Serratiopeptidase, a proteolytic enzyme derived from Serratia E-15 species enterobacteria, is widely used in medical field for its anti-inflammatory, anti-edemic properties, and analgesic properties. It is being used commonly in various specialties such as orthopedics, otolaryngology, gynecology, surgery, pulmonology, ophthalmology, and dentistry. Research has shown that serratiopeptidase is the most effective anti-inflammatory agent compared to other enzyme preparations. This article reviews the efficacy, safety, and applications of serratiopeptidase in oral surgery. This article also discusses the mechanism of action of serratiopeptidase, its contraindications and complications. From the recently published literature, it is clear that the role of serratiopeptidase as a therapeutic agent in oral and maxillofacial surgery is expanding and they hold a promising future as a broad-spectrum anti-inflammatory drug with minimal side effects and complications. Further, research will broaden their applications in the field of medicine and dentistry.

**Keywords:** Analgesic, Anti-inflammatory, Oral surgery, Infections, Proteolytic enzymes, Serrapeptase, Serratiopeptidase, Third molar surgery.

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**INTRODUCTION**

Enzymes are extremely potent substances and their therapeutic applications in medical field are increasing due to its efficacy and safety. Enzymes are derived from plants (papase and bromelain), animals (trypsin and chymotrypsin), bacteria (streptokinase, streptodornase, and serratiopeptidase), and fungi [1].

Serratiopeptidase (serralyzin/serrapeptase/Serratia-protease) is a proteolytic enzyme which is predominately used for its anti-inflammatory properties. Initially, trypsin, chymotrypsin, and bromelain were used [2]. During the 1950s in the USA, parenteral trypsin was found to be very useful in treating inflammation associated with sports injuries, rheumatoid arthritis, ulcerative colitis, atypical viral pneumonia, and postsurgical edema. Serratiopeptidase was first used in Japan for therapeutic purposes [3]. Later parenteral enzymes were replaced by enteric-coated oral formulations. Research conducted in Japan and Europe during the 1980s and 1990s showed that serratiopeptidase was the most effective anti-inflammatory agent compared to other enzyme preparations [4,5]. Since then it is in use for over 40 yrs in Europe and Japan for the treatment of pain and inflammation associated with various conditions. Recent literature studies reported that serratiopeptidase can be used as an effective anti-inflammatory agent after oral surgical procedures. This article reviews the properties, mechanism of action, efficacy, and uses of serratiopeptidase in oral surgery and their future applications.

**SYNTHESIS OF SERRATIOPEPTIDASE**

Serratiopeptidase is produced by Serratia species E-15, non-pathogenic enterobacteria, found naturally in silkworm Bombyx mori which helps the emerging moth in dissolving its cocoon. Serratiopeptidase for medical purposes is obtained by purification from culture of Serratia E-15 species bacteria (fermentation biotechnology) [6].

**CHEMICAL STRUCTURE**

Serratiopeptidase is a metalloprotease containing a zinc atom with a molecular weight of 45,000–60,000 and consists of 470 amino acids which are important for its proteolytic activity (Fig. 1). The enzyme was characterized to be free of any sulfur-containing amino acids such as cysteine and methionine [7,8]. The enzyme belongs to serralysin group of enzymes EC number 3.4.24.40 and is known to cleave the peptides with linkages of Asn-Gln, Cys503H-Gly, Arg-Gly, and Tyr-Tyr as well as the bond between His-Leu, Gly-Ala, Ala-Leu, Tyr-Leu, Gly-Gly, Phen-Tyr, and Tyr-Thr, showing broad substrate specificity. The enzyme has maximal activity at pH 9.0 and at a temperature of 40°C and is completely inactivated by heating at 55°C for 15 min [9].

**ADMINISTRATION OF SERRATIOPEPTIDASE**

It is preferred over other proteolytic enzymes such as trypsin and chymotrypsin as it has high potency with negligible side effects. It is administered orally as an enteric-coated tablet to avoid degradation by enzymes in gastrointestinal tract. Normal dosage is 10 mg [20,000 U] 3 times a day to be taken on an empty stomach or 2 h after food. It is available as a sole drug or in combination with other enzyme preparations and analgesics. It is usually available as a fixed dose combination with non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac, aceclofenac, ibuprofen, tramadol, and paracetamol. In the treatment of infections, it is administered with various antimicrobials as it increases their tissue penetration. It is orally effective and equivalent to diclofenac sodium as an anti-inflammatory agent in both acute and chronic phases of inflammation [10].

Kaur and Singh [11] designed and developed albumin nanoparticles that can be used to effectively deliver serratiopeptidase at the site of inflammation in treating conditions like rheumatoid arthritis. For children, powder form of enzymes is also available. It is advised not to take serratiopeptidase for more than 4 weeks for chronic inflammatory or infective conditions. This can prevent clot formation and can cause serious bleeding problems for those with bleeding disorders or in the event of an injury; hence, it has to be stopped at least 2 weeks before any surgical procedure. Administered orally it is absorbed from intestine, enters into systemic circulation in unchanged form and can penetrate into all tissues through blood or lymph, especially inflamed areas in an enzymatically active form [12]. Serratiopeptidase binds to alpha2-macroglobulin in the blood in a 1:1 ratio, thus does not elicit allergic reaction but retains its enzymatic activity and high concentration of drug is transferred to the site of infection/inflammation in 1 hour [13,14].
Yamasaki et al. [3] in 1967, showed that serratiopeptidase is a potential anti-inflammatory agent. It decreases the amount of fluid in the tissues, thus the fluids, and facilitates the drainage of the fluid, thereby reduces swelling. This also enhances tissue repair and reduces pain. It dissolves the dead tissue surrounding the injured area without harming living tissue, thereby accelerating healing. Several studies have proved that orally administered proteolytic enzymes can specifically control the inflammatory cytokines and the onset of chronic inflammation [15-17]. Serrapeptidase and other proteolytic enzymes are effective in controlling and modulating inflammatory processes are referred to as “adjunct therapeutic agents” [18]. It also modifies cell-surface adhesion molecule that guides inflammatory cells to their target site of inflammation. These adhesion molecules are known to play an important role in the development of arthritis and other autoimmune disorders [19].

Serratiopeptidase alleviates pain by inhibiting the release of bradykinin from inflamed tissues. It also acts by breaking down fibrin and other dead or damaged tissue, thus dissolving blood clots and atherosclerotic plaques.

Serratiopeptidase hydrolyses bradykinin, histamine, and serotonin, thereby reduces swelling and improves microcirculation and expectation of sputum [20]. Thus, it reduces capillary permeability and also breakdown of proteins and exudates and hence supports wound healing. It decreases neutrophil count and alters the viscoelasticity of sputum, thereby clears mucous secretions in patients with chronic airway disease [4,21].

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diclofenac at therapeutic equivalent doses. According to Viswanatha Swamy and Patil [37], proteolytic enzymes have anti-inflammatory activity and exhibit synergistic effects with aspirin in rat inflammation models in both acute and subacute phases of inflammation. A study showed that serratiopeptidase can be used in the conservative treatment of patients with carpal tunnel syndrome [38].

THERAPEUTIC APPLICATIONS IN ORAL SURGERY

Serratiopeptidase is used mainly in post-traumatic and post-operative inflammatory conditions (after any minor and major oral surgical procedures), orodental infections.

Third molar surgery

Surgical removal of impacted lower third molar teeth is a very common procedure in oral surgery. It is always associated post-operative swelling, pain, and trismus. Various studies were conducted to evaluate an effective drug to control the post-operative complications. Enzyme serrapeptase was found to be very useful in controlling post-operative swelling.

Al-Khateeb and Nusair [39] conducted a prospective, intraindividual, randomized, double-blinded, and crossover study on 24 patients. Treatment group received 5 mg serratiopeptidase with 1000 mg paracetamol tablets and control group was given placebo with 1000 mg paracetamol for 7 days. Serratiopeptidase caused significant reduction in swelling and pain intensity in the 2th, 3th, and 7th post-operative day after lower third molar surgery. However, the drug had no effect on post-operative trismus.

Murugesan et al. [40] carried out a randomized study on 110 patients to evaluate the usefulness of serratiopeptidase compared to dexamethasone in impacted lower third molar surgery. Postoperatively, 1 mg dexamethasone was given thrice daily in the first group and 10 mg serratiopeptidase was given thrice daily in the second group for 3 days. The patients were reviewed on the 1st, 3rd, 5th, and 7th post-operative days. They found that dexamethasone was more effective in reduction of post-operative swelling and pain when compared to serratiopeptidase. Hence, they concluded serratiopeptidase can be used as an alternative to corticosteroids to control inflammation in cases where corticosteroids are contraindicated. Both the drugs had no beneficial effects in relieving trismus.

Chappi et al. [41] conducted a similar study on 100 patients to find the efficacy of serratiopeptidase in the management of post-operative complications after lower third molar surgery. The patients were randomly divided into two groups and drugs were administered orally in divided doses. Postoperatively, one group received methylprednisolone 12 mg/day and the other group was given serratiopeptidase 20 mg/day for 5 days. The patients were followed-up on the 1st, 3rd, 5th, and 7th post-operative days. On comparing methylprednisolone with serratiopeptidase, they concluded that methylprednisolone exhibited better pain relief, while serratiopeptidase is very effective in controlling postsurgical swelling and trismus and did not affect the wound healing. Hence, synergistic combinations of these two drugs would be more effective than individual drug when widespread post-operative sequelae are expected after lower third molar surgery.

Al-Sandook et al. [42] did a study on 30 patients in which 15 patients were given serratiopeptidase and 15 patients received conventional treatment for 3 days. They demonstrated that proteolytic enzymes possessed good anti-inflammatory and analgesic properties when administered for lower third molar surgery.

Chopra et al. [43] evaluated and compared the efficacy and safety of paracetamol, serratiopeptidase, ibuprofen, and betamethasone in reducing swelling and pain following lower third molar surgery. In this randomized, double-blinded, and placebo-controlled trial, 150 patients were randomly divided into one of the five groups to receive treatment 3 times a day for 7 days with ibuprofen 600 mg, betamethasone 0.5 mg, paracetamol 1 g, serratiopeptidase 20 mg, or placebo. Serratiopeptidase showed analgesic and anti-inflammatory activity, but it was not significant, whereas ibuprofen and betamethasone were effective in reducing post-operative swelling and pain compared to serratiopeptidase or paracetamol groups.

Chaïwat et al. [44] in their study to evaluate the efficacy of serratiopeptidase on post-operative pain, swelling, and trismus following lower third molar surgery, found no significant difference between the serratiopeptidase and control groups. In the study by Surachai [45], no significant difference was found between the serratiopeptidase group and nil medication group in the reduction of facial swelling after impacted lower third molar surgery. It was a trial with small sample size of 40 patients which is a limitation of the study.

Infections

It helps in prevention and treatment of a variety of infections. Serratiopeptidase enhances the bactericidal effect of antibiotics in cultures and prevents the formation of biofilms, hence useful in treating prosthetic infections [22]. It increases the permeability of desired tissues which enhances the absorption of antibiotics to the site of infections, thereby potentiating the action of antibiotics [46,47]. Thus, they are a useful adjunct to antibiotics in both acute and chronic infections. Selan et al. [48] in their in vitro study showed that serratiopeptidase greatly enhances the activity of antibiotics (ofloxacin) on sessile cultures of pathogens and can inhibit biofilm formation. Thus, serratiopeptidase can be used for the treatment of prosthetic device infections and infections caused by biofilm-forming bacteria. Serratiopeptidase enhances the activities of many antibiotics by improving the penetration of antibiotics in infected sites.

It is useful in orodental infections and reduces the healing time by 50% [49]. Intra-articular serratiopeptidase has also been found useful in the eradication of infection caused by biofilm-forming bacteria in experimental animal model. It is very useful in controlling airway infections and inflammations. In many studies, it has been shown that using serratiopeptidase and/or other proteolytic enzymes along with antibiotics or other medications, healing occurs much faster [50,51].

Major surgical procedures

Tachibana et al. [52] conducted a multcenter, randomized, and double-blinded study to evaluate the efficacy of serratiopeptidase in 174 patients undergoing Caldwell-Luc antrostomy for chronic empyema. 88 patients in the treatment group received 30 mg/day of serratiopeptidase and 86 patients in the control group received placebo. The degree of post-operative swelling in the serrapeptase-treated patients was significantly less than in the placebo group and no side effects were reported with the drug.

Traumatic injuries

Garg et al. [53] evaluated and compared the efficacy and safety of serratiopeptidase and aceclofenac in reducing swelling and pain following traumatic soft tissue injury. Serratiopeptidase showed significant anti-inflammatory effect with mild analgesic action, whereas aceclofenac exhibited superior analgesic effect as compared to serratiopeptidase. Serratiopeptidase can be used as an anti-inflammatory agent in traumatic bony and soft tissue injuries in oral and maxillofacial region.

DISCUSSION

Inflammation occurs due to many conditions in humans. NSAIDs and corticosteroids are the commonly used drugs to combat inflammation. However, they are not without side effects and are also costly; hence, their judicious use is mandatory. Serratiopeptidase can be a useful alternative to these drugs as an anti-inflammatory agent in conditions where the former drugs are contraindicated [54]. It can be prescribed alone or preferably in combination, and other analgesics when superior analgesic action is desired. When prescribed in combination with NSAIDs/corticosteroids, serratiopeptidase has superior anti-inflammatory and analgesic action.
Proteolytic enzymes can play an important role in future in treating patients with nosocomial, viral, and resistant infections, especially in pediatric and geriatric age groups. Its safety profile, lack of development of resistance, and inability to show tolerance makes it a preferred supplemental drug to many antimicrobials to treat infections [55, 56].

Serrapeptidase is produced in highly controlled laboratory conditions adhering to good clinical practice protocols. Serrapeptidase alone or in combination with NSAIDs is costly and has been marketed widely by the pharmaceutical companies. It should be prescribed if the benefits of the drug outweigh the cost burden to the patient. Thus, prescription of proteolytic enzymes should be decided on evidence-based medicine and not to be influenced by medical representatives [57]. Although the clinical efficacy and safety of serrapeptidase has been proven in many studies, most of the evidence is based on animal experiments, few uncontrolled clinical trials, and randomized controlled clinical trials of poor quality. Thus, there is a need for further extensive experimental and clinical research in this area [30, 31, 58-60].

CONCLUSION

Serrapeptidase has a well proven excellent anti-inflammatory action with moderate analgesic properties. Serrapeptidase can be used for effectively managing swelling and pain after any minor/major dental or oral surgical procedures and facial trauma either alone or in combination with NSAIDs/corticosteroids. It can be used as an adjunct therapeutic agent along with antimicrobials in the treatment of orofacial infections. Furthermore, its use and application in the areas of human health are well documented and continue to be a major aspect of inflammation and pain management protocol in many clinics around the world. The role of serrapeptidase as an anti-inflammatory drug in oral and maxillofacial surgery is expanding and they hold a promising future as a broad-spectrum anti-inflammatory drug with minimal side effects and complications.

REFERENCES


