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A comparative study to assess the efficacy, safety cost of Serratiopeptidase in humans

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Abstract
Aim: Study was undertaken to compare the anti-inflammatory effects of Serratiopeptidase (10mg) in Combination with one of the most frequently prescribed NSAIDs diclofenac sodium with diclofenac sodium alone in patients with mild to moderate osteoarthritis of knee and surgical postoperative patients were allocated into 3 groups that were compared with each other.
Material and Method: One of the group received serratiopeptidase and diclofenac the 2nd group received Diclofenac only patients and the 3rd group did not receive any medication. The study enrolled 60 patients with confirmed osteoarthritis of knee and 60 surgical post operative patients. A total of 120 patients. Efficacy parameters consisted of WOMAC scores and VAS score for osteoarthritis patients and for Surgery patients it was ASEPSIS scores and VAS scores. They were evaluated on day 0 (before the start of treatment) and day 7 (after the treatment) in Osteoarthritic patient. In surgical postoperative patients it was evaluated on day 0 and day 7 post operatively.
Results: In osteoarthritis patients there was a considerable decrease in WOMAC scores and VAS scores in both groups at the end of 1 week. The decrease in WOMAC scores in Experimental group (Serratiopeptidase + Diclofenac) were comparatively more than the control group (Diclofenac). But was not found statistically significant. In Surgery patients there was a significant decrease in the Asepsis scores and VAS scores in all 3 groups. The decrease in VAS scores were comparatively more in Experimental group and control group when individually compared with No Medication group and was found to be statistically significant. Decrease in VAS scores were comparatively more in control group than in experimental group but was not statistically significant. This showed that healing of the wound was same in all 3 groups while analgesic activity was more in Experimental and control group as compared to No medication group.
Conclusion: It is strongly recommended that only non-steroidal anti-inflammatory drugs should be prescribed for inflammatory conditions till the efficacy of drugs like s serratiopeptidase is proved by large scale, double blind multi-centric, randomised controlled trial.

Keywords: Anti-inflammatory, Serratiopeptidase

Introduction
Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids are the commonly used class of drugs for the treatment of inflammation. The suppression of inflammation with glucocorticoids is of enormous clinical utility and has made these drugs among commonly prescribed agents. In addition there are many drugs which are marketed without clear scientific evidence of efficacy.
Serratiopeptidase is a proteolytic enzyme obtained from non pathogenic bacteria Serratia E15 species belonging to enterobactericeae family. It is produced in the intestines of silk worms to break down cocoon walls. Structurally it is an endopeptidase having high molecular weight [1, 2]. Not enough pharmacokinetic data of Serratiopeptidase in human beings is available. Serratiopeptidase is often co-prescribed with NSAIDs and various combinations are also available in the market [3]. Serratiopeptidase drug has been prescribed widely but substantial evidence regarding its efficacy is not available. The writing overview demonstrates that there is scarcity of data in regards to adequacy of Serratiopeptidase and its collaboration with NSAID's
In our hospital set up Serratiopeptidase is prescribed along with NSAIDs for the treatment of variety of inflammatory conditions. Diclofenac Sodium is one of the most commonly prescribed drug for relieving inflammation in osteoarthritis and post operatively for management of surgical wound. As debates about the job of proteolytic proteins like Serratiopeptidase on aggravation despite everything exist, the current investigation was attempted to test mitigating action of this compound.
Therefore a study of comparison of anti-inflammatory effects of Diclofenac sodium with and

without Serratiopeptidase was carried out in symptomatic osteoarthritis patients and post operative patients.

Materials and Methods

This study was conducted in a tertiary care centre in Krishna Institute of Medical Sciences Karad. An open labelled, comparative prospective, interventional study involving 120 human patients. 60 patients suffering from mild to moderate osteoarthritis of knee attending Orthopaedics O.P.D which were clinically confirmed and 60 I.P.D post-operative patients with clean wounds from surgery ward were enrolled into the Study. Institutional Ethic's Committee approval was taken prior to the initiation of the Study. The voluntary written informed consent was taken from each patient before his/her entry into the study.

Source of recruitment

After fulfilling inclusion criteria, patients recruited for the study were randomly assigned in 1:1 fashion to either of the two treatment groups consisting of 30 patients each in orthopaedic patients. Control (Group A) was prescribed Diclofenac sodium tablets 50 mg (Voveran)1 tab b.i.d. for 1 week and Experimental (Group B) with Diclofenac Sodium 50mg (1 tab b.i.d. for 1 week) + Serratiopeptidase 10mg. (Bidanzen) [1 tab t.d.s. for 1week]

Similarly after fulfilling the inclusion criteria, post operative patients admitted to the surgical ward were chosen and enrolled into three groups randomly. Control (Group A) Diclofenac sodium tablets 50 mg. (Voveran) 1 tab b.i.d. for 1 week. Experimental (group B)Diclofenac sodium 50 mg 1 tab b.i.d for 1 week +Serratiopeptidase 10 mg.(Bidanzen)[1 tab t.d.s. for 1week] and Medication (Group C)Without any anti-inflammatory or analgesic drugs.

Efficacy Parameters

Severity of pain was measured on visual analogue scale (0-10) scale. [78, 79] measurements were repeated after 7 days during the time of follow up in osteoarthritis patients and patients with post operative surgical wound after the initiation of the treatment.

The WOMAC OA index (Western Ontario and McMasters Universities Osteoarthritis Index) is divided into 3 dimensions pain, stiffness and level of difficulty during different daily activities (80). Each dimension has several subdimensions and each one is graded according to Likert scale. [81] In WOMAC's index, score of each item of pain at week 0 was added to find out total pain score at week 0 and week1 for each patient, similarly total stiffness score and total level of difficulty score at week 0 and week 1 were found out for each patient.

The total pain score, total stiffness score and total level of difficulty score were added to find out total womac score at the end of 0 and 1 week for each patient.Means of total scores for pain, stiffness and level of difficulty were calculated for each group at 0 and end of 1 week These mean symptom scores were used to compare the efficacy of medication.

Asepsis score

The reduction in post operative pain after both the treatment patterns were measured with the help of VAS score at 0 week and 1 week. Similarly healing of the post operative wound of each patient was measured by Asepsis wound score at 0 and 1week [82]

Safety and tolerability

The safety and tolerability of drug treatment were assessed by monitoring of the adverse events. Every adverse event encountered during the drug therapy was recorded in the case record form during each follow up of 1 week.

Results

Orthopaedic patients

The difference in the scores in 0 week and 1 week were calculated in both groups and their respective means were calculated. The means of both the groups were compared by using unpaired t test. The mean of the difference in scores for pain in the experimental group is comparatively greater than the scores for control group but this difference is not statistically significant (P=0.39). Similarly there was no significant difference in mean scores in stiffness in 2 groups (P=0.263). The scores for level of difficulty in two groups were also not statistically significant (P=1.08).

Surgery Patient

Table 1 Shows the comparison of mean of the difference in Asepsis and VAS scores in all three groups. It was observed that there was a significant decrease in the Asepsis scores in all three groups in a span of 1 week as mentioned in the above tables. The mean of difference in scores in the experimental group was found to 3.1 as compared to 2.8 in control group and 2.1 in the no medication group. After application of ANOVA it was found there was no statistically significant difference in all three groups with a P value of 0.056.

Table 1: Comparison of mean of the difference in asepsis and VAS Scores in all three groups

	Control Group ± S.D	Experimental group ± S.D	No Medication ± S.D	P value
Difference in Asepsis Score	2.8 ± 1.59	3.1 ± 1.29	2.1 ± 1.07	0.056
Difference in VAS score	3.7 ± 1.55	3.5 ± 1.39	2.4 ± 0.88	0.0055

It was observed that there was a significant decrease in VAS in all three different groups in a span of 1 week as shown in the above tables. The mean of the difference in VAS scores in the experimental group was found to be 3.5 as compared to 3.7 in the control group and 2.4 in the no medication group. On application of ANOVA for calculation of the statistical significance it was seen that the difference in values were statistically significant with a P value of 0.0055.Comparison of individual pairs showed that there was no significant difference Experimental and control groups while the difference in scores of Experimental and no medication groups was statistically significant and difference in scores of Control and no medication group was statistically significant.

Adverse effects

Patients enrolled in the study were instructed to inform or report the occurrence of adverse effects as soon as possible, it was found that patients tolerated Serratiopeptidase very well and a very few adverse effects were reported by the patients. During the entire course of the study it was found out that there was no serious adverse events that were reported and required stoppage of medication.

Discussion

The present study was aimed to evaluate the efficacy of serratiopeptidase, an oral proteolytic enzyme obtained from a non pathogenic bacteria Serratia E15 [1] in controlling the inflammation associated with knee osteoarthritis and post operative patients. We compared the antiinflammatory effects of combination of diclofenac and serratiopeptidase with that of diclofenac only in the above mentioned patients.

Technique for dealing with the clinical indications in the above arrangement of patients is planned for meddling with provocative procedure to restrain the force and abbreviate the length of clinical indications of irritation. Numerous non-steroidal anti inflammatory drugs have been used to reduce inflammation by inhibiting prostaglandin synthesis [4]. Enzymes like chymotrypsin, serratiopeptidase have been used to reduce inflammation with conflicting results. In this study to improve the gastrointestinal tolerability of the patients dose of diclofenac was reduced from 150 mg to 100mg/day [5].

The efficacy of treatment in orthopaedic patients were assessed by observing the improvement in the symptom scores in pain, stiffness, level of difficulty in various daily activities by using WOMAC osteoarthritis index and overall intensity of pain by using visual analogue scale Score. Similarly the efficacy parameters in surgery patients were Asepsis score and VAS score. Our study failed to elicit out the antiinflammatory effects of serratiopeptidase in patients with mild to moderate painful osteoarthritis and surgical post operative patients.

In our study in osteoarthritis patients, there was a significant percentage of reduction in VAS score and WOMAC score both in patients receiving diclofenac as well as diclofenac and serratiopeptidase. When reduction in the WOMAC score were compared in both the groups there was no much significant difference, in both treatment groups thereby showing a similar efficacy, same was the case with VAS scores.

In surgical post operative patients there was a significant reduction in postoperative pain measured by VAS scores and similarly significant reduction in Asepsis scores was found in all three groups of patients receiving diclofenac and diclofenac plus serratiopeptidase and No medication group. When the reduction in Asepsis scores were compared in all 3 groups there was no such significant difference at the end of one week. The reduction in Asepsis scores were slightly greater in experimental group but it was not statistically significant while comparing it with rest of the groups. This showed that the post operative wounds healed even without administration of antiinflammatory agents and Serratiopeptidase did not add to the anti inflammatory activity of Diclofenac.

Our study failed to detect the antiinflammatory effect of Serratiopeptidase. Similarly a study conducted in Lady Hardinge Medical college New Delhi where in relative efficacy of various analgesic and antiinflammatory were tested, failed to show significant analgesic or antiinflammtory effects of serratiopeptidase [6]. Most likely findings could be questionable absorption of Serratiopeptidase from gastrointestinal tract. As serratiopeptidase, structurally is a polypeptide chain, its absorption from the gastrointestinal tract in an intact form is doubtful. Also Serratiopeptidase is having high molecular weight, presuming that these preparations do have some action, there seems to be no plausible explanation for the mechanism of their transport across intact gut mucosa. Regardless of whether these proteins get away from the attack of stomach related juices in the stomach and the small digestive system, the vehicle instrument for these long anchors amino acids require to be stalled before they are moved to the circulation system. The doubt that why this enzyme being a foreign protein is not fixed by the immune system remains unanswered another important point is that very meagre pharmacokinetic data is available regarding Serratiopeptidase. Its status of use in pregnant and lactating females is unknown.

The short coming of studies that were published in various journals advocating the efficacy of serratiopeptidase are as follows. The sponsorship issues from the companies are not made clear in this studies. Study by Panagaria A, reported that serratiopeptidase therapy may prove to be useful alternative mode of conservative treatment in patients with carpel tunnel syndrome. This study included a small sample of just 20 patients with placebo as the control treatment. Also this study gave serratiopeptidase to patients along with another anti-inflammatory agent –nimesulides [7].

Esch PM, (1989) closed from their examination that serratiopeptidase has all the earmarks of being a successful groundwork for the post-employable decrease of upper lower leg joint expanding in correlation with old style moderate estimates like utilization of ice This study showed just 50% reduction in swelling in patients receiving Serratiopeptidase on the 3rd postoperative day, which would have been reduced naturally without any intervention. As well as the test substance was not compared with NSAIDs [8]. In Our study we also observed a decrease in inflammation and pain in No Medication group of the post operative patients.

The limitations of the study should be considered. It was an open label study because of non feasibility and financial restrictions. For greater evidence a double blind study has to be conducted. It was a mono-centric study a bias might be induced as different geographical locations might influence the pathophysiology of the disease process differently. In this study the drug serratiopeptidase did not cause any side effects separately, even some other studies investigating the systemic use of serratiopeptidase demonstrated no adverse effects for the same drug.(9) To increase G.I tolerability the dose of the diclofenac was reduced to b.i.d. daily.

An average cost of a serratiopeptidase tablet is Rs. 6.51 which is much greater than an average cost of NSAID like Diclofenac which is Rs.1.43. Thus a useless addition of serratiopeptidase to the treatment increases the cost of the treatment by 5.5 times approximately for a week. Non steroidal calming drugs are the built up class of medications for the treatment of aggravation which are less expensive and savvy. The present study failed to ellicit out the anti-inflammatory effects of the enzyme in the described clinical set up. Therefore addition of such a costlier drug Serratiopeptidase to treatment of inflammation, adds to the economic burden of the poor population without any apparent clinical benefit. Also it adds to the healthcare cost to the society when such expensive drugs with doubtful efficacy are prescribed over cheaper drugs with proven efficacy. We therefore feel that this drug is not at all cost effective.

Experts of the advanced medication do once in a while utilize elective cures with method of reasoning that they appear to have some activity and do no damage, as for this situation of Serratiopeptidase. There is by all accounts more observation than science here and it likewise needs notice that these medications are costly and the majority of the conditions where the medication is utilized are self restricting. It is also a worrying fact that the giant multinational manufacturers target these products towards countries like India where evidence based practise yet to catch on. The fact supporting this statement is that this drug is not marketed in countries like US

and UK [10].

Professionals of medicine should be more careful while administering serratiopeptidase to the patient. Not only it is unethical to subject the patient to unaffordable and costlier treatment when cheaper and established treatment alternatives is available, but also breaches the chain of scientific principles by prescribing a drug not approved for specific condition. The cost of the medicine can be heavy burden for the patients with limited economic resources and health care providers should be very sensitive about this fact. It is advisable to prescribe NSAIDs which are of proven efficacy and cheaper.

This study failed to show the significantly improved outcome of the serratiopeptidase as an anti-inflammatory agent. Still this study can be an important guide for those who are planning a similar study. It is recommended that a further stratified, double blinded, multi-centric well controlled study of serratiopeptidase should be considered in the future to evaluate its anti-inflammtory effect.

Conclusion

In osteoarthritis patients there was a considerable decrease in WOMAC scores and VAS scores in both groups at the end of 1 week. The decrease in WOMAC scores in Experimental group (Serratiopeptidase + Diclofenac) were comparatively more than the control group (Diclofenac). But was not found statistically significant. In Surgery patients there was a significant decrease in the Asepsis scores and VAS scores in all 3 groups. The difference in Asepsis scores at the end of 1 week were not statistically significant when compared among 3 groups. While the decrease in VAS scores were comparatively more in Experimental group and control group when individually compared with No Medication group and was found to be statistically significant. Decrease in VAS scores were comparatively more in control group than in experimental group but was not statistically significant. This showed that healing of the wound was same in all 3 groups while analgesic activity was more in Experimental and control group as compared to No medication group. Serratiopeptidase was well tolerated by the patients. As add on therapy, in the treatment of inflammation was 5.5 times costlier than diclofenac sodium alone without any apparent clinical benefit. It is strongly recommended that only non-steroidal anti-inflammatory drugs should be prescribed for inflammatory conditions till the efficacy of drugs like s serratiopeptidase is proved by large scale, double blind multi-centric, randomised controlled trial.

Conflict of Interest: No Conflict of interest

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