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RESEARCH ARTICLE

PERI-OPERATIVE ROLE OF PROTEASES (BROMELAIN + RUTOSIDES) IN SURGICAL PATIENTS- A PROSPECTIVE CLINICAL TRIAL

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ABSTRACT

Background: Proteases are naturally occurring enzymes that have received traditional footage in medical treatment. Enzyme preparations have also entered modern medicine since 1960s. Trypsin, Bromelain and Rutoside preparations have recently boomed into the medical prescriptions, claiming a better resolution of inflammatory symptoms, thereby anticipating a faster healing of the surgical wound. This study aims to prospectively approach and determine the efficacy of these newer proteases with respect to certain fixed parameters of surgical prophylaxis. **Methods:** A prospective study on 50 elective surgery patients during a period of 12 months comparing placebo with bromelain trypsin and rutoside oral combinations. **Results:** Statistically significant reduction in post-operative oedema, seroma and hematoma formation, reduced pain and surgical site infection with better surgical scar coupled with reduction in secondary suturing rates were observed. **Conclusion:** The current study thus concludes that oral protease combinations in the peri operative period favorably accelerates healing process culminating into a shorter and better recovery.

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INTRODUCTION

The present study attempts to correlate the physiology of surgically induced inflammation with the beneficial effects of oral bromelain trypsin rutoside combinations (Enzoheal). Wound healing is a complex process of sequential steps culminating in remodeling of fibronectin meshwork into a healthy surgical scar (Henderson, 1971; Xue and Jackson, 2015). Over the recent years clinical trials have shown trypsin, bromelain and rutoside fixed dose combinations as a very potent and safer alternative to NSAIDS in relieving surgical oedema and inflammation and thereby promote faster wound healing. Trypsin is produced in Pancreas. It has shown in vivo and in vitro abilities to inhibit the rise of C-reactive protein as well as enhance the rise of alpha1 antitrypsin and alpha 2 macroglobulin (Tina Kauss *et al.*, 2008). Bromelain is a crude pineapple extract demonstrating appreciable in vitro and in vivo anti-inflammatory, antithrombotic and fibrinolytic properties (Bromelain, 2001). Rutoside is a natural flavone derivative having remarkable anti-inflammatory, antiallergenic and immunomodulatory properties (Tina Kauss *et al.*, 2008).

Indications

- Resolution of oedema and post-operative inflammation.
- Resolves veno- thrombus and thrombophlebitis used in

Gynaecological, ENT, Orthopaedic, General surgery,

Ophthalmological, Breast, Chest and various other specialities.

Contraindications

- Cardiac and Renal impairment.
- Active Peptic ulcer disease
- High vitreous pressure
- Hypersensitivity reactions to any or all of the contents.

METHODS

A total of 60 electively posted general surgery patients were taken up for the study dividing them into 2 groups. Group I, the Control/Placebo group (n=30), were given placebo in place of the combination drug. Group II, the Study group (n=30), were given oral fixed dose combination of (Trypsin 48mg + Bromelain 90mg + Rutosides 100mg). All the 30 patients in this group received 1 tablet of ENZOHEAL, twice daily with food from Day 2 post-operative period X 10 days. The presence of Oedema, Seroma, Haematoma and Surgical site infection were observed on all 60 patients on Day 3,5,7 and 10. Recovery time was noted for all 60 patients.

Inclusion criteria

- Only clean cases and electively posted were taken up.
- Co-morbidities like uncontrolled Diabetes and Hypertension were eliminated
- The age group ranged from 20 – 50 years.
- All patients had a thorough pre-operative investigative work-up with pre-requisite PAC clearance.

Exclusion criteria

- Emergency cases
- Clean – contaminated cases
- Contaminated cases like debridement and amputations.

All patients received intra-operative 1gm single shot third generation cephalosporins at the induction of anaesthesia. Post operatively all patients received tab Cefuroxime 500 in BD dosage for 5 days.

RESULTS

Post-operative oedema: Post-operative oedema on Day 3, was noted in 20 patients (66.66%) of the Placebo group. The Study group recorded only 05 cases (16.66%). On Day 5, the Study group recorded 03(10%) cases with oedema while the Placebo group recorded 10 (33.33%). Oedema was seen rapidly regressing or not discernable in majority of the Study group who received fixed dose combinations. By Day 7, only 02 cases (6.66%) of the Study group had minimal oedema which totally disappeared by Day 10. The Placebo group on the other hand continued to show persistence of oedema in 08 cases (26.6%) by Day 7 and 6 cases (20%) by Day 10.

Serous discharge: Post-operative serous discharge was noted in 53.33% (16) of the Placebo group on Day 3, while the Study group recorded 16.66% (05) cases as having serous discharge on change of primary dressings. The Study group showed a rapidly improving trend as Day 5 and Day 7 recorded only 03 cases (10%) and 01 case (3.33%) respectively as against the Placebo group which was slow at inflammatory serous discharge regression recording 12 cases (40%) on Day 5 and 08 cases (26%) on Day 7. By Day 10 wound site discharge has totally stopped in the Study group while it went on persisting on 04 patients (13.33%) in the Placebo group.

Haematoma formation: The Placebo group recorded haematoma in 20% (06 cases) by Day 3, which subsequently reduced to 6.66% (02 cases) by Day 5 and 3.33% (01 case) by the 7th Day. The Study group recorded only 02 cases (6.66%) on Day 3 and total resolution by Day 5. The Placebo group however recorded total resolution only by Day 10.

Surgical site infection: Both the groups recorded surgical suture line infection from Day 3, recording 16.66% (05 cases) for the Placebo group and 6.66% (02 cases) for the Study group. By Day 5 the Study group maintained 6.66% recordings and became totally infection free from Day 7 onwards. The Placebo group however in spite of similar antibiotic coverage showed addition of 02 more cases raising the records to 23.33% (07 cases) by Day 5 and Day 7. Only letting out of purulent discharge by stitch removal aided recovery to reduce the records to 02 cases (6.66%) by Day 10.

Recovery time: Overall recovery time of less than one week was noted in 20 of the 30 patients of the Placebo group and 25 of the 30 patients in the Study group. Delayed recovery of over one week was noted in 10 and 05 patients of Placebo and Study group respectively.

Statistical data analysis: Statistically significant improvement was seen in the Study group as compared to the Placebo group on all parameters including oedema, serous discharge, haematoma, surgical site infection. Recovery time <1 week was 83.3% in the Study group as against 66.66% in the Placebo group.

Table 1. Post-operative oedema compared between Group I(Placebo) and Group II (Study)

Post-op day N=30	3 rd		5 th		7 th		10 th	
	No	%	No	%	No	%	No	%
Group I	20	66.66	10	33.33	08	26.6	06	-
Group II	05	16.66	03	10.00	02	6.66	20	-

Table 2. Post-operative serous discharge comparison between Group I and Group II

Post-op day N=30	3 rd		5 th		7 th		10 th	
	No	%	No	%	No	%	No	%
Group I	16	53.33	12	40	08	26	04	13.33
Group II	05	16.66	03	10	01	3.33	-	-

Table 3. Haematoma formation comparison

Post-op day N=30	3 rd		5 th		7 th		10 th	
	No	%	No	%	No	%	No	%
Group I	06	20	02	6.66	01	3.33	-	-
Group II	02	6.66	-	-	-	-	-	-

Table 4. Surgical site infection

Post-op day N=30	3 rd		5 th		7 th		10 th	
	No	%	No	%	No	%	No	%
Group I	05	16.66	07	23.33	07	23.33	02	6.66
Group II	02	6.66	02	6.66	-	-	-	-

Table 5. Recovery time

Group I N=30	< 1 Week	> 1 Week
	20	10
Group II N= 30	< 1 Week	> 1 Week
	25	05

DISCUSSION

As with all forms of injury surgical wound also shows acute rise in acute phase reactants namely alpha1 antitrypsin and alpha2 macroglobulin. These act as protease inhibitors which if un controlled can significantly delay healing. While alpha1 antitrypsin shows affinity for elastase-chymotrypsin-cathepsin G cascade, alpha2 macroglobulin is affined to cathepsin G. (Sulniute *et al.*, 2016; Ambrus *et al.*, 1967). Both the acute phase reactants finally act by inhibiting plasmin which prevents fibrinolysis with consequent maintenance of inflammatory oedema and delay in healing.⁹ Oral combinations target this early step by competitive inhibition with alpha1 antitrypsin and alpha2 macroglobulin thereby releasing plasmin which shortens and reduces the entire inflammatory cascade and facilitates quick tissue repair.¹⁰ The anti-

inflammatory properties of Bromelain mainly centre around inhibition of arachidonic acid pathway by decreasing generation of thromboxane thereby tilting the thromboxane/prostacyclin ratio in favour of prostacyclin. It further inhibits PGE2 and also directly acts on the nociceptors (Taussig *et al.*, 1988; Felton *et al.*, 1980). Rutoside on the other hand exerts anti-inflammatory, anti-allergic and immune modulatory activity. It has been shown to decrease capillary permeability, inhibit platelet aggregation thereby improving circulation. It also strengthens the capillaries and reduces venous oedema (La Cassa *et al.*, 2000). Another interesting information shows that the combination reduces the constant loss of albumin and pre-albumin after surgical procedures subsequently helping to prevent life threatening post-operative complications like shock (Kondreddy *et al.*, 2019).

Conclusion

The present study sample is not adequate to firmly stamp upon the findings but it can be an eye opener for further research on such combinations which are safer natural alternatives to the age old NSAIDS used in the peri-operative period who have proven deleterious effects on the cardiac, renal and various other organs of our body. The present study only clinically establishes the claims of such combinations in a surgical backdrop.

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