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A PROSPECTIVE COMPARATIVE STUDY TO EVALUATE EFFICACY, SAFETY AND COST EFFECTIVENESS OF DICLOFENAC AND THEIR COMBINATION WITH VARIOUS PROTEOLYTIC ENZYMES IN ORTHOPAEDIC DEPARTMENT OF TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Objectives: To evaluate efficacy, safety and cost effectiveness of diclofenac, serratiopeptidase and chymotrypsin/trypsin as add on in reducing swelling and pain following upper and lower limb fracture. **Methodology:** This is a prospective, observational study Including 150 patients with upper and lower limb fractures admitted in orthopaedic department of tertiary care teaching hospital. Patients were randomly divided into 3 groups (50 of each), Group-1 tablet diclofenac prescribed, and group-2 tablet serratiopeptidase with diclofenac prescribed and group-3 tablet chymotrypsin/trypsin with diclofenac prescribed. Evaluation of swelling reduction was made by using tape measurement. Pain was assessed by using visual analogue scale at day 0, then daily up to 5 days. Adverse drug reactions were also recorded. **Result:** Reduction of swelling within group was significant (P=<0.0001). Comparison of reduction of swelling in all three groups was statistically not significant ($p > 0.05$). Reduction in pain score in three groups was significant, but decrease was more in group 1. Cost of therapy was more in group 2 and group 3 as compared to group 1. **Conclusion:** Patients in Group 2 and 3 showed more anti-inflammatory effect than of group1. However it is not statistically significant. Diclofenac showed more analgesic effect as compared to proteolytic enzymes. Cost of therapy in group 2 and 3 is more. Mild to moderate adverse effects were reported in group 1 and 2. Most common side effect reported was gastritis, in group1.

KEYWORDS: inflammation in post-op fractures, anti-inflammatory, analgesics drugs, proteolytic enzymes.

INTRODUCTION

Inflammation is a complex reaction to injurious agents such as microbes and damaged usually necrotic cells that consist of vascular responses, migration and activation of leukocytes and systemic reactions. Inflammation characterised by pain and swelling, is a protective reaction of the vascularised tissue to injury as well as necrotic cells and tissues resulting from the injury and to initiate the repair of damage done to the tissues.[1] The inflammatory response is characterized by a transient local vasodilation and increased capillary permeability, infiltration of leukocytes and phagocytic cells, and tissues degeneration and fibrosis.[2]

The two most common conventional treatments for inflammatory disorders are corticosteroids and NSAIDs. NSAIDs are among the most widely used of all therapeutic agents worldwide for their anti-inflammatory and analgesic effect, but their prolonged use often leads to gastric intolerance, peptic ulceration and water and salt retention.[3]

Proteolytic enzymes are with good efficacy, high GI tolerability associated with less adverse effects. In the early 1950s it was discovered that intravenous trypsin could unexpectedly relieve the symptoms of many different inflammatory conditions.[3] Proteolytic enzymes have a role in the reduction of swelling and oedema but extent of effectiveness is unknown[4][5] The use of oral systemic enzyme therapy e.g. serratiopeptidase, bromelain, trypsin and chymotrypsin is another preventive strategy for limiting postoperative swelling.[6]

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. It does not inhibit prostaglandins and is safe to the gastrointestinal system.[4][7] Co-administration of oral systemic enzymes and NSAIDs may produce pronounced anti-inflammatory/anti-edemic effect without side effects but the cost of these preparations is very high[8][9]

Proteolytic enzymes have been used for pain and inflammation usually available as a fixed dose combination with various NSAIDs like diclofenac, aceclofenac, paracetamol. It is also given along with various antimicrobials to increase their tissue penetration by its proteolytic effects. But the cost of these preparations is very high, hence the present study was carried out to evaluate and compare the anti-inflammatory effects, safety and cost of serratiopeptidase, trypsin and chymotrypsin as add on therapy to conventional treatment for post-operative pain and swelling in patients with upper and lower limb fractures.

MATERIAL AND METHODS

This was a one year prospective and observational study included 150 patients with upper and lower limb fractures, aged more than 15 years of either sex, attending department of orthopaedics at P.D.U Government medical college, Rajkot. The study protocol was approved by institutional ethics committee (Human).

Inclusion criteria: Patients with upper limb injury included radius fracture, ulna fracture, elbow fracture and lower end of humerus fracture and lower limb injury included tibia fracture, fibula fracture, knee fracture and lower end of femur fracture patients were included in study.

Exclusion Criteria: patients with upper femur fracture, upper humerus fracture, hip fracture, shoulder fracture, wrist and ankle fracture, patients who were unconscious, patients with multiple fractures and with infected wound. Patients with cardiovascular, renal, hepatic/respiratory disorders, and pregnant and lactating women and patients with active peptic ulcer, bleeding disorders and allergy to NSAIDS were excluded.

A written informed consent was taken from each patient after explaining them about procedure.

Patients were divided into 3 groups. 50 patients enrolled in each group. In group 1 patient received tablet diclofenac sodium 3times orally after meal. In group 2 patients received tablet serratiopeptidase 15 mg with diclofenac sodium 50 mg three times a day orally 1 hour before meal. In group 3 patients received tablet chymoral forte 1, 00,000 IU with diclofenac sodium 50 mg s three times a day per orally, 1 hour before meal. Efficacy of treatment was assessed by measuring the limb volume (swelling) and pain score. Swelling was measured by using tape measurement method [10]. Baseline limb circumference of injured and control limb were measured on day 0 before treatment started, then circumferences of injured limb were measured daily up to 5 days. Patients were asked to lie supine. The tape measure was placed flat on the supporting surface.

In case of leg injury, legs were marked at 4 cm intervals from ankle joint to knee joint and circumferential limb volume was measured. In case of forearm injury, from wrist joint to elbow joint. For lower thigh injury from knee joint to mid-thigh, for lower humerus injury from elbow joint to mid arm. The limb volume of interest were determined by the sum of segment volume(Vs) was measured from two adjacent limb circumference value separated by length L. C1 and C2 was measured circumferences at either ends of the chosen segment of length. Length L=4 cm in every case.

$$Vs= L/12\ \Pi\ (C1^2+C1C2+C2^2) \qquad [1].$$

Pain was assessed by using visual analogue scale which is a 10cm horizontal line stretching from ‘no pain’ (marked 0) to pain as bad as it could be (marked 10) having 1 cm inter-divisions from 0-10 indicating pain intensity.[11] Patients were instructed by investigator to rate their pain intensity on VAS at day 0, then daily up to 5 days.

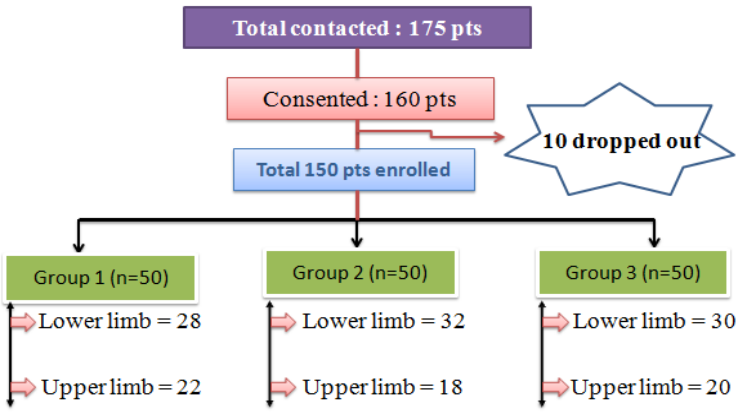
All measurements were made by the same investigator throughout the study. Adverse drug reactions reported by patients were recorded and causality assessment was done according to WHO-UMC scale.

Statistical Analysis

The statistical analysis was performed with Graph pad prism 7 statistical software. Wilcoxon signed rank Test used for nonparametric data to compare reduction of limb volume within group. Kruskal-wallis test used to compare limb volume of all three groups of nonparametric data. Paired t-test and Anova test was used for parametric data to compare swelling volume of within group and between groups respectively.

RESULTS

150 Patients of upper and lower limb fracture were included in the study. Patient’s recruitment was done 50 patients of each group. The average age of subjects in group 1 was 41.26 ± 11.93 years, in group 2 was 40.44 ± 9.70 years and in group 3 was 42.26 ± 12.15 years. A total 175 patients were contacted for the study out of which 160 consented for participation in the study, out of them a total 10 patients were droup-outs.150 patients, 50 in each group completed the study. Out of 50 patients in each group, in group 1 number of patients with lower and upper limb injury was 28 and 22 respectively. In group 2 number of patients with lower and upper limb injury was 32 18 respectively. In group 3 numbers of patients with lower and upper limb injury was 30 and 20 respectively. Minimum limb volume recorded was 374.7 ml with lower end of radius injury subject in group 3. And maximum limb volume recorded was 1781.8 ml with leg injury subject in group 3.



Group 1: Diclofenac sodium, Group 2: Diclofenac sodium + Serratiopeptidase
Group 3: Diclofenac sodium + trypsin, Chymotrypsin

Table 1: Swelling Assessment (ml) in Group 1, Group 2 and Group 3 at day 0 (Before Treatment) and day 5 in Lower Limb.

Drug	Lower limb (volume in ml)				
	Mean of volume at day 0	Mean of volume at day 5	Difference	% Of reduction of swelling	p- value (wilcoxon)
diclo (group-1) n= 28	863.48 ± 304.5	760.57 ± 277.59	102.91 ± 26.91	12.24%	<0.0001
diclo+ Serratiopeptidase (group- 2) n= 32	983.65 ± 176.87	766.23 ± 160.88	217.42 ± 15.99	22.45%	<0.0001
diclo+ chymotrypsin (group- 3) n= 30	1006.61 ± 262.58	804.48 ± 232.54	202.13 ± 30	20.49%	<0.0001

At 5th day of treatment percentage of reduction in volume in patients with lower limb injury was 12.24% in group 1 , 22.45% in group 2 and 20.49% in group 3 (table 1) and in patients with upper limb injury was 14.90% in group 1, 22.97% in group 2 and 22% in group 3 (table 2). Reduction in limb volume in three groups were statistically significant to their pre-treatment levels. Reduction of swelling within group was significant (P=<0.0001). Comparison of reduction of swelling in all three groups was statistically not significant (p > 0.05).

After 5 day of treatment reduction of swelling for lower limb was more in group 2, i.e. 217.42 ± 15.99 ml as compared to group 3, i.e. 202.13 ± 30 ml and group 1, i.e. 102.91 ± 26.91 ml. (table 1). And for upper limb reduction of volume was more in group 2, i.e. 150.89 ± 27.57ml as compared to group 3, i.e. 128.88 ± 32.54 ml and group 1, i.e. 89.54 ± 19.67. But these differences between groups were not statistically significant. (Table 2).

Table 2: Swelling Assessment (ml) in Group 1, Group 2 and Group 3 at day 0 (before treatment) and day 5 in upper limb.

Drug	Upper limb (volume in ml)				
	Mean of volume at day 0	Mean of volume at day 5	Difference	% Of reduction of swelling	p- value (paired t-test)
diclo (group-1) n=22	603.18 ± 146.92	513.64 ± 127.25	89.54 ± 19.67	14.90%	<0.0001
diclo+ Serratiopeptidase (group- 2) n=18	646.82 ± 107.02	495.93 ± 79.45	150.89 ± 27.57	22.97%	<0.0001
diclo+ chymotrypsin (group- 3) n=20	576.29 ± 152.28	447.41 ± 119.74	128.88 ± 32.54	22%	<0.0001

Average reduction of VAS in patients with lower limb injury in group 1 was 2.8, in group 2 was 2.2 and in group 3 was 1.7. Average reduction of VAS in patients with upper limb injury in group 1 was 3, in group 2 was 2.1 and in group 3 was 2.1 (table 3). None of the patients required to be put on another analgesic or any alteration in treatment.

Adverse drug reactions were recorded in form and causality assessment was done. 6 (12%) patients experienced adverse drug reaction in group 1 and 5

(10%) in group 2. All were mild to moderate and did not require any alteration / discontinuation of treatment. The most common side effect was gastritis. 01 (2%) was skin rash, 01 was epigastric pain (2%) and 04 (8%) was gastritis in group 1. 01 (2%) was gastritis, 02 (4%) subjects reported dyspepsia, 02 (4%) subjects nausea and sedation in group 2.

Cost of therapy was calculated. Average cost of therapy of 5 days in group 1 was Rs. 157.23, in group 2 was Rs. 231.10 and in group 3 was Rs. 329.23.

Table 3: Average VAS score in Group 1, Group 2 and Group 3 at day 0 (before treatment) and day 5 in both lower and upper limb.

Drug	Lower limb (average of vas score)			Upper limb (average of vas score)		
	Day 0	Day 5	Difference	Day 0	Day 5	difference
Diclo (group- 1)	6.6	3.8	2.8	6.4	3.4	3
Diclo+ Serratiopeptidase (group- 2)	6.5	4.3	2.2	6	3.9	2.1
Diclo+ Chymotrypsin (group- 3)	6.5	4.8	1.7	6	3.9	2.1

DISCUSSION

Most common cause of upper and lower limb injury was road traffic accident followed by fall down. Injury causes pain and inflammation at the site of injury. Pain is one of the most troubling aspects of inflammation. Diclofenac is cheap and easily available, so most commonly used in clinical practice. Proteolytic enzymes commonly prescribed with NSAIDs with claims more effective and better tolerability. To assess these claims this study was conducted. In the present study efficacy, safety and cost effectiveness of diclofenac sodium, serratiopeptidase and chymotrypsin/ trypsin in reducing swelling and pain in patients with upper and lower limb injury were evaluated.

In this study diclofenac alone was effective in reducing pain and swelling in patients with upper and lower limb injury. Combination of diclofenac and serratiopeptidase and chymotrypsin found also effective, however there was no statistically significant reduction in swelling. So there is no significant difference in the efficacy. Reduction of pain score in three groups was significant, but decrease was more in group 1 than group 2 and group 3. Kamat et al (IJGO 2008) showed that use of diclofenac with serratiopeptidase in episiotomy cases: better efficacy in controlling pain, less need for rescue medication.[12] Mane et al (IJCRR 2011) concluded, Pain was found to be aggravated in some patients when combination of both NSAIDs and serratiopeptidase was prescribed after root canal treatment.[13] In the double blind study, serratiopeptidase was superior to placebo for improvement of breast pain, swelling and induration.[14] Cost of therapy of five days in group 1 was Rs. 157.23 , in group 2 Rs. 231.10 Rs and in group 3 Rs.329.23 Rs. So volume reduction was more seen in group 2 & 3 but statistically not significant and cost of therapy also high in group 2 & 3.

CONCLUSION

In conclusion, Serratiopeptidase and chymotrypsin/ trypsin like proteolytic enzymes showed more anti-inflammatory action than diclofenac alone, however it was not statistically significant and diclofenac showed more analgesic effect as compared to proteolytic enzymes.

Cost of therapy was considerably higher with add on proteolytic enzyme therapy as compared to diclofenac therapy alone.

There is no any significant benefit in ADR profile with add on of proteolytic enzymes.

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