in patients with various orthopaedic conditions, attending the orthopaedic out-patient department (OPD).

METHODS

Study population and design

We conducted a prospective, observational study, evaluating the efficacy of a commercially available fixed dose combination of trypsin, bromelain and rutoside trihydrate in 100 subjects attending the orthopaedics OPD at Dhadiwal Hospital, Nashik, Maharashtra, India. This study was reviewed and approved by the Shree Institutional Ethics Committee, Nashik, Maharashtra, India (Registration number: ECR/1149/Inst/MH/2018 /RR-21). Subjects were enrolled from September 28, 2021 to November 13, 2021.Written informed consent was obtained from all subjects who were ready to comply with study-required visits. Subjects with orthopedic conditions, accompanied by chronic pain and/or swelling at baseline, and prescribed oral fixed dose combination of trypsin, bromelain and rutoside trihydrate for a minimum period of 8 days were included in the study. 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 are excluded from the study.

Study medication

All enrolled patients were instructed to take Phlogam® (Aksigen Hospital Care Limited, Mumbai) tablets 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] as follows- 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.

Study assessment

Subjects were monitored for safety and efficacy of the study drug till the completion of the study. Pain was graded by the patient using a verbal rating scale - no pain, mild pain, moderate pain, or severe pain, at baseline (pre-dose) and on days 3 and 8. Swelling was graded by the investigator using a verbal rating scale - none (no swelling), mild (swelling confined to the surgery area), moderate (swelling beyond the surgery area), or severe (swelling spreading beyond the surgery area), at baseline (pre-dose) and on days 3 and 8.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. Safety assessments were carried out based on clinical observations, laboratory data at the beginning and at the end of the study and evaluation of the adverse events reported during the study.

Statistical analysis

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.

Ethical approval

This study was reviewed and approved by the Shree Institutional Ethics Committee, Nashik, Maharashtra, India (Registration number: ECR/1149/Inst/MH/2018 /RR-21).

RESULTS

Patients

Hundred subjects were enrolled in the study, out of which 52 were females and 48 were males. The mean age of the patients was 56 years (range 20-79 years). All 100 subjects completed the 8-day observation period, and their data was analysed. Demographic summary and the different conditions treated is tabulated in Table 1; polyarthralgia was the most common condition.

Table 1: Demography of subjects and treated indications.

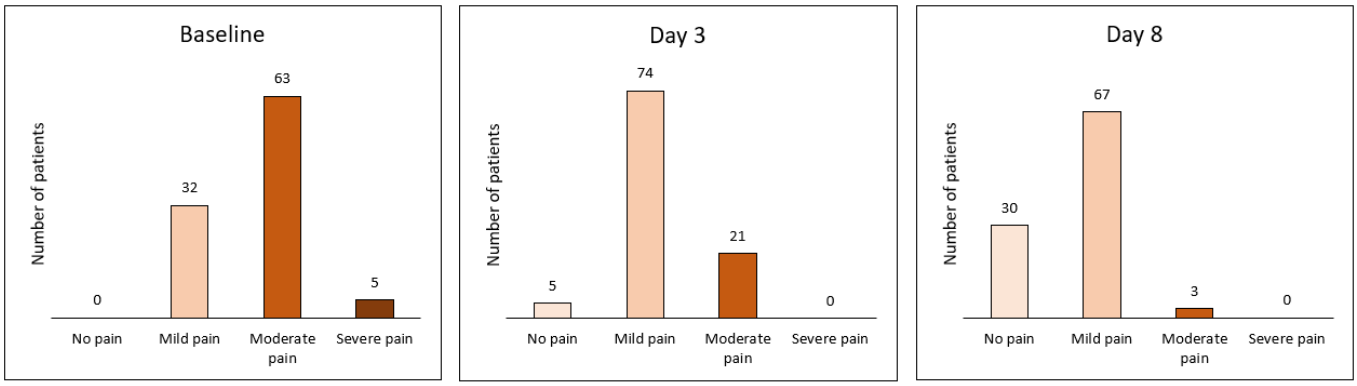
Particular	Value
Age (years) - mean (range)	56 (20-79)
Gender (Male: Female)	48:52
Indications (n)	
Polyarthralgia	35
Osteoarthritis	16
Soft tissue swelling around joints	14
Post fracture pain and swelling	13
Back pain	10
Knee joint pain	9
Other painful conditions	3

Assessment of pain

Out of 100 patients, 68 reported moderate or severe pain at baseline. At day 3, no patient had severe pain, while 21 reported moderate pain; majority (79) reported either mild or moderate pain. At day 8, only 03 patients reported moderate pain, no patient had severe pain, while the remaining 97 reported either mild (67) or no pain (30). The mean scores for pain were 1.73, 1.16, 0.73 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).

Assessment of swelling

Out of the 100 patients, the investigator reported moderate swelling in 74 patients at baseline, while 1 had severe swelling. At day 3, the investigator reported moderate swelling in only 4 patients, while mild swelling was reported in 79 patients and the rest 17 had no welling. At day 8, only 1 patient had moderate swelling, while the remaining 99 had either mild (40) or no swelling (59). The mean scores for swelling were 1.76, 0.87, 0.42 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).

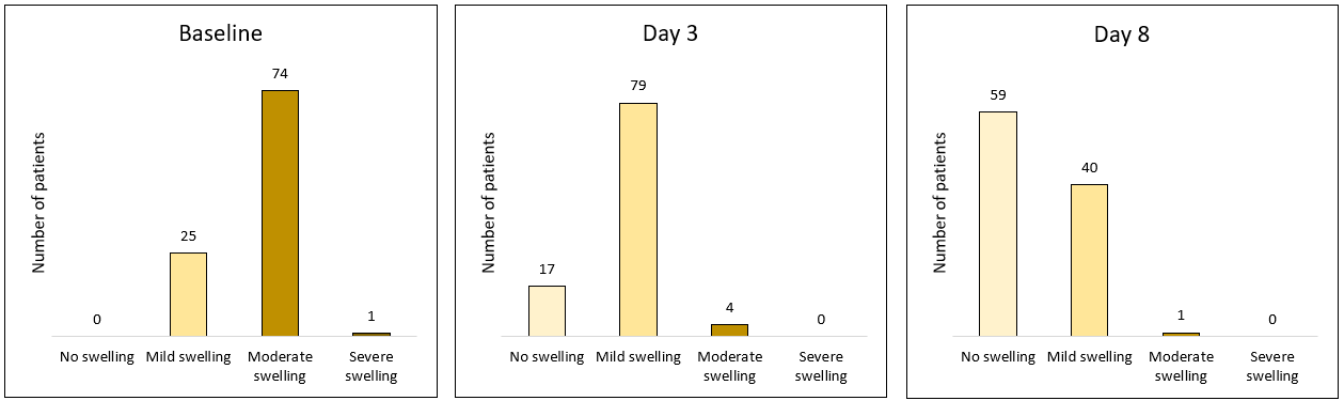


Mean pain score – **1.73**

Mean pain score – **1.16**
paired t test: p<0.0001

Mean pain score – **0.73**
paired t test: p<0.0001

Figure 1: Change in mean pain intensity scores during the study.



Mean swelling score – **1.76**

Mean swelling score – **0.87**
paired t test: p<0.0001

Mean swelling score – **0.42**
paired t test: p<0.0001

Figure 2: Change in mean swelling scores during the study.

Patient-reported global assessment of improvement

At day 3, 72 patients reported good improvement and 16 patients reported very good improvement in pain and swelling. At day 8, 56 patients reported very good/ excellent improvement in pain and swelling; 42 reported good improvement (Figure 3).

Investigator-reported global assessment of improvement

At day 3, the investigator reported good improvement in pain and swelling in 57 patients, and very good-excellent improvement in 37 patients. At day 8, the investigator reported good-excellent improvement in 97 patients (Figure 4).

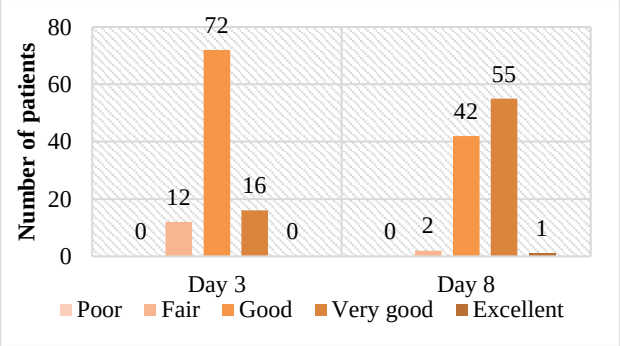


Figure 3: Patient-reported global assessment of improvement in pain and swelling.

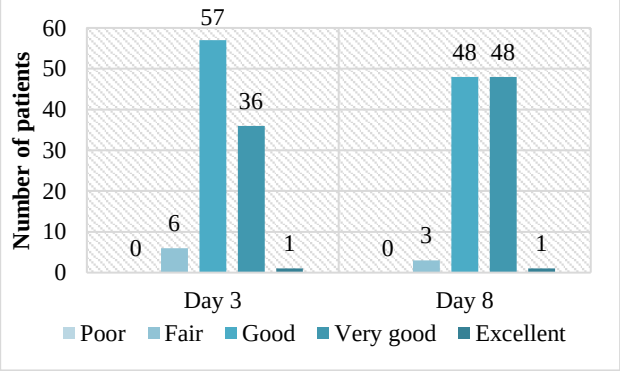


Figure 4: Investigator-reported global assessment of improvement in pain and swelling.

DISCUSSION

In many of the orthopaedic conditions, the aims of treatment are to control pain, minimize joint damage and improve or maintain function and quality of life. The modalities involve medications, non-pharmacologic therapies, physical or occupational therapy, splints or joint assistive aids, patient education and support, weight loss and surgery. Among the medications, the most frequently prescribed class of drugs is NSAIDs, accounting for more than three-fourths of the prescriptions in osteoarthritis. However, they are known to be associated with gastro-intestinal irritation, renal (glomerular perfusion) disturbances and increased risk of serious vascular events.[2] This, along with their limited efficacy in controlling the basic pathology of inflammation and edema, limits their utility in many of the conditions. Also, when used chronically, as is expected in many of the rheumatic conditions, NSAIDs can exacerbate several chronic diseases including heart failure and hypertension and can interact with several other drugs.[3]

Oral enzyme therapy with proteolytic enzymes-flavonoid combinations have been used in traditional medicine for a long time. The therapeutic use of these combinations is empirically based but is also supported by scientific studies. In the last few decades, we have been able to better understand the various pharmacological properties of these combinations with the help of advances in the fields of immunology, biochemistry, and molecular biology. Also, considering the relatively better safety profile of these natural-origin drugs, this therapy provides a very promising alternative to conventional therapies for managing chronic rheumatic conditions.[4]

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 diverse orthopaedic conditions affecting the joints and soft tissues surrounding the joints as early as day 3 of treatment. By day 8, 97% patients had no/mild pain. The improvement was reflected in swelling, with 99% patients reporting no/mild swelling by day 8. The findings of global assessment of improvement reported by patients and investigator were consistent with these results, where both reported good to very good improvement in majority cases.

There are many such studies in literature, wherein enzyme therapy has shown significant clinical benefits in chronic rheumatic conditions like osteoarthritis (OA) and rheumatoid arthritis (RA) with excellent safety profile. These reports span right from the 1960s, when Cohen and Goldman reported in a series of case reports, that bromelain in dosages of 20 or 40 mg for 3-4 times daily up to 13 months, led to positive clinical effects in 28 patients of moderate or severe rheumatoid or OA, without any adverse events.[5] In two other studies involving 19 and 42 RA patients, respectively, enzyme therapy over 12 months led to significant decrease in circulating immune complexes.[6] These findings were further bolstered by a comparative study in 156 patients with RA, in which 6 months of enzyme therapy led to significantly greater reduction in the levels of interferons and cytokines like IL-1β and TNF-α, than with NSAID and methotrexate therapy.[6]

Two randomized blinded studies compared enzyme therapy to diclofenac in a total of 130 patients of knee OA.[7,8] In both these studies, enzyme therapy led to similar reduction in pain and swelling, with one study reporting better reduction in joint tenderness with enzymes compared to diclofenac. An oral enzyme combination was also compared to diclofenac in a study of 50 patients with closed fracture lower end radius. The combination of bacterial proteases, papain, bromelain, vitamin C and rutoside showed better reduction of edema, although pain relief was better with diclofenac. The combination was reported to be safer than diclofenac.[9]

A pooled re-analysis of data from 6 trials in 774 knee OA patients, confirmed these results, but also identified that although enzyme therapy did not lead to laboratory value derangements, diclofenac treatment led to changes in key hepatic enzymes in ~72.6% and red blood parameters in ~86.3% of patients.[10] This is further supported by compiled data from multiple studies that indicate that the enzyme-flavonoid combination is safer than NSAIDs.[6]

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

CONCLUSION

Trypsin-bromelain-rutoside combination treatment led to statistically significant improvement in the mean pain and swelling scores as early as day 3 and further improvement by day 8. The improvement was more notable in the swelling component, where the mean swelling score was reduced by half by day 3 and almost three-fifths of the patients achieved complete resolution of swelling by day 8. This enzyme-flavonoid therapy can, thus, provide a safer alternative in patients with various orthopaedic conditions and reduce 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

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Cite this article as: Dhadiwal RK, Khemnar BM, John J. Oral enzyme therapy using trypsin-bromelain-rutoside combination to counter pain and swelling in orthopaedic conditions: a single-centre experience. Int J Res Orthop 2022;8:532-6.