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A Prospective Comparative Study of *serratiopeptidase* and *aceclofenac* in Upper and Lower Limb Soft Tissue Trauma Cases

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Abstract - The aim of this study was to evaluate and compare the efficacy and safety of serratiopeptidase and aceclofenac in reducing swelling and pain following soft tissue injury. This study included 100 patients with soft tissue injury to upper limb, lower limb or both. They were randomly divided into two groups of 50 each to receive serratiopeptidase and aceclofenac. Evaluation of efficacy was made using tape measurement (for swelling), and visual analogue scale (for pain) on day 0, week 1 and week 2. Serratiopeptidase showed significant anti-inflammatory effect and mild analgesic effect. None of the patient was required to be put on another analgesic or any alteration in treatment. Aceclofenac showed superior analgesic effect as compared to serratiopeptidase. Mild to moderate adverse effects were reported. The most common adverse effect reported was dyspepsia. All were mild and did not require any alteration or discontinuation of treatment.

Keywords: *Serratiopeptidase; anti-inflammatory; analgesic; swelling; soft tissue injury.*

I. INTRODUCTION

Inflammation Nature's double edged sword characterised by pain and swelling, is a protective reaction of the vascularised tissue to injury, intended to eliminate the cause of cell injury as well as necrotic cells and tissues resulting from the injury and to initiate the repair of damage done to the tissues [1]. Inflammation can be either acute or chronic. Acute inflammation is characterised by 5 cardinal signs [2]: Rubor (redness), Calor (heat), Tumor (swelling), Dolor (pain), Functio laesa (loss of function). Inflammation is triggered by the release of chemical mediators from injured tissues and migrating cells, which includes: histamine, serotonin [3], bradykinin [4], thromboxane A₂, prostacyclin (PGI₂), prostaglandin E₂, D₂, F₂, leukotrienes B₄, C₄, D₄, E₄ [5], Cytokines-IL-1 and TNF α . Pain is the main reason for visiting the emergency department in more than 50% of cases [6] and is present in 30% of family practice visits [7]. Several epidemiological studies from different countries have reported widely varying prevalence rates for chronic pain, ranging from 12-80% of the population [8]. Pain is defined by International Association for the study of Pain [9] as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Pain is the result of stimulation of peripheral receptors which transmit impulses through pain pathways to the

brain. The two most common conventional treatments for inflammatory disorders are- Corticosteroids and Non Steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are among the most widely used of all therapeutic agents worldwide for their anti-inflammatory and analgesic effect. The mechanism of action is inhibition of prostaglandin synthesis. Aceclofenac is a Non-steroidal anti-inflammatory drug (phenylacetic acid derivative) with preferential COX-2 inhibition. It is metabolised to 4-hydroxyaceclofenac and diclofenac inside inflammatory cells. It inhibits cytokines like interleukin-1 (IL-1), tumor necrosis factor (TNF), and prostaglandin E₂ (PGE₂) production [10]. In the early 1950s it was discovered that intravenous trypsin could unexpectedly relieve the symptoms of many different inflammatory conditions, including rheumatoid arthritis, ulcerative colitis and atypical viral pneumonia [11]. Proteolytic enzymes have a role in the reduction of swelling and edema but the extent of effectiveness is unknown. Serratiopeptidase a proteolytic enzyme derived from non-pathogenic enterobacteria *Serratia* sp E-15 [12] has anti-inflammatory and anti-edemic activity in a number of tissues [13]. Antiinflammatory mechanism involve degradation of inflammatory mediators, suppression of oedema, activation of fibrinolysis, reduction of immune complexes and proteolytic modification of cell-surface adhesion molecules which guide

inflammatory cells to their targets [14]. Analgesic effect is believed to be due to cleavage of bradykinin, a messenger molecule involved in pain signalling [14]. This study evaluated and compared the efficacy and safety of serratiopeptidase and aceclofenac in reducing swelling and pain following soft tissue injury.

II. MATERIAL AND METHODS

This 2 week randomized, prospective, parallel group, controlled and open study included 100 patients with soft tissue injury to upper or lower limb or both, aged 15-60 years, of either sex, attending out patient department of Department of Orthopaedics at M.M.I.M.S.R, Mullana. The study protocol was approved by institutional ethical committee, M.M.I.M.S.R, Mullana, Ambala. Patients with ligament sprains (not requiring any surgical repair), muscle strains and soft tissue contusions, post-traumatic bursitis, tenosynovitis, synovitis or peri-arthritis, due to fall or hit as their mode of injury were included in the study. Patients of fractures along with soft tissue injury, Unconscious patients with multiple fractures, infected wounds, patients requiring any surgical intervention under general or spinal anesthesia, cardiovascular, renal, hepatic, or respiratory disorders, diabetes mellitus, pregnant and lactating women, hyperacidity and active peptic ulcer, bleeding disorders, history of allergy to aspirin, NSAIDs were excluded. X ray of the injured limb was carried out for all the patients.

Patients fulfilling the criteria were randomized according to a computer software (Microsoft excel) generated randomization schedule. Patients were be divided into 2 groups of 50 each. Group 1, patients were given tablet serratiopeptidase 10 mg three times a day per orally, 1 hour before or 2 hours after meals for a period of 2 weeks. In Group 2, patients were given tablet Aceclofenac 100 mg two times a day per orally, after meals, for a period of 2 weeks. A written informed consent was taken from each patient after explaining them about the procedure. Baseline limb circumference of normal and injured limb both was measured on day 0 and then the treatment was started. Limb circumference was measured on subsequent visits at week 1 and week 2 and patients were instructed by investigator to rate their pain intensity on VAS at day 0, week 1 and week 2. For analyses the limb volume (in ml) of the subjects were categorised in those were having swelling less than 200ml, 200 ml – 400 ml, 400 – 600 ml, 600 – 800 ml and more than 800 ml.

Efficacy of treatments was assessed by measuring the limb volume (swelling) and pain score. Swelling was recorded using Tape measurement method [15]. All

circumference measurements were made with a gulick tape. 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. For thigh injury, from knee joint to groin. Arms were similarly measured, 4 cm increments were marked from elbow joint to shoulder joint. In case of forearm, from middle metacarpophalangeal joint to elbow joint and for ankle and foot injury, increments were marked from middle metatarsophalangeal joint to ankle joint. For each of the separations, segment volumes were determined before and after treatment using a Truncated cone model equation [16] Eq. 1. The limb volume of interest were determined by the sum of the segment volumes. Corresponding limb segment volume (V_s) was measured from two adjacent limb circumference values separated by length L . C_1 and C_2 are measured circumferences at either ends of the chosen segment of length L . $L = 4$ cm in every case.

$$V_s = L/12\pi(C_1^2 + C_1C_2 + C_2^2) \quad (1)$$

Pain was assessed using visual analogue scale [17] which is a 10 cm horizontal line stretching from 'no pain' (marked 0) to 'pain as bad as it could be' (marked 10) having 1 cm interdivisions from 0-10 indicating increasing pain intensity. All measurements were made by the same investigator throughout the study. Adverse drug reactions reported by patients during the study were also recorded.

III. STATISTICAL ANALYSIS

Wilcoxon Test was used to compare two dependent groups like the values obtained on the swelling volumes of the subjects in each drug groups for the three consecutive time intervals i.e. before treatment, after 1st week and after 2nd week. Mann – Whitney (MW) test was used to compare two independent groups like the values obtained on the swelling volumes and pain scores of the subjects in two drug groups i.e. Serratiopeptidase and Aceclofenac at three different time intervals i.e. before treatment, after 1st week and after 2nd week. $P < 0.05$ was considered statistically significant. The statistical analysis was performed with the SPSS 16.0 V Statistical Software.

IV. RESULTS

100 patients of soft tissue trauma to upper limb, lower limb or both were randomly distributed to one of the two study groups. The average age of subjects in group 1 was 32.90 ± 12.22 years and in group 2 was 38.98 ± 11.90 years. A total of 118 patients were contacted for the study out of which 113 consented for

participation in the study out of them, a total of 13 patients were drop-outs, and 100 patients, 50 in each group completed the study. Injury due to falling down was most common mode of injury in both the groups, 74% and 70% subjects respectively. Most commonly injured limb was reported to be leg in both the groups, 20% and 22% respectively. Minimum limb volume recorded was 72.12 ml with wrist injury subject in group 2 and Maximum limb volume recorded was 871.9 ml with leg injury subject in group 1. At 1st week, after treatment of 7 days, the percentage decrement in limb volume (ml) was more in subjects in group 1, i.e. 4.6 ± 2.7 % (ml) ($p= 0.0001$) as compared to subjects in group 2, i.e. 3.5 ± 2.4 % (ml) ($p= 0.0001$). (table 1, figure 1). At 2nd week, after treatment of 14 days, the percentage decrement in limb volume (ml) was more in subjects in group 1, i.e. 5.6 ± 4.2 % (ml) ($p= 0.0001$) as compared to subjects in group 2, i.e. 5.1 ± 3.9 % (ml) ($p= 0.0001$). (table 2, figure 2). Reduction in limb volume in two groups was statistically significant at 1st week and 2nd week but decrease in swelling from baseline to 2nd week was more in group 1. In all the patients average pain score was statistically same ($p > 0.05$) in both the groups at baseline.

Reduction in pain score in two groups was statistically significant at 1st week and 2nd week ($p= 0.0001$) but decrease was more in group 2, except in patients with limb volume 600-800 ml where reduction in pain score was statistically not significant ($p > 0.05$) in both the groups (table 3). None of the patients in group 1 required to be put on another analgesic or any alteration in treatment.

07 (14%) patients experienced adverse drug reactions in group 1 and 33 (66%) in group 2; all were mild and did not require any alteration or discontinuation of treatment. The most common was dyspepsia 35 (35%) out of 100 patients. 05 (10%) subjects reported nausea and 01 (2%) subject reported dyspepsia and 01 (2%) subject nausea with dyspepsia in group 1. 16 (32%) subjects reported dyspepsia, 08 (16%) subjects reported dyspepsia with epigastria pain, 05 (10%) subjects reported dyspepsia with gastric irritation and 04 (8%) subjects reported dyspepsia with gastric irritation and epigastria pain. All 33 subjects complained of dyspepsia in group 2.

Table 1:Swelling Assessment (ml) of Subjects in Group 1 and Group 2 at 1st week and before Treatment

Study groups	Before Treatment	1 st week Treatment	Arithmetic Difference	Percentage Difference	p – value (Wilcoxon)
Group1	264.86 ± 188.39	252.78 ± 183.22	-(12.07 ± 5.16)	-(4.6 ± 2.7)	0.0001
Group2	312.71 ± 194.23	301.65 ± 189.51	-(11.05 ± 4.71)	-(3.5 ± 2.4)	0.0001
p – value (MW)	0.129	0.121			

Table 2:Swelling Assessment (ml) of Subjects in Group 1 and Group 2 at 2nd week of Treatment and before treatment

Study groups	2 nd Treatment week	Before Treatment	Arithmetic Difference	Percentage Difference	p – value (Wilcoxon)
Group1	250.02 ± 180.41	264.86 ± 188.39	-(14.84 ± 7.97)	-(5.6 ± 4.2)	0.0001
Group2	296.66 ± 186.65	312.71 ± 194.23	-(16.04 ± 7.56)	-(5.1 ± 3.9)	0.0001
p – value (MW)	0.139	0.129			

Table 3: Average VAS Score in Group 1 and Group 2 at 1st week, 2nd week and before treatment

Limb volume (ml)	Average VAS Score			
		Before	1 st week	2 nd week
less Than 200 ml	Group 1	5.74	2.81	1.55
	Group 2	5.41	0.95	0.09
	p – value (MW)	0.467	0.0001	0.0001
200 – 400 ml	Group 1	5.63	2.38	1.62
	Group 2	5.50	0.30	0.0
	p – value (MW)	0.856	0.0001	0.0001
400 – 600 ml	Group 1	6.75	3.50	2.25
	Group 2	6.64	2.07	0.36
	p – value (MW)	0.944	0.52	0.0001
600 – 800 ml	Group 1	6.00	4.50	1.50
	Group 2	6.75	2.00	0.50
	p – value (MW)	0.800	0.267	0.533

DISCUSSION

A Soft tissue injury (STI) is the damage of muscles, ligaments and tendons throughout the body. Common soft tissue injuries usually occur from a sprain, strain, a one off blow resulting in contusion or overuse of a particular part of the body. Soft tissue injuries can result in pain, swelling, bruising and loss of function [18]. These injuries are very common in sport but also occur in road traffic accidents and in the accidents of everyday life, including at work.

In the present study efficacy and safety of serratiopeptidase and aceclofenac were evaluated and compared on swelling and pain in patients with soft tissue trauma.

In this study, serratiopeptidase was found to cause significant reduction in swelling (limb volume). The decrease in swelling observed at 1st week and 2nd week from baseline was more as compared to decrease observed by aceclofenac and was statistically significant. Serratiopeptidase was also found to have mild analgesic effect. Similar observations have been made on serratiopeptidase by Aso et al [19] in 1981 on 70 patients of fibrocystic breast disease and concluded serratiopeptidase to be superior to placebo for breast pain, swelling and induration. Another trial by Tachibana M et al [20] in 1984 also concludes the efficacy of serratiopeptidase as anti-inflammatory enzyme. Esch et al [21] conducted a double blind study to determine the effect of serratiopeptidase on postoperative swelling and pain in 66 patients who were

treated for rupture of knee ligament. The patients were given serratiopeptidase and showed 50% reduction in swelling and became pain free more rapidly compared with controls. In a double blind study, serratiopeptidase was superior to placebo for improvement of breast pain, swelling and induration [22]. The effect of serratiopeptidase an anti-inflammatory, anti-oedemic, fibrinolytic and in pain relief has been described by Mazzone A et al [23] in 1990.

In animal studies also efficacy of serratiopeptidase as an anti-inflammatory have been described [24]. Another animal study showed that serratiopeptidase is orally effective and possesses anti-inflammatory activity, which is nearly equivalent to diclofenac sodium in both acute and chronic phases of inflammation [25].

Aceclofenac was found to have superior analgesic effect than serratiopeptidase in the present study. Our findings are in conformity with study conducted by Dooley M et al [26]. in 2001 who showed aceclofenac to be an effective agent in the management of pain. Other studies also concludes the analgesic efficacy of aceclofenac [27].

Figure 1: Box Plot Comparison of limb Volume (in ml) in Group 1 and Group 2 at 1st week of Treatment

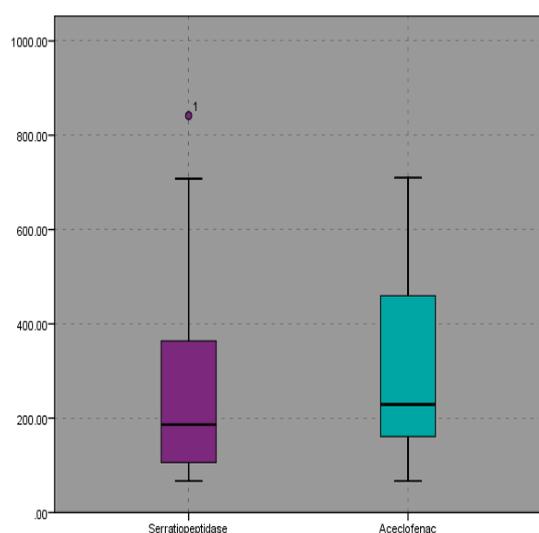
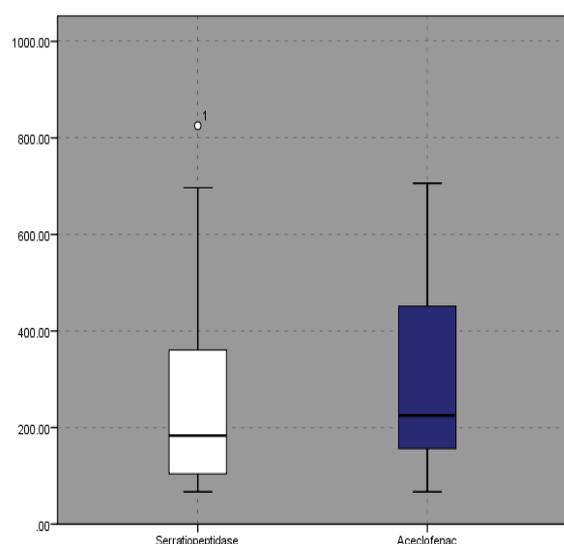


Figure 2: Box Plot Comparison of limb Volume (in ml) in Group 1 and Group 2 at 2nd week of Treatment



CONCLUSION

In the present study serratiopeptidase showed significant anti-inflammatory effect and mild analgesic effect. None of the patient was required to be put on another analgesic or any alteration in treatment. Aceclofenac showed superior analgesic effect as compared to serratiopeptidase. Mild to moderate adverse effects were reported. The most common adverse effect reported was dyspepsia. All were mild and did not require any alteration or discontinuation of treatment.

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