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Role of Proteolytic Enzymes in Reducing Post Operative Pain and Swelling Following Third Molar Surgery - A Review

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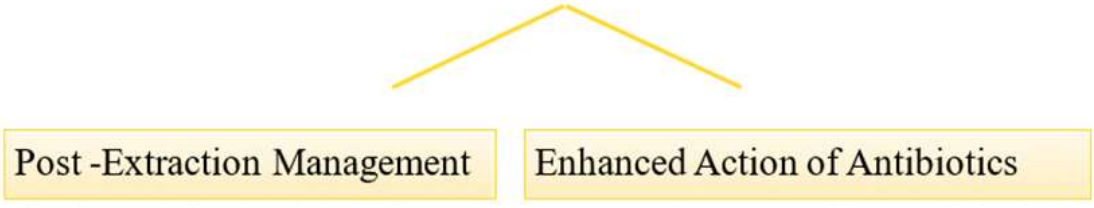
ABSTRACT

In routine dental practise, impacted third molars are commonly removed. Third molars have such a higher impaction rate than those of other teeth. Impacted teeth may be asymptomatic or be associated with pathologies such as caries, pericoronitis, cysts, tumours, and root resorption of the adjacent tooth. However, this procedure is accompanied by a variety of postoperative complications, which include persistent pain, swelling, trismus, and paresthesia due to nerve injury.In this article we are going to discuss about the importance or applications of the enzymes in reducing post operative pain and swelling following third molar extraction either alone or in combination with other NSAIDS in the field of dental practice for the better anti-inflammatory or analgesics effects ; enzymes have been widely used in the medical field such as arthritis, fracture of the bone or in oedema. Along with anti- inflammatory action these drugs have anti-oedema properties, healing properties and fibrinolytic properties as like trypsin-chymotrypsin.

INTRODUCTION

Dentistry includes operative or surgical procedures mostly. However, for a majority of dental ailments, dentists still rely on medications, either alone or as part of preoperative/ postoperative management. These include anesthesia, analgesics, antibiotics, dietary supplements, steroids or anti-anxiety drugs, etc. And now a days for the better anti- inflammatory or analgesics effects of drugs; enzymes have been widely used in dentistry also and in this discussion, we are going to give a review on few of the enzymes which includes serratiopeptidases, chymotrypsin, other. Studies have shown that Removal of impacted teeth needs a surgical procedure where soft tissue flap is raised and associated tooth or bone or both are cut and the tooth is removed. Such surgical procedures usually result in injury of tissues, involving inflammation and repair processes.In order to avoid or minimize post surgical complications, such as pain, swelling, and trismus, surgeons have either modified surgical techniques, or advise the patients to use proteolytic enzymes, such as trypsin, chymotrypsin, papain, serratiopeptidase, and bromelain (pineapple enzyme), along with routine antibiotics, analgesics, and corticosteroids. The benefits of administering enzymes after surgical procedures demonstrated both in vitro and in vivo are anti-inflammatory, antithrombotic, and fibrinolytic.



Role of Proteolytic Enzymes in Oral Surgery

Serratiopeptidase:

Serratiopeptidase protease also known as serral-ysin/serratia- protease/serrapeptase is a proteolytic enzyme derived from the non-pathogenic Enterococci bacteria serratia seen in the intestines of silworms (*Enterobacterium serratia)* widely used as anti inflammatory or analgesic, In dentistry it is used for post- operative reduction of pain and swelling after minor surgical procedures[1] Enteric oral formulation of this enzyme is being used commonly in

various specialities like surgery, orthopaedics, otolaryngology, gynaecology and dentistry for its anti- inflammatory and anti-edemic properties[2].Serratiopeptidase acts as an anti-inflammatory agent to reduce mild to moderate pain and inflammation[3].SP has an increased anti inflammatory activity when used along with other antibiotics such as ampicillin, cephalexin, minocycline is useful in dental infections[4]

MECHANISM OF ACTION:

The action of SP demonstrated in studies is their direct influence on the movement of immune cells. Serratiopeptidase also works by modifying cell-surface adhesion molecules [5]Enzyme regulates polymorphonuclear neutrophils and other lymphocytes at the site of inflammation and also reduces capillary permeability by histamine, bradykinin, and serotonin; and breaks down exudates and proteins thus, facilitates the absorption of decomposed products through blood and lymphatics.Also SP helps in reducing fluid retention in affected areas, which induces proper drainage and faster recovery[3]

Pharmacokinetics

After oral administration, Serratiopeptidase is absorbed through the intestines and transported directly into the bloodstream.[2]

Pharmacodynamics

Serratiopeptidase works in three ways:

1. Anti-inflammatory: serratiopeptidase induces reduction of the swelling by thinning and decreasing the fluid,which helps in the drainage of the fluid, the enzyme activity dissolves the damaged tissue in the injured part so that healing is accelerated.[2,4,5]
2. Analgesic: it may help to eliminate pain by inhibiting the release of pain-inducing amines like bradykinin from inflamed tissues [2]
3. Fibrinolytic/caseinolytic: it may be beneficial in breaking other dead or damaged tissue without harming living tissue. This could enable the dissolution of blood clots[2]

Dosage

SP can be taken in the usual adult dose range of 15 mg to 60 mg per day. Serratiopeptidase should be taken on an empty stomach or at least two hours after eating, and no food should be consumed for about half an hour after taking it. It can also be used in conjunction with other NSAIDS such as paracetamol&aceclofenac and diclofenac [2].

Drug interactions

There have been no clinical studies that show any drug interactions. When combined with Warfarin, Clopidogrel, or Aspirin, as well as other natural remedies like garlic, fish oil, or turmeric, there is an increased risk of bleeding or bruising.[2]

DRUG SAFETY :

There have been no reported adverse effects in SP studies, but it can cause allergic reactions and other side effects such as erythema multiforme, joint pain, and abdominal upsets.

Bromelain:

Bromelain is a cysteine protease [6]which is a crude aqueous extract from stem and fruit of pineapple is known as bromelain. Bromeliaceae, of which pineapple, Ananas comosus is the best known[7].It was first identified by Marcano in 1891 in pineapple juice, and *Heinecke* discovered higher amounts of bromelain in the stem than the fruit in 1957.The presence of proteolytic enzymes in pineapple juice was found in 1891,the active substance was isolated [8]It compress of different thiol endopeptidases and other components like phos-phatases, glucosidase, peroxidases, cellulases, glycoproteins, carbohydrates, and several protease inhibitors.It acts by affecting the concentration of the cyclo-oxygenase 2 enzyme and thereby leukocyte activation.Bromelain has possess many properties which includes anti-inflammatory, anti-edemic, anti-tumor and immunomodulatory effects.[7,9]

These proteinases are used in the treatment of inflammatory and malignant disorders.

- additives for chemotherapy (to reduce side effects of drugs and to improve quality of life);
- radiotherapy additives (to reduce inflammation and edoema);
- surgery additives (to reduce edoema and improve wound healing);
- lymphedema additives to reduce lympho- congestion, detritus, exsudate viscosity, and stimulation of phagocytosis of associated leukocytes). [10]

Absorption and Bioavailability

The amount of bromelain absorbed by the body is about 12 gm/day, bromelain can be prescribed without any major side effects, it is absorbed from the gastrointestinal tract in a functionally intact form; approximately 40% of labeled bromelain is absorbed from intestine in high molecular form [9]

Pharmacodynamics and Pharmacokinetics Profiles of Bromelain

The mechanisms of action of bromelain have not yet been fully known.However, the anti-inflammatory activity of this are on three different pathways which is seen in several in vivo and in vitro studies. The first is the kallikrein-kinin pathway; bromelain regulates the plasma fibrinogen levels and blood levels of bradykinin and enhances serum fibrinolytic activity by activating factor XI, which activates plasma prekallikrein Secondly, bromelain acts on the arachidonic acid pathway it modulates proinflammatory prostaglandins and enhances the anti- inflammatory mediators, increasing platelet cyclic adenosine monophosphate (cAMP), and the levels of prostaglandin (PG) I2 and PGE1. Finally, bromelain modulates cell-migration immunity: acting on the migration of neutrophils to inflammation sites [11]

DOSAGE:

Bromalein can be used at a daily dose of 200 to 2,000 mg/kg over a long period and cane be considered as non toxic,studies have shown that administration of bromalein through oral route is absorbed through the intestines ans remains biologically active with a half life of 6-9 hours and plasma concentration of 5,000pg/ ml by 48 hours after oral multi dosing of 3g/day [6]

TOXICITY:

According to Taussig et al. bromelain has very low toxicity with an LD50 (lethal doses) greater than 10 g/kg in mice, rates, and rabbits, Eckert et al.after giving bromelain (3000 FIP unit/day) to human over a period of ten days found no significant changes in blood coagulation parameters.[9]

Bromelain promotes the absorption of antibiotics

It has been known for a number of years that bromelain is capable of enhancing the tissue permeability of penicillins and tetracyclines after oral administration. This increases absorption and leads to an improved diffusion after subcutaneous and intramuscular application of the antibiotics. Higher serum and tissue levels are obtained, and side effects are reduced

Trypsin-chymotrypsin

Both trypsin and Chymotrypsin are a family of serine proteases, and these two types of proteases originally synthesized in the pancreas[12] in the inactive form of zymogen precursors (trypsinogen andchymotrypsinogen) for the purpose of stopping unnecessary cellular activity and controlling when and where enzyme activity occurs. These active forms of enzymes also aid in the digestion of food. Trypsin and Chymotrypsin give the body the extra boost it might need for smoother digestion of proteins as well as for reducing inflammation and fighting infection.Trypsin and Chymotrypsin provides better resolution of inflammatory symptoms and promotes speedier recovery of acute tissue injury than several of the other existing enzyme preparations.

Thus, the clinical activities of TC include

- Fibrinolytic activity - TC breaks down the fibrin barrier thus improving and restoring circulation, resolving edema, hematoma and pain, promoting phagocytosis to remove the debris an accelerate recovery.
- Reduction in Plasmin Inhibitor levels within 3-5 days to post- surgery.
- Release of Intestinal Plasminogen activators - Studies have shown that TC brings about release of Plasminogen activators from the intestinal mucosa and those are absorbed into the systemic circulation along with TC thus, contribute further to bringing about fibrinolysis; thereby increasing tissue circulation and decreasing edema.

Due to these antioxidant, anti-inflammatory, antifibrinolytic, antiedema properties these can be indicated in dentistry in number of ways-

- Post-operative wounds,
- Oedema and hematoma caused after LA injection,
- Prevention of inflammation of the surgical stitches,
- After tooth extraction especially in case of impacted teeth or wisdom tooth,
- Peri-apical abscess (where SP might have negative effects) (5),
- Maxillofacial surgery,

- Post-traumatic oedema,
- Soft tissue injury & maxillofacial fractures and dislocation after trauma,
- TMJ arthritis
- Oral ulcers – due to its antioxidant & healing properties by removing the dead tissues.

Combination of TC enzyme may consist of purified proteolytic enzyme concentrate providing 50,000/1,00,000/2,00,000 armour units of Trypsin and Chymotrypsin in the ratio 6:1. And it is possibly safe up to the dosage of 800,000 units per day of this combination up to 7-10 days.

Adverse effects include :

- Gastric upset
- Corneal edema
- Allergy or anaphylaxis with symptoms include itching,shortness of breath. swelling of the lips or throat, shock, loss of consciousness, and death (rare).

Role of Trypsin: Chymotrypsin in Tissue Repair:

Trypsin: chymotrypsin is a widely used oral proteolytic enzyme combination which helps in the fastens the repair of surgical, traumatical and orthopaedic injuries, its has anti inflammatory, anti oedematous, anti infective properties and helps in reducing inflammation and facilitates the repair process[13,14]

Trypsin	Fibrinolysis, leading to breakdown of thrombi proteins Reduces the release of inflammatory mediators like Interferon gamma (IFNγ, thus limiting the further activation of macrophages.) Wound healing and tissue repair	Displacement of "bound plasmin# from plasma (e.g., α2-antitrypsin); free plasmin mediates fibrinolysis Cleavage of molecules on antigen presenting cells (APCs), thereby increasing the activation threshold of T cells Promotion of macrophage differentiation to a more healing/repairing profile (M2), rather than inflammatory profile (M1) [Mediated by trypsin activation of PAR1 and PAR2 receptors on macrophages]

DRUG INTERACTION:

The therapeutic efficacy of Acetylcysteine can be decreased when used in combination with Chymotrypsin and trypsin

Pharmacodynamics

Chymotrypsin is a digestive enzyme synthesized in the pancreas that plays an essential role in proteolysis, or the breakdown of proteins and polypeptides.

Conclusion:

The use of Proteolytic enzyme therapy via oral route has good results in the anti-inflammatory, analgesics role, especially with tissue healing, they enable early resolution of wound repair and are of considerable benefit in alleviating many of the physical and psychological symptoms that confront the patient. There have been few adverse drug responses documented with these treatments, most of which are mild skin allergies, Gastrointestinal disturbances, with no substantial impact on the liver or kidney. Furthermore, clinical studies have revealed that different persons respond well to varied combinations of these enzymes. The most critical factor in administering these enzymes with other medications is patient selection. proteolytic enzyme are a safe and effective adjunctive therapy in the control and reduction of edema, inflammation, and pain associated with induced trauma resulting from oral surgical procedures.

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