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Original Research Article

Proteases and tissue repair: peri operative role of chymotrypsin: trypsin in surgical patients

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ABSTRACT

Background: Proteolytic enzymes have been used to facilitate tissue repair ever since ancient times. Trypsin: Chymotrypsin, proteolytic enzyme oral preparation which has been in clinical use ever since 1960s, provides a better resolution of inflammatory symptoms and promotes speedier recovery of acute tissue injury by minimising the fibrinolytic shut down. This paper revisits the role and clinical utility of chymotrypsin: trypsin oral combination in tissue repair, in surgical patients. The aim of the present study was to determine the efficacy of chymotrypsin n trypsin in reducing post-operative oedema and haematoma formation and its role in surgical prophylaxis and scar formation.
Methods: A prospective study was done on 50 electively posted surgical patients during a period of 6months comparing placebo with chymotrypsin and trypsin oral combination.
Results: Statistically significant reduction in post-operative oedema, seroma and haematoma formation and reduction in pain and incidence of suture site infection, better cosmetic appearance of the scar and decline in need for secondary suturing was noted.
Conclusions: From the current study, it is thus concluded that trypsin: chymotrypsin prophylaxis pre-operatively and post-operative treatment in surgical patients hastens the healing process and significantly reduces the recovery time.

Keywords: Chymoral forte, Chymotrypsin: trypsin, Proteases

INTRODUCTION

This study is an attempt to understand the physiological factors responsible for inflammation and consequent oedema formation, and the beneficial effects of chymoral forte DS. During wound healing, the formation and remodeling of the extracellular matrix involves a series of events that occur in a sequential fashion.[1] The clot formed during the process of healing is composed mainly of fibronectin and fibrin.[2] Later on plasmin, breaks down the fibrin barrier to restore circulation. As a response to trauma the liver releases acute-phase proteins such as alpha 1 antitrypsin and alpha 2-macroglobulin which bind to plasmin and hence fibrinolysis is shut down. Trypsin: chymotrypsin combination minimizes fibrinolytic shut down and the severity of the inflammatory phase could be reduced.[3]

Indications

- Resolves oedema post operatively and modulates inflammation associated with various conditions including accidental and surgical trauma.[4]
- Inflammation of a vein associated with thrombus, Thrombophlebitis
- Gynaecological surgery such as vasectomies and caesarean post operatively.
- In dentistry specially for tooth extraction, periapical abscess and maxillofacial surgery.[5]

- Implement in bronchitis for the reduction in viscosity of mucus and sputum.[6]
- Fractures and dislocation, sprains and strains.[7]
- In ocular trauma such as macular oedema, black eye, hyphema, uveal tract inflammation, subconjunctival hemorrhage, extra-ocular trauma.[8]
- In ENT such as nasal fractures, para pharyngeal abscess.[8]
- Conjunction with conventional therapy in treatment of patients with cancer of breast, lungs, head etc.

Contraindications

In patients with kidney/liver impairment, peptic ulcer disease, high vitreous pressure and in patients presenting with hypersensitivity reactions to the drug.

METHODS

A total of 50 electively posted surgical patients were selected. The patients were grouped into two categories: group I (n = 25) were given placebo in place of trypsin: chymotrypsin preparation, categorized as the control group/placebo group ; group II (n = 25) patients were treated with oral preparation of trypsin:chymotrypsin in the ratio of 6:1 with an enzymatic activity of 200,000 A.U./tablet (tab. chymoral forte). These patients received 1 tablet of chymoral forte 3 times a day × 5-10 days post operatively and 3 days prior to surgery. The presence of oedema, seroma, haematoma and suture site infection were measured on day 2,3,5,7 and 10. Also, recovery time required for the patient was evaluated.

Only clean and electively posted surgical cases were selected and patients with significant co morbidities like uncontrolled diabetes mellitus, hypertension etc. were eliminated from our study. The mean average age group of individuals taken in both the groups ranged from 20-40years. Routine blood investigations like complete blood picture, urine routine and microscopy, renal functional tests, liver function tests, ECG, chest X ray was done to all the patients from both the groups prior to surgery. Patients with all the investigations with in normal limits and a baseline hemoglobin of greater than or equal to 10 were included in the present study. Intra operatively a single shot of third generation cephalosporins antibiotic, cefotaxime 1gm intravenously has been administered to all the patients from both the groups at the time of induction during anaesthesia. Post operatively a uniform antibiotic coverage of cefotaxime 200mg in tablet form (oral preparation) over a period 5 days was given to individuals of both placebo group and chymoral forte treated group.

Exclusion criteria

- Emergency cases,
- Clean contaminated cases,
- Amputations and debridements.

RESULTS

Post-operative oedema

Post-operative oedema in placebo group was noted in 64% of individuals on day 2 whereas patients treated with chymoral forte 3 days prior to surgery, oedema was noted in only 24%. On day 3, oedema in placebo group persisted in 64% patients, however in patients treated with trypsin:chymotrypsin combination, oedema subsided to 20%. By day 5 oedema was noted in 52% patients in group 1 and 12% in group 2 patients. By day 7 no oedema was noted in chymotrypsin trypsin treated group whereas oedema continued to persist in 32% and 28% of patients in placebo group even on day 7 and day 10 respectively (Table 1).

Serous discharge

Post operatively, serous discharge was noted in 52% of control group where in group 2, that is patients treated with oral preparation of trypsin:chymotrypsin combination, discharge was seen in only 16% patients. On day 3 an increase in post-operative discharge was noted in group 1 from 52% to 60%. Similar trend was noted in group 2 where serous discharge was noted in 24% of patients. Consequently, in 44% of patients from group 1 discharge persisted, where as in group 2, in 12% of patients' serous discharge from incision site was noted. By day 7 serous discharge was noted in 16% of patients from group 1, whereas discharge from wound site completely subsided in trypsin:chymotrypsin treated group. However, even on day 10 serous discharge continued to persist in 8% of patients from control group.

Haematoma formation

In 24% of patients from placebo group, post-operative haematoma was noted on day 2, in comparison to trypsin: chymotrypsin treated group, where haematoma was noted in only 12% of patients. By day 3 in 20% from placebo treated group haematoma persisted and 8% from group 2. Furthermore, haematoma was seen in 4% of patients from placebo treated group and none from patients in chymotrypsin trypsin group by day 5.

Suture site infection

Onset of suture site infection was noted from day 3 in both group 1 and group 2 patients, which consisted of 12% of patients from placebo treated group and 8% of patients from oral trypsin:chymotrypsin treated group. With similar antibiotic coverage for both the groups, 20% of patients from group 1 and 8% of patients from group 2, incision site infection in the form of purulent discharge persisted on day 5. Even with adequate antibiotic coverage and drainage, pus discharge from incision site was noted in 20% of patients from placebo group, however the percentage declined to 8% in trypsin:chymotrypsin treated group. By day 10 suture site

infection completely resolved in group 2 patients in comparison to 8% of patients from placebo treated group, where suture site infection persisted.

Recovery time

Overall recovery time of less than 1 week was noted in 17 out of 25 patients in placebo treated group and 20 out of 25 patients from oral preparation of trypsin chymotrypsin treated group. Delayed recovery (i.e., >1week) was noted in 8 out of 25 patients from group 1 and 5 from 25 patients of group 2.

Analysis of the data

Statistically significant improvement was noted in chymotrypsin:trypsin group (II) compared to the placebo group where post operatively oedema was noted in only 24% of patients in group II and in 64% of patients in group I on day 2.

Table 1: Post-operative oedema in individuals treated with placebo (group 1) and with chymotrypsin:trypsin oral preparation group 2.

Post OP day	Day 2		Day 3		Day 5		Day 7		Day 10	
(n=25)	No.	%	No.	%	No.	%	No.	%	No.	%
Group I	16	64	16	64	13	52	8	32	7	28
Group II	6	24	5	20	3	12	3	12	-	-

Table 2: Post-operative serous discharge in individuals treated with placebo (group 1) and with chymotrypsin:trypsin oral preparation.

Post OP day	Day 2		Day 3		Day 5		Day 7		Day 10	
(n=25)	No.	%	No.	%	No.	%	No.	%	No.	%
Group I	13	52	15	60	11	44	4	16	2	8
Group II	4	16	6	24	3	12	1	4	-	-

Table 3: Haematoma formation.

Post OP day	Day 2		Day 3		Day 5		Day 7		Day 10	
(n=25)	No.	%	No.	%	No.	%	No.	%	No.	%
Group I	6	24	5	20	1	4	-	-	-	-
Group II	3	12	2	8	-	-	-	-	-	-

Table 4: Suture site infection.

Post OP day	Day 2		Day 3		Day 5		Day 7		Day 10	
(n=25)	No.	%	No.	%	No.	%	No.	%	No.	%
Group I	-	-	3	12	5	20	5	20	2	8
Group II	-	-	2	8	2	8	1	4	-	-

Table 5: Recovery time.

(n=25)	Recovery time <1week	Recovery time >1week
Group I	17	8
Group II	20	5

Oedema totally subsided by day 10 in group II where in 28% of patients from group I oedema persisted. 60% of patients from group I showed serous discharge by day3 in comparison with 24% of patients from group II. Presence of haematoma was noted in 12% on patients from group II where as 24% of control group demonstrated haematoma on day2 post operatively.

However, the incidence of suture site infection for both the placebo group (24%) and the chymotrypsin: trypsin group (12%) was lower without any significant difference. Recovery time was less than 1week in 80% of patients in chymotrypsin:trypsin group and 68% of placebo group.

DISCUSSION

Following an acute injury, there is a sharp rise in the levels of the protease inhibitors α1-antitrypsin and α2-macroglobulin. These acute phase reactants inhibit several proteolytic enzymes, which if uncontrolled can lead to unregulated inflammation and impair healing. The

order of affinity of α1-antitrypsin with proteolytic enzymes is as follows: elastase>chymotrypsin>cathepsin G>trypsin>plasmin.[9,10] Similarly, α2-macroglobulin shows greatest affinity with cathepsin G. At this point, it must be reiterated that plasmin causes fibrinolysis and its inhibition prevents fibrinolysis. Therefore, a steep rise in α1-antitrypsin and α2-macroglobulin following acute injury leads to a period of fibrinolytic shutdown, with consequent maintenance of inflammatory response and oedema and delay in repair.[11] Oral combination of trypsin:chymotrypsin targets this early stage of inflammation. Since α1-antitrypsin shows greater affinity for trypsin and chymotrypsin compared to plasmin, oral supplementation of the enzyme complex ensures that plasmin remains available for fibrinolysis and the period of fibrinolytic shutdown is shortened.[12] As a result, local microcirculation is restored, inflammatory oedema is cleared, and tissue repair is facilitated.

Another mechanism which contributes to improved healing with trypsin:chymotrypsin combination is that it helps in maintaining high levels of α1-antitrypsin for a long duration.[12] Consequently, the activity of proteolytic enzymes and their degradative effects are countered, leading to reduction in inflammatory milieu, ROS and oxidative stress, and faster healing.[13] Additionally, the enzyme preparation also increases enzymatic and non-enzymatic antioxidant levels, which further augments its antioxidant and anti-inflammatory efficacy.[14] The anti-infective property of the enzyme complex may be explained by enhanced phagocytic activity of natural killer cells and macrophages due to trypsin.[14] It is also interesting to note that the combination has been shown to reduce the constant loss of albumin and pre-albumin after surgical procedures. Consequently, it may prevent many of the life-threatening postoperative complications, such as shock.[3] Overall, the use of trypsin:chymotrypsin in patients with acute injury reduces inflammatory oedema and tissue destruction, which in turn facilitates rapid healing.[15] Sample size is a major limitation of the present study. The present study could not accurately grade the oedema nor quantify the seroma in post-operative wounds and factors like influence of co morbidities on wound healing was not studied separately as a variable.

CONCLUSION

Trypsin:chymotrypsin combination hastens repair in surgical patients, shows high bioavailability without losing its biological activities as an anti-inflammatory, anti-edematous, fibrinolytic, antioxidant, and anti-infective agent. These properties help in resolving signs and symptoms of inflammation due to tissue injury and facilitate the repair process. It also demonstrates analgesic effects and reduces the pain associated with healing. It is thus concluded that trypsin:chymotrypsin treatment in patients hastens the healing process and reduces the recovery time.

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