USAGE OF FDC OF SERRATIOPEPTIDASE AND DICLOFENAC IN ORTHO PRACTICE

Content

Background and Objective of the Survey

The usage of the fixed-dose combination (FDC) of serratiopeptidase and diclofenac in orthopedic practice offers valuable benefits for patients with various musculoskeletal conditions, including inflammatory joint disorders, soft tissue injuries, and postoperative pain management.

Serratiopeptidase, a proteolytic enzyme derived from bacteria, exhibits anti-inflammatory, analgesic, and fibrinolytic properties. It works by breaking down inflammatory proteins and fibrin deposits, reducing swelling, pain, and tissue damage associated with musculoskeletal injuries and inflammation. By promoting tissue healing and resolution of inflammation, serratiopeptidase can help improve mobility and functional outcomes in patients with orthopedic conditions.

Diclofenac, a nonsteroidal anti-inflammatory drug (NSAID), complements the action of serratiopeptidase by inhibiting the synthesis of prostaglandins, which are mediators of pain and inflammation. Diclofenac provides additional pain relief and anti-inflammatory effects, helping to alleviate symptoms such as joint pain, swelling, and stiffness in patients with orthopedic conditions.

The FDC of serratiopeptidase and diclofenac offers several advantages in orthopedic practice. By combining two complementary mechanisms of action in a single tablet, the FDC provides synergistic effects, resulting in enhanced pain relief and anti-inflammatory efficacy compared to monotherapy with either drug alone. This can lead to improved patient satisfaction, faster recovery times, and reduced reliance on additional pain medications.

The objective of the survey is:

To evaluate the usage of FDC of serratiopeptidase and diclofenac in ortho practice

Methodology of the Survey

A survey was conducted to evaluate the usage of FDC of serratiopeptidase and diclofenac in ortho practice. A total of 125 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Diclofenac
- Serratiopeptidase
- The Enzyme and Its Properties
- Therapeutic Aspects of Serratiopeptidase
- Clinical Significance

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Acute pain occurs as a result of tissue damage either accidentally due to an injury or as a result of surgery. Acute postoperative pain is a manifestation of inflammation due to tissue injury. The management of postoperative pain and inflammation is a critical component of patient care. The aim of this series of reviews is to present evidence for relative analgesic efficacy through indirect comparisons with placebo, in very similar trials performed in a standard manner, with very similar outcomes, and over the same duration. Such relative analgesic efficacy does not in itself determine choice of drug for any situation or patient, but guides policy-making at the local level.

Single dose trials in acute pain are commonly short in duration, rarely lasting longer than 12 hours. The numbers of participants is small, allowing no reliable conclusions to be drawn about safety. To show that the analgesic is working it is necessary to use placebo. There are clear ethical considerations in doing this. These ethical considerations are answered by using acute pain situations where the pain is expected to go away, and by providing additional analgesia, commonly called rescue analgesia, if the pain has not diminished after about an hour. This is reasonable, because not all participants given an analgesic will have significant pain relief. Approximately 18% of participants given placebo will have significant pain relief, and up to 50% may have inadequate analgesia with active medicines. The use of additional or rescue analgesia is hence important for all participants in the trials.

Clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years. Trials have to be randomised and double blind. Typically, in the first few hours or days after an operation, patients develop pain that is moderate to severe in intensity, and will then be given the test analgesic or placebo. Pain is measured using standard pain intensity scales immediately before the intervention, and then using pain intensity and pain relief scales over the following 4 to 6 hours for shorter acting drugs, and up to 12 or 24 hours for longer acting drugs. Pain relief of half the maximum possible pain relief or better (at least 50% pain relief) is typically regarded as a clinically useful outcome. For patients given rescue medication it is usual for no additional pain measurements to be made, and for all subsequent measures to

be recorded as initial pain intensity or baseline (zero) pain relief (baseline observation carried forward). This process ensures that analgesia from the rescue medication is not wrongly ascribed to the test intervention. In some trials the last observation is carried forward, which gives an inflated response for the test intervention compared to placebo, but the effect has been shown to be negligible over 4 to 6 hours. Patients usually remain in the hospital or clinic for at least the first six hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration.

Clinicians prescribe non-steroidal anti-inflammatory drugs (NSAIDs) on a routine basis for a range of mild-to-moderate pain. NSAIDs are the most commonly prescribed analgesic medications worldwide, and their efficacy for treating acute pain has been well demonstrated. They reversibly inhibit cyclooxygenase (prostaglandin endoperoxide synthase), the enzyme mediating production of prostaglandins and thromboxane A2. Prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive processes. However, relatively little is known about the mechanism of action of this class of compounds aside from their ability to inhibit cyclooxygenase-dependent prostanoid formation. Since NSAIDs do not depress respiration and do not impair gastrointestinal motility as do opioids they are clinically useful for treating pain after minor surgery and day surgery, and have an opiate-sparing effect after more major surgery.

Diclofenac[1]

Diclofenac is a benzene acetic acid derivative used to treat the pain and swelling associated with rheumatic disorders since 1974, and is one of the most widely used NSAIDs in the world, especially outside the USA. Almost eight million prescriptions for diclofenac were dispensed in England in 2007, the most common doses being 75 mg and 150 mg given daily in divided doses. It is available in two different formulations, diclofenac potassium and diclofenac sodium, with the sodium salt used much more frequently (7.9 of the eight million prescriptions in England in 2007). Diclofenac potassium is formulated to be released and absorbed in the stomach. Diclofenac sodium, usually distributed in enteric-coated tablets, resists dissolution in low PH gastric environments, releasing instead in the duodenum. The potassium and sodium formulations present different hypothetical advantages; the immediate-release potassium

formulation might provide pain relief more quickly, whereas the delayed-release formulation might minimise gastric exposure theoretically minimising the risk of adverse gastrointestinal events (this is unlikely as NSAID-related gastrointestinal adverse effects are more closely linked with systemic (overall) concentration). The clinical bearing of these differences has yet to be established.

A major concern regarding the use of conventional NSAIDs postoperatively is the possibility of bleeding from both the operative site (because of the inhibition of platelet aggregation) and from the upper gastrointestinal tract, (especially in patients stressed by surgery, the elderly, frail, or dehydrated). Other potentially serious adverse events include acute liver injury, acute renal injury, heart failure, and adverse reproductive outcomes. Research has also implicated diclofenac in haematological abnormalities. However, such complications are more likely to occur with chronic use and NSAIDs generally present fewer risks if used in the short term, as in the treatment of postoperative pain.

Mechanism of Action[2]

Diclofenac is an NSAID belonging to the family of phenylacetic acids and acts to decrease inflammation as other class drugs do. It also has analgesic properties and antipyretic effects that are shared by other NSAIDs. Diclofenac employs its action by inhibiting the activity of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) by inhibiting the synthesis of prostanoids such as prostaglandin-E2 (PGE2), prostacyclins, and thromboxanes, which are essential components of the inflammatory and nociceptive response. It competitively inhibits arachidonic acid from binding to COX-1 and COX-2. Diclofenac inhibits COX-1 and COX-2 relatively equally, although evidence suggests that it has selective COX-2 inhibition, about four times that of the inhibition of COX-1 during in vitro experimentation. This value is far from the reported 20-fold selectivity of COX-2 inhibition of the more selective COX-2 inhibitors like rofecoxib, but diclofenac's activity can be compared more accurately to that of celecoxib. Diclofenac and other NSAIDs also have effects in blocking the production of thromboxanes, especially thromboxane-B2 (TXB2). Diclofenac is regarded as one of the most effective inhibitors of the production of PGE2; the primary prostanoids are elevated during an inflammatory response.

COX-1 is a constitutively active enzyme that is expressed almost ubiquitously over the human body. The level and activity of COX-1 are thought to be rather stable and participates in the

maintenance of normal activity of platelets, blood flow into renal tissues, and protection of the gastric mucosa from harmful acidity, among other processes. COX-2 is an inducible enzyme that is overly expressed during times of tissue damage and in the presence of inflammatory mediators that also have nociceptive properties and induce pain. These include thromboxanes, leukotrienes, and prostaglandins. Diclofenac's effect of COX-2 inhibition appears to occur mostly at the site of target tissues such as synovial fluid and joint capsules. However, the inhibition of COX enzymes in other tissues, such as the stomach, may cause the depletion of many protective substances and can lead to the development of gastric irritation, for example. Many of these mechanisms of action are considered putative by the clinical community.

Diclofenac's peripheral analgesic effects are attributable to its activity in decreasing the availability of sensitized peripheral pain receptors via down-regulation, which appears to be accomplished by stimulating the L-arginine nitric oxide cGMP pathway via activation of ATP-sensitive potassium channels. Also, evidence suggests that diclofenac also has activity in reducing the previously increased levels of substance P, a known pro-inflammatory neuropeptide with nociceptive activity in the synovial fluid of patients with rheumatoid arthritis.

The mechanism of action of diclofenac inhibiting downstream arachidonic acid metabolite production may explain its efficacy in treating actinic keratosis and preventing progression to more malignant disease. This way, topical diclofenac may inhibit the production of epithelial growth factors that would otherwise promote angiogenesis and inhibit apoptosis in proliferating tissue. However, this mechanism is still subject to testing and debate.

Administration[2]

Diclofenac preparations pair the drug with a salt such as sodium, potassium, or epolamine salt. Diclofenac sodium can be administered orally as a tablet or suspension, intramuscular in solution, intravenous in solution, transdermal in gel, or rectal routes as a suppository. Diclofenac potassium is available for oral administration in oral tablet or suspension forms. Diclofenac epolamine is available as a transdermal patch.

When orally administered, diclofenac is absorbed rapidly and binds to albumin in the plasma. The drug concentrates in synovial fluids, where it renders its targeted action as an NSAID for

relief musculoskeletal inflammation and ailments. It has both extended-release and immediate-release forms that vary in doses. Oral administration of diclofenac, like other NSAIDs, carries the risk of gastrointestinal upset and is recommended to consume the medication with food or milk in all age groups. In addition, there are formulations of diclofenac combined with misoprostol to mitigate gastrointestinal adverse effects. It is common practice for clinicians to prescribe gastric acid-reducing therapies such as proton pump inhibitors (PPI) for concomitant use with NSAIDs to reduce the risk of more serious gastrointestinal (GI) adverse reactions. Recommendations may include taking over-the-counter antacids as a form of gastroprotection.

Diclofenac, like other NSAIDs, should be administered at the lowest effective dose to achieve clinical goals to limit the risk of adverse reactions and toxicity.

Oral diclofenac sodium can be administered in delayed-release or immediate-release tablets in 25 to 150 mg tablets to achieve a total daily dose of 100-150 mg per day. These doses are for ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis. Topically, diclofenac sodium is available in gel preparations ranging from 1 to 3% concentrations. Gel with 1 to 2% diclofenac sodium is indicated for topical administration for osteoarthritis for up to 16 g per day for monoarthritis joints and up to 32 g per day for polyarthritic joints. The 3% diclofenac sodium preparation is reserved for treating actinic keratosis and is to be applied twice daily as hybrid therapy. Intravenous diclofenac sodium can be administered as a 37.5 mg bolus injection every 6 hours for acute moderate to severe pain. Intramuscular diclofenac solution comes as a 75 mg/3 mL solution for managing moderate to severe pain, and administration is generally by injection into large muscle groups such as the thigh or buttocks. Ophthalmic preparations are to be administered as 1 to 2 drops per affected eye four times daily following cataract surgery and for treatment of photophobia and eye pain.

Generally, diclofenac potassium is administered in either 25 mg or 50 mg doses 1 to 4 times per day for total doses between 50 to 200 mg per day. This treatment is the indicated regimen for migraines, osteoarthritis, generalized pain, primary dysmenorrhea, and rheumatoid arthritis.

Diclofenac epolamine is available as a 1.3% transdermal patch to be applied twice daily over the affected area to relieve pain and inflammation.

Adverse Effects[2]

Diclofenac has many similar adverse effects shared with the NSAID family of drugs due to the inhibition of COX enzymes. Because diclofenac appears to act more selectively on COX-2 inhibition, it has an increased associated risk of cardiovascular events and less risk for gastrointestinal events, but this article will also examine the gastrointestinal risk for completeness. The following side effects involve systemic effects that arise from systemic exposure to diclofenac. These are less likely to be involved in the topical application of the medication, as there is less risk of systemic exposure to the drug.

Cardiovascular: all NSAIDs, especially more selective COX-2 inhibitors, carry an increased risk of myocardial infarction (MI), heart failure, stroke, and death. The risk of these events is worse for patients with pre-existing susceptibility for cardiovascular disease and with increasing doses. Therefore, it is crucial to use the lowest effective dose for the treatment of the patient's condition. COX-2 inhibition decreases the synthesis of prostaglandin-I2 (PGI2), which has cardioprotective effects in the form of preventing thrombogenesis, increased blood pressure, and generation of atherosclerotic plaques. The risk of these events is worse for patients with pre-existing susceptibility for cardiovascular disease and with increasing doses. COX-2 inhibition decreases the synthesis of prostaglandin-I2 (PGI2), which has cardioprotective effects in the form of preventing thrombogenesis, increased blood pressure, and generation of atherosclerotic plaques. COX-1 is responsible for synthesizing thromboxane A2 (TXA2), a prothrombotic species, and the imbalance between TXA2 and PGI2 may contribute to these increased cardiovascular events.

Gastrointestinal (GI): NSAIDs that block COX-1 activity have correlations with GI complications due to the inhibition of the synthesis of gastroprotective agents such as PGE2 and other prostaglandins. This inhibition leads to decreased mucin production by gastric epithelial cells, less bicarbonate secretion, and less epithelial cell turnover, among other actions. This characteristic of the drug leads to an overall increased risk of acid-mediated damage to gastric epithelial cells and decreased ability to reproliferate the damaged areas and lead to GI injury ranging from mild erosion to frank ulceration visible through endoscopy. It is important to consider that studies have shown that GI damage occurs over extended periods of exposure to the adverse GI effects of NSAIDs. Therefore, clinicians frequently prescribe a gastroprotective agent such as a PPI or PGE2 analog to decrease acid production or increase gastroprotective activity, respectively. However, more selective COX-2 inhibitors such as

diclofenac have decreased risk of GI adverse effects such as bleeding, perforation, and ulceration.

Renal: Extended NSAID use also correlates with the development of renal complications. Similar mechanisms of protective prostaglandin synthesis are involved in this and center on decreased PGE2 and PGI2 activity—these act to dilate the blood vessels in the kidney to allow for proper perfusion for the tissue. Decreased prostaglandin synthesis has links with decreased renal perfusion and the development of acute kidney injury (AKI). This risk increases in patients with prior history of kidney damage and reduced perfusion pressure.

Hepatic: NSAIDs, including diclofenac, can cause drug-induced hepatic damage and increases in liver transaminase levels. These events are usually transient and reversible. Although rare, patients exposed to long-term NSAID treatment can develop hepatitis and face a life-threatening adverse effect. These are more prevalent in patients taking long-term diclofenac for rheumatoid arthritis.

Anaphylaxis: Anaphylaxis to NSAID medications is an uncommon reaction but is still worth noting. Patients with a history of anaphylactic reactions to this drug class are at a higher risk of developing a similar reaction to diclofenac. Symptoms of these types of reactions can include urticaria, flushing, changes in heart rate, bronchospasm, angioedema, hypotension, and others.

Hematologic: increased risk of bleeding has correlations with NSAID use due to the effects of inhibiting platelet aggregation and adhesion via COX-1 inhibition. Also, in rare instances, patients can experience neutropenia and aplastic anemia.

Dermatologic: the topical application of diclofenac may cause mild to moderate skin irritation at the application site.

Contraindications[2]

Like other selective COX-2 inhibitors, diclofenac is contraindicated with an FDA boxed warning in patients with a history of increased cardiovascular risk such as MI or stroke. Diclofenac should not be used in bypass graft surgery of coronary artery due to a higher risk of MI and stroke. Diclofenac is also listed as a Beers list drug and should be avoided in elderly patients due to potential adverse effects involving the cardiovascular and gastrointestinal

systems. It is also contraindicated in patients with a history of anaphylactoid reaction to NSAID drugs.

Also, diclofenac is contraindicated in patients with mild or severe renal insufficiency due to potential negative effects of decreased renal perfusion. Clinicians should not use diclofenac or other NSAIDs in patients with a history of GI bleeds or ulcerations. Special monitoring is a consideration in patients with a history of *Helicobacter pylori* infection. Formulations of diclofenac with misoprostol are contraindicated in pregnant females due to possible side effects involving loss of pregnancy associated with misoprostol.

Monitoring[2]

Patients taking diclofenac should be monitored frequently for symptomatic relief to maintain the lowest effective dose to limit the emergence of potential adverse effects. Blood pressure requires regular monitoring to assess the possible development of hypertension. Symptoms of GI distress, including the development of symptoms associated with gastroesophageal reflux disease (GERD) and lower GI bleeds, should be assessed in patients. Prescribers should observe renal function due to the adverse effects involving kidney perfusion. Regular blood testing including complete blood count (CBC) is crucial to monitor potential adverse effects on platelet function and count and subsequent risk of bleeds. Regular liver function testing is also necessary.

Toxicity[2]

Diclofenac's potential for toxicity is associated with polymorphisms of the cytochrome P450 gene family, which affects the patient's potential for drug metabolism. OTC NSAID toxicity is not uncommon but is generally limited to mild symptoms with a low risk of serious effects. These effects are usually limited to GI upset, nausea, and dizziness. Severe overdose may lead to more serious symptoms involving seizure, coma, cardiovascular events, and metabolic acidosis.

There is no antidote for diclofenac (or other NSAID toxicity). Therefore, treatment is supportive. NSAID toxicity is manageable with the maintenance of circulation and breathing

in critical patients. Patients with limited GI toxicity can receive activated charcoal to avoid GI contamination. Clinicians should address acid-base balance in patients.

Serratiopeptidase[3]

Conventionally, serratiopeptidase is produced from *Serratia marcescens*, a Gram negative opportunistic pathogen in nutrient rich growth medium. The details of production process and media optimization were explained in earlier review. It has been shown to have maximum activity at pH 9.0 and temperature 40 °C and is inactivated at 55 °C in 15 min. It is stable in a wide range of pH (pH 3–10) as revealed in the circular dichroism study, where it showed stable secondary structure. The gene encoding serratiopeptidase is made up of 470 amino acids, devoid of sulfur containing amino acids. The enzyme is produced, purified, characterized and modeled using SWISS-MODEL by where authors have authenticated the structure by assessing the Ramachandran plot using PROCHECK server.

Presently, the demand of serratiopeptidase for the industry and pharmaceuticals is being satisfied by wild or mutant strains of *Serratia marcescens*. However, the pathogenic nature of the organism and hazard associated with the bulk biomass released after fermentation necessitates the research on the development of recombinant molecule. Attempts have been carried out to express serratiopeptidase genes in *Escherichia coli* using suitable vectors. The failure of many of the attempts attributed to the unregulated intracellular expression of proteases causing cell lysis, growth inhibition, instability of the expression plasmids, lack of protein expression, or deposition of the proteins into non-functional misfolded aggregates. Recently, have demonstrated a production of recombinant serratiopeptidase in *Escherichia coli* successfully. Further, have elucidated the optimized growth media and process conditions for the large scale production of the recombinant serratiopeptidase.

Absorption and safety of serratiopeptidase

Meagre literature is available on the absorption and safety of serratiopeptidase in the human body. It is known that orally taken serratiopeptidase gets absorbed through the intestine and transported into the blood. The intestinal absorption of serratiopeptidase has been tested in rats by evaluating its concentration in plasma, lymph, and inflammatory tissue extract using the sandwich enzyme immunoassay technique. The study showed that the concentration of

serratiopeptidase in plasma and lymph is dose dependent. Peak plasma concentration was reached at 0.25−0.5 h after intake and the enzyme was measurable upto 6 h. Further, demonstrated that the concentration of serratiopeptidase was higher in inflammatory tissue that that of in plasma. The authors proposed that serratiopeptidase is absorbed from the intestine and distributed to inflammatory sites *via* blood or lymph. Serratiopeptidase forms a complex with plasma protease inhibitor alpha-1 macroglobulin in the ratio of 1:1 as observed in a rat study. This binding masks its antigenicity with 20 % retention of its original caseinolytic activity. This complex helps to transport serratiopeptidase *via* blood to the target sites. The dosage of serratiopeptidase generally ranges from 10−60 mg per day (2000/mg Unit activity). It is highly recommended to get a prescription for serratiopeptidase from health experts because its dosage requirement varies depending on the application and disease state.

Serratiopeptidase is a natural molecule that is being used for decades, hence commonly considered as safe. The safety of this enzyme in different areas of therapeutics is supported by several studies in which no side effects or adverse events were reported. However, some studies have reported adverse effects of this molecule, but at a rare frequency. The explanation of the same has been provided above in the respective section of this review. Further, Stevens-Johnson syndrome and buccal space abscess have also been reported as side effects of this molecule. These side effects may be dose dependent or possibly due to a combination effect when used with other drugs. Detailed, scientifically designed controlled clinical studies need to be conducted to further examine the safety profile.

Mode of delivery of serratiopeptidase

Common problems associated with drug delivery are poor solubility, toxicity, instability, incompatibility, and poor penetration. Each drug needs a suitable delivery system depending on its characteristics. Serratiopeptidase suffers high risk of enzymatic degradation in the gastrointestinal tract due to its proteinacious nature. Further, its hydrophilic nature causes low permeability through the intestinal membrane. These factors impose the use of a very high dosage for significant effects. Controlled and sustained released of serratiopeptidase is vital approach to decrease the frequency of dosing and to improve patient compliance. Hence, different delivery modes have been studied including magnetic nanoparticles, microspheres, encapsulation in liposomes, and emulsification. *In vitro* release profiles and *in vivo* efficacy are important parameters need to be studied to develop suitable delivery modes.

New modes of delivery have been evaluated in cases of dentistry and wound healing. Novel effective biocompatible moist system for complete wound management was studied by. Poly(D,L-lactic-co-glycolic acid) microspheres of serratiopeptidase and gentamicin were entrapped into polyvinyl alcohol-gelatin hydrogel. *In vitro* and *in vivo* studies showed the direct sustained release of serratiopeptidase along with antibiotics at the wound site leading to a better and faster healing process. developed a topical formulation of serratiopeptidase in the form of an ointment and a gel and evaluated its anti-inflammatory effects. The authors highlighted that topical application circumvents the drawbacks of oral delivery including anorexia, nausea, and GI disturbance, if any. An optimized formulation was evaluated for *in vitro* release profile and *in vivo* anti-inflammatory action where it showed satisfactory inhibition of ear edema in a rat study. The absence of any allergic reaction in rats supports the safety profile of the serratiopeptidase formulation. Enteric dispersion of serratiopeptidase with the polymer Eudragit has shown promising results for controlled release of the drug.

The Enzyme and Its Properties[4]

Japanese researchers were the first to report and introduce the anti-inflammatory drug serratiopeptidase to the world. Enzyme formulations were created, and were widely used as medicines. After 1970, these enzyme formulations were eventually successfully marketed worldwide. The clinical studies carried out by researchers in Europe and Japan suggested serratiopeptidase as a potent anti-inflammatory drug. Hence, the demand for enzyme began increasing worldwide. Serratiopeptidase is a metalloprotease enzyme with a molecular weight of 45–60 kDa. The enzyme contains zinc at the active site. Serratiopeptidase belongs to the group serralysin and has an EC number of 3.4.24.40. The enzyme consists of 470 amino acids which are important for its proteolytic activity. The enzyme is devoid of sulfur-containing amino acids such as cysteine and methionine. Serratiopeptidase showed maximum activity at pH 9 and 40 °C, and can be inactivated at 55 °C for 15 min.

Anti-Inflammatory Action of Serratiopeptidase

Inflammation is an innate immune response that causes redness, swelling, and pain in the human body. It is regarded as a response of the human body against any irritant, and can be caused by many reasons, such as pathogens, injuries, and damage of cells. Hence, inflammation

can be regarded as a healing mechanism of our bodies to maintain homeostasis. It has been observed that NSAIDs are the most commonly used drugs for inflammation. Anti-inflammatory drugs can interact with (cyclooxygenase) COX-I and COX-II molecules. Among these enzymes, COX-I is responsible for the breakdown of arachidonic acid, which is responsible for the production of interleukins and prostaglandins. Serine proteases are known to have a great affinity for these molecules, and can act as anti-inflammatory agents. The enzymes regulated inflammatory cytokines, modified cell adhesion molecules, and acted at the site of inflammation. In the absence of this enzyme, pain and swelling occurred at the area of injury and initiated the release of prostaglandins. (Figure 1a). This led to the onset of cascade reactions. Serratiopeptidase has the ability to bind with cyclooxygenase and suppress the release of interleukins and prostaglandins. (Figure 1b). The oral administration of serratiopeptidase tablets reduce pain and inflammation. The enzyme has its mode of action on arachidonic acid pathway (COX I and COX II), and acts on the cyclooxygenase pathway, but not on the lipooxygenase pathway (LOX). The lipooxygenase pathway (LOX) is involved in the regulation of inflammation by mediating the catalysis of SPM (specialized pro-resolving mediators) biosynthesis, and non-specific NSAID inhibition.

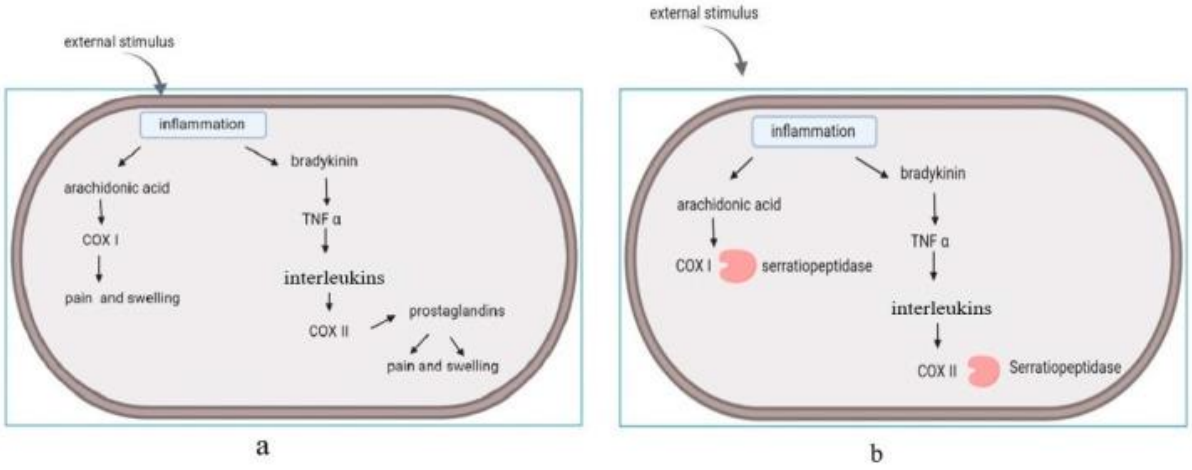

Figure 1. Arachidonic acid pathway: (a) release of interleukins and prostaglandins induce the pain and swelling. (b) Mode of action: serratiopeptidase acts on the cyclooxygenase enzyme (COX I and COX II) and suppresses the release of interleukins and prostaglandins

Wound-Healing Activity of Serratiopeptidase

In addition to the anti-inflammatory property, the enzyme also helps in wound healing. The enzyme acts by dissolving the dead tissue around the wound and hydrolyses bradykinin, serotonin, and histamine. This improves the microcirculation at the site of injury and results in wound healing. There are four phases in a typical wound healing mechanism. These include the hemostasis phase, the inflammatory phase, the proliferative phase, and the maturation phase. This enzyme can enhance microcirculation and help to maintain hemostasis. Serratiopeptidase is known to reduce the capillary permeability induced by histamine, bradykinin, and serotonin, and has the ability to break the abnormal exudates and proteins as well as to improve the absorption of decomposed products through blood and lymphatics. Serratiopeptidase, along with metronidazole, was found to be effective in improving wound healing in rabbits. Another finding regarding serratiopeptidase was related to the tissue repair mechanism. At the site of an inflamed wound, the enzyme assisted in reducing the amount of fluids drained to the wound and facilitated microcirculation, hence improving tissue repair. In a recent comparative study, the effectiveness of an enteric-coated tablet comprising fixed-dose combination (FDC) of trypsin 48 mg, bromelain 90 mg, and rutoside trihydrate 100 mg with serratiopeptidase 10 mg was observed. The results showed that serratiopeptidase was less effective than trypsin, bromelain, and rutoside trihydrate. One reason for the lower efficiency may be a low dosage. A higher concentration of the drug may be more stable at gastric pH, and can facilitate the healing process.

Antibiofilm Activity of Serratiopeptidase

In biofilms, serratiopeptidase can alter the pathogenic phenotype of a bacterium. The use of dispersion agents may improve the effectiveness of current therapeutics. The enzymatic agents dispersin B, lysostaphin, alpha amylase, V8 protease, and serratiopeptidase were tested against methicillin-resistant and susceptible strains of *S. aureus* biofilms, both individually and in combination with vancomycin and rifampicin. When coupled with any of the dispersal agents, the effectiveness of the antibiotics was increased. Lysostaphin and serratiopeptidase were found to be the most effective dispersion agents against all of the tested strains. Serratiopeptidase, a proteolytic enzyme, was originally suggested by Selan et al. for the treatment of biofilm-related illnesses nearly twenty years ago. Most recently, an *S. epidermidis* (a high-slime-producing strain) infected rat model was treated with an

intramuscular injection of serratiopeptidase. It was noted that 94.4% of the infected mice were recovered when compared to 62.5% in the group treated with antibiotics. In the in vivo animal models, serratiopeptidase effectively acted against bacteria that produced biofilms. The antibiofilm function of enzyme may enhance the effectiveness of antibiotics in reducing *Staphylococcal* infections.

Another observation regarding the serratiopeptidase enzyme based on its anti-biofilm activity was against a fully matured *Staphylococcus aureus* biofilm. The researchers constructed an Spep mutant by replacing the glutamic acid in the catalytic site with another amino acid (alanine), and evaluated the anti-biofilm activity of the Spep mutant. The research reports revealed that there was no proteolytic activity for the mutant strain; nevertheless, it was able to retain its anti-biofilm activity. Serratiopeptidase is known to exhibit the property of modifying the adhesion molecules and thereby reducing the cell surface proteins. Selan et al. reported that the enzyme could alter the biofilm association of virulent strains, and that it showed activity against a completely developed biofilm. Biofilms are normally difficult to destroy. Serratiopeptidase, in combination with other antibiotics, exhibited potent anti-bioflim activity. The serratiopeptidase enzyme has reduced the expression of *Listeria monocytogens* cell surface proteins such as Ami4b, internalin B, Act A, and autolysin. The enzyme significantly precluded the adhesion of *Listeria monocytogens* in the human digestive tract. According to previous reports, interestingly, it was found that the enzyme has the ability to interact only with the cell adhesion molecules that formed the biofilm. No cytotoxic activity was recorded. The enzyme showed its effect on discrete surface proteins such as At1. It can act on these surface proteins by altering adhesins and autolysins. In a study reported by Artini et al., it was stated that serratiopeptidase and carboxypeptidase showed activity against biofilm formation of different strains of *Staphylococcus aureus* and *Staphylococcus epidermidis*. The test results of the previous studies showed that only serratiopeptidase inhibited the activity of all strains. The enzyme has the ability to modify the phenotype of virulent bacteria and enhance anti-bacterial properties. Another interesting fact was reported regarding the enzyme: it regulates the recruitment of immune cells to the site of inflammation. The efficacy of serratiopeptidase against biofilm-forming bacteria was proven in experimental animal models. The enzyme serratiopeptidase increased the effectiveness of antibiotics in the treatment of *Staphylococcal* infections. The enzyme can be supplemented with antibiotics for more effective medication.

Mucolytic Activity of Serratiopeptidase

Sputum production, nasal congestion, and cough are observed as some of the prevalent symptoms in COVID-19 patients. Mucolytics can increase bronchial mucus output or decrease mucus viscosity and make it easier to cough up the mucus. Serratiopeptidase may be helpful due to its caseinolytic and mucolytic effects on sputum. In patients with respiratory disorders, serratiopeptidase has improved mucociliary transportability and mucociliary clearance by lowering neutrophils and modifying the viscoelasticity of sputum. Research has revealed a new combination therapy for COVID-19. A combination of vitamin D and serratiopeptidase acts as a strong mucolytic agent, and has the ability to fight against the severe effects of COVID-19 syndrome. Kim et al. has detailed the occurrence of other symptoms such as rhinorrhoea, hypogeusia, and nasal congestion in a large number of patients. Treatment methods such as administration of bronchodilators and mucolytic agents, along with tracheal suction, were the remedial measures for such patients. Several proteolytic enzymes are known to act in a synchronized manner in the control and coordination mechanism of viral entry, viral propagation, and establishment in host cells. The serratiopeptidase enzyme plays a vital role in the treatment of COVID-19 infection. Sharma et al. has conferred the possibility of serratiopeptidase being used as a mucolytic drug in COVID-19 patients. It was found that serratiopeptidase can inhibit the cytokine storm in COVID-19 patients. The elevated expression of transforming growth factor (TGF-α), IL-6, and other chemokines may lead to cytokine storms in COVID-19 patients. Increased levels of IL-6 may cause acute lung disorders. This condition can be treated with medicines. Serratiopeptidase has been suggested as an effective medicine to treat the severe complications of COVID-19. Another post-COVID syndrome is cardiovascular disorder due to increased levels of D-dimers, as well as fibrin or fibrinogen products. The cytokine storm may increase the risk of atherosclerosis and cardiac arrest. The fibrinolytic activity of serratiopeptidase, along with its proteolytic and anti-inflammatory activity, increased its potential for reducing the severity of vascular complications in COVID-19 patients. Kase et al. has detailed the importance of serratiopeptidase as a mucolytic agent, and compared the mucolytic activity of serratiopeptidase with seaprose. Seaprose is a proteolytic enzyme commonly used in the treatment of bronchitis. Both enzymes showed considerable mucolytic activity in the in vivo animal models.

Hemolytic Activity of Serratiopeptidase

The formation of blood clots in blood vessels is a major cause for cardiovascular disorders. Serine proteases are a group of enzymes that includes fibrinolytic enzymes. Serratiopeptidase, which is a serine protease, has high substrate specificity and fibrinolytic activity. The enzyme serratiopeptidase has been shown to contain the property of blood clot lysis, and is able to remove arterial blocks and cysts. The serine metalloprotease extracted from marine *Serratia marcescens* subsp. *sakuensis* showed efficient fibrinolytic activity. Shank et al. compared the hemolytic activity of both mutant and wild type *Serratia marcescens*. Mutant strains of *Serratia marcescens* exhibited hyper hemolysis. The compound serratamolide, a small cyclic amino-lipid produced by *Serratia marcescens,* was reported as an effective hemolytic and anti-microbial agent. It has been observed that the swrW gene played an important role in the biosynthesis of serratamolide, also known as serrawettin. Serratamolide was previously reported as a broad-spectrum antibiotic. The swrW gene is responsible for the production of serratamolide. Wasserman et al. reported that mutations in swrW gene expression or the hexS transcription factor gene (an inhibitor of the swrW gene) enhance the production of serratamolide. In vitro cytotoxic activity of serratamolide was reported against corneal limbal epithelial cells, as well as sheep and mouse red blood cells. The compound serratamolide extracted from *Serratia marcescens* will be an effective anti-microbial and anti-cancer agent in the future.

Synergistic Property of Serratiopeptidase

Maheshwari et al. found that the enzyme was capable of displaying a vast synergistic antimicrobial property with penicillins, fluoroquinolones, tetracycline, and cephalosporins. In combination with antibiotics, the enzyme can exhibit more intense synergistic activity in preventing biofilms. Bacteria have the potential to colonise on any surface and orchestrate a coordinated response. According to reports, COX inhibitors prevent the growth of biofilms effeciently. Previous findings have suggested that cyclooxygenase-dependent synthesis of prostaglandins is necessary for biofilm development. COX inhibitors effectively inhibited the biofilm formation when combined with aspirin, etodolac, diclofenac, celecoxib, nimesulide, ibuprofen, and meloxicam. After 48 h of incubation with aspirin, etodolac along with diclofenac, which were COX-II inhibitors, showed the greatest effect, while aspirin showed 95% inhibition against biofilms. Presently, researchers are focusing more intently on

combination therapy to enhance the anti-inflammatory activity of serratiopeptidase. Vancomycin and rifampicin, combined with enzymatic agents such as serratiopeptidase, dispersin B, alpha-amylase, V8 protease, and lysostaphin, showed an ample amount of action against biofilms formed by methicillin-resistant susceptible strains of *S. aureus* . The efficiency and synergistic action of antibiofilms and serratiopeptidase was improved when combined with dispersal agent. Serratiopeptidase is the most effective dispersion agent against most biofilm-forming bacterial strains.

Table 1: Synergistic property of enzyme with different antibiotics.

Antibiotics	**Effect of Enzymes**
Ofloxacin	Enhanced the activity of ofloxacin and inhibited biofilm formation.
Azithromycin	Effective against different strains of biofilm forming *Staphylococcus* sp.
Levofloxacin	Eradicated > 90% of the preformed biofilm.
Vancomycin and rifampicin	Effective in dispersing most of the biofilm forming bacteria

Therapeutic Aspects of Serratiopeptidase[4]

The anti-inflammatory effects of serratiopeptidase, aspirin, trypsin, and chymotrypsin in Albino rats against carrageenan-induced paw edoema were compared by Viswanatha, Swamy, and Patil. In both acute and subacute types of inflammation in rats, serratiopeptidase had superior anti-inflammatory action both on its own and in combination with aspirin. Along with a histological analysis, several inflammatory indicators, such as C-reactive protein, glutathione, myeloperoxidase, and nitric oxide, were found. When compared to the control group, serratiopeptidase decreased the disease activity index and stopped the formation of nitric oxide, as well as colonic shortening, glutathione depletion, spleen enlargement, and lipid peroxidation. Serratiopeptidase-treated mice had significantly lower C-reactive protein levels than the control mice. Moreover, the use of serratiopeptidase decreased myeloperoxidase, a

significant enzyme marker of inflammation. These findings support serratiopeptidase's ability to reduce inflammation, and thus it has been recognized as a multi-channel enzyme in terms of its wide application in treatments. The enzyme has been successfully applied in atherosclerosis, in which plaques in arteries were dissolved by the proteolytic action of the enzyme. When compared with other enzymes, serratiopeptidase has been successfully used in ortholaryngiology. Researchers have reported the fibrinolytic activity of serratiopeptidase and successfully used it in fibrinolytic therapy. Another known application of serratiopeptidase is in dental implantation, where soft and hard gums developed inflammation upon peri implants, and anti-inflammatory enzymes were used as a treatmen. Serine proteases, along with other drugs, are commonly used in orthopedic medicines to treat chronic inflammation, pain, and swelling. The enzyme has great affinity with COX I and COX II, which are pain mediators. An appropriate study on dosage of the enzyme must be conducted in order to control levels of the enzyme concentration in plasma, as it was found that the amount of enzymes in blood varies with body mass. In 2022, it was reported that the enzyme was not able to bind with LOX or to block lipoxygenase-catalyzed biosynthesis of specialized pro-resolving mediators. A pre-clinical study reported by Jadav et al. indicated that serratiopeptidase was orally effective, and had anti-inflammatory activity which was equivalent to diclofenac sodium in both chronic and acute phases of inflammation. Serratiopeptidase can be used to treat osteoarthritis in combination with metformin. Ateia et al. reported the impact of metformin and serratiopeptidase on knee osteoarthritis in obese patients. Metformin and serratiopeptidase combination tablets were efficient in the treatment of knee osteoarthritis. Ai-Khateeb and Nusair's. clinical study reports revealed the effect of serratiopeptidase in pain reduction, trismus, and post-operative swelling after molar surgery. Small studies in the field of dentistry, otorhinolaryngology, and orthopaedics have revealed reductions in pain and inflammation for ailments such as carpal tunnel syndrome, arthritis, and tooth extraction. Serratiopeptidase tablets have also been used in the treatment of pneumonitis, joint pain, and dermatitis. According to clinical case reports, serratiopeptidase did not show many adverse effects in treated patients. Very few studies have been reported on the anti-cancer activity of serratiopeptidase. The in vitro cytotoxic activity of serratiopeptidase against colon cancer cell lines (Caco-2) was reported by Araghi et al.. The findings of previous reports suggested that the enzyme has anti-cancer potential, but further in vitro and in vivo mechanistic pathway studies are needed in order to confirm the biological activity of the enzyme.

Clinical Significance[4]

Enteric coated tablets are the most commonly available form of serratiopeptidase. Panthi et al. formulated enteric coated tablets for serratiopeptidase, which exhibited persistent, stable, and significantly high drug release in the intestine. In general, glyceryl monooleate-based systems give protection to metallo-enzymes in the gastric environment. In addition, they enhanced the sustained release of the enzyme after oral administration. Shah and Paradkar suggested that a microenvironment-controlled, in situ, cubic phase transforming glyceryl monooleate system may give protection to serratiopeptidase as well as meticulous release. Serratiopeptidase has been used in traumatic and postoperative inflammation, laryngitis, bronchitis, expectoration of sputum in bronchial asthma, gynecology, venous inflammatory disease, cystitis, epididymitis, traumatic swelling, carpal tunnel syndrome, osteoarticular infection, sinusitis, rhinitis, and dentistry. This has caused an increase in demand for the production of the enzyme, and various combinational drugs have been develope. The tablets were taken orally on an empty stomach or 30 min before food. According to clinical studies, when compared to methylprednisolone, serratiopeptidase showed low analgesic action and efficient management of edema and trismus. The oral administration of this enzyme can reduce inflammation and pain in AIDS, as well as in hepatitis B & C infections. This led to an increase in the use of serratiopeptidase in the field of medicine. Cancer nanomedicine has created a revolution in the field of medicine. Serratiopeptidase in combination with nanodrug delivery systems has been an emerging technology in cancer therapy. Anti-inflammatory agents such as serratiopeptidase may help in overcoming the adverse effects of anti-cancer agents. Jaiswal and Mishra reported that the co-delivery of curcumin and serratiopeptidase along with nanoparticles showed enhanced anti-cancer activity against HeLa and MCF-7 cells. Serratiopeptidase can be viewed as a viable competitor in contemporary medicine. Hence, the synergistic activity of serratiopeptidase has a vital role in emphasizing its clinical importance.

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4. Nair SR, C SD. Serratiopeptidase: An integrated View of Multifaceted Therapeutic Enzyme. *Biomolecules*. 2022;12(10):1468.

Survey Form

1) How many patients suffering from pain do you see in your daily practice?

a. 1 - 5
b. 5 – 10
c. > 10

2) What are the most common causes of pain presenting in your daily practice?

a. Acute musculoskeletal pain
b. Pain due to trauma
c. Post-operative pain
d. Pain due to injury
e. Any other

3) In post-operative patients, inflammation is one of the main causes of pain.

a. True
b. False

4) Which is your first choice for treatment of post-operative pain?

a. NSAID (Topical analgesic gel/Spray)
b. NSAIDs
c. NSAID + Serratiopeptidase

5) Which proteolytic enzymes do you prefer for wound management (Post traumatic/surgical/infection)?

a. Serratiopeptidase
b. Trypsin/chymotrypsin
c. Trypsin + Bromelain + Rutoside Tihydrate
d. None of the above

6) Which NSAID will you prefer to combine with Serratiopeptidase for wound management (Post traumatic/surgical/infection)?

a. Aceclofenac
b. Diclofenac
c. Ibuprofen

7) What factors influences your decision for choosing the FDC in Ques 6.?

a. Fast onset of action
b. Better efficacy
c. Proven safety
d. Patient acceptance

8) In which indications do you prescribe Serratiopeptidase?

a. Post-traumatic pain
b. Low back pain
c. Cervical pain
d. Spondylitis (inflammation in spinal bones)
e. Osteoarthritis
f. All of the above

9) In your clinical experience which of the following combination provides better pain relief?

a. Aceclofenac + Serratiopeptidase
b. Diclofenac + Serratiopeptidase

10) Serratiopeptidase enhances the action of some antibiotics.

a. Agree
b. Disagree

11) What is the maximum duration of treatment with above combination?

a. 7 – 14 days
b. 14 – 21days
c. < 21 days

12) A FDC is always better to prescribe than monotherapy.

a. Agree
b. Disagree

13) Which is the commonest side effect with NSAIDs that your patients complain of?

a. Indigestion – including stomach aches, feeling sick and diarrhoea.
b. Stomach ulcers – these can cause internal bleeding and anaemia; extra medicine to protect your stomach may be prescribed to help reduce this risk.
c. Headaches.
d. Drowsiness.

14) What attributes you keep in mind while prescribing a NSAID?

a. Safety
b. Efficacy
c. Cost
d. All of the above

15) A combination of Diclofenac and Serratiopeptidase is always better for postoperative pain management than monotherapy?

a. True
b. False

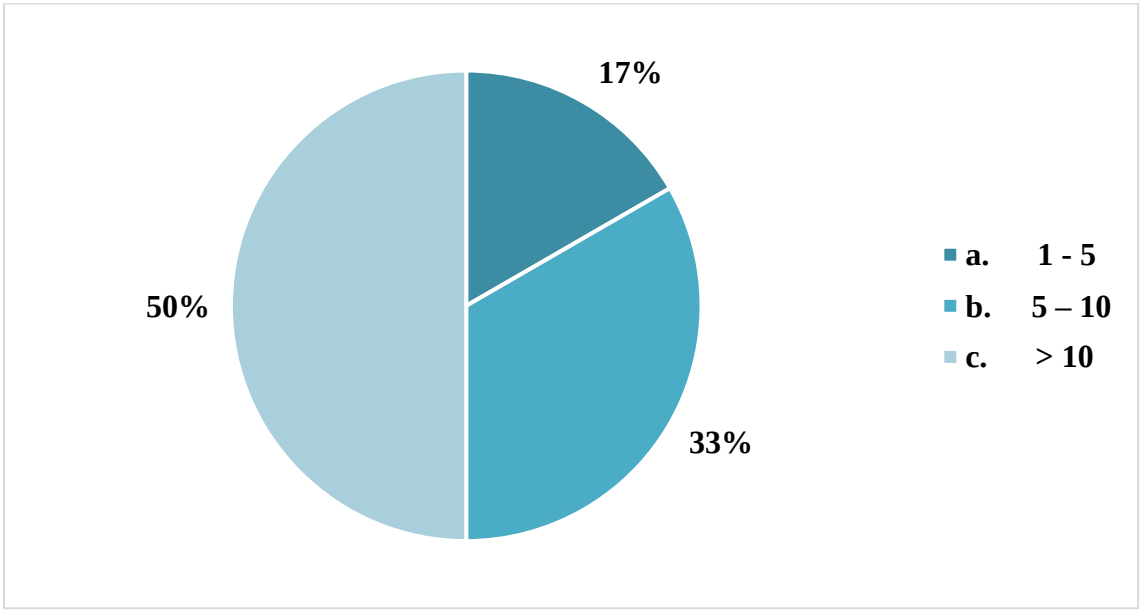
Survey Findings

1) How many patients suffering from pain do you see in your daily practice?

a. 1 - 5

b. 5 – 10

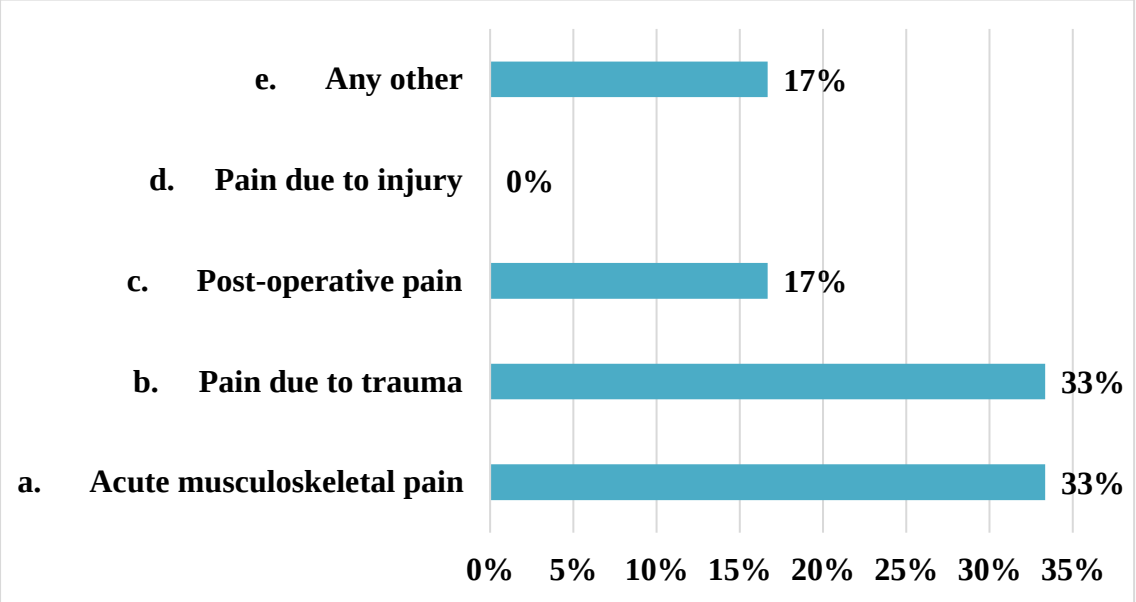
c. > 10



50% of doctors see > 10 patients suffering from pain in their daily practice.

2) What are the most common causes of pain presenting in your daily practice?

a. Acute musculoskeletal pain
b. Pain due to trauma
c. Post-operative pain
d. Pain due to injury
e. Any other

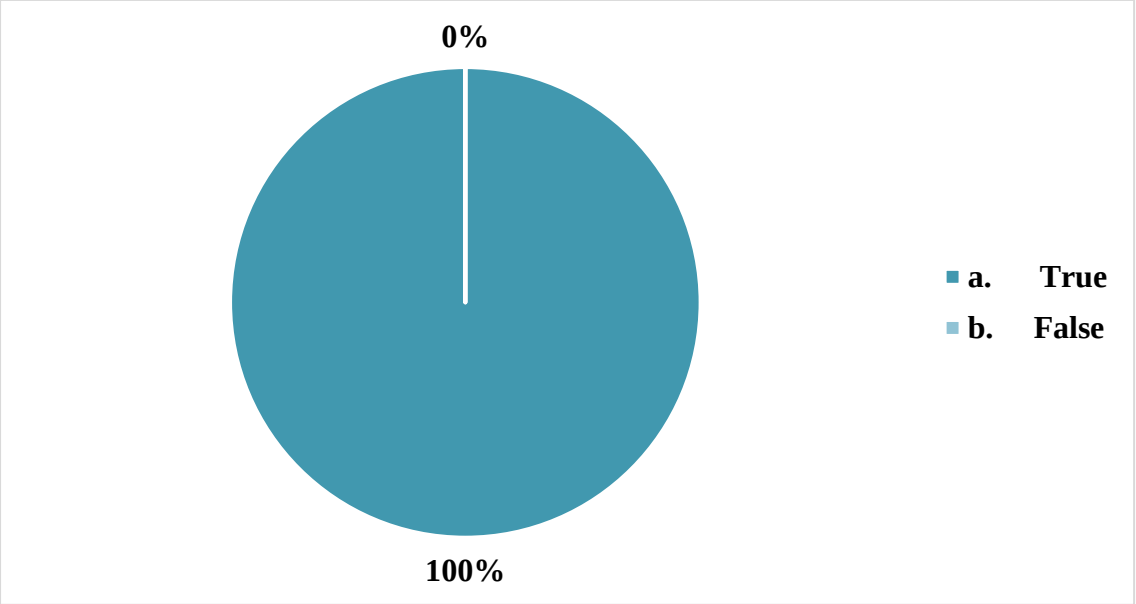


As per 33% of doctors, the most common causes of pain presenting in their daily practice is acute musculoskeletal pain, whereas for another 33% of doctors the cause is pain due to trauma.

3) In post-operative patients, inflammation is one of the main causes of pain.

a. True

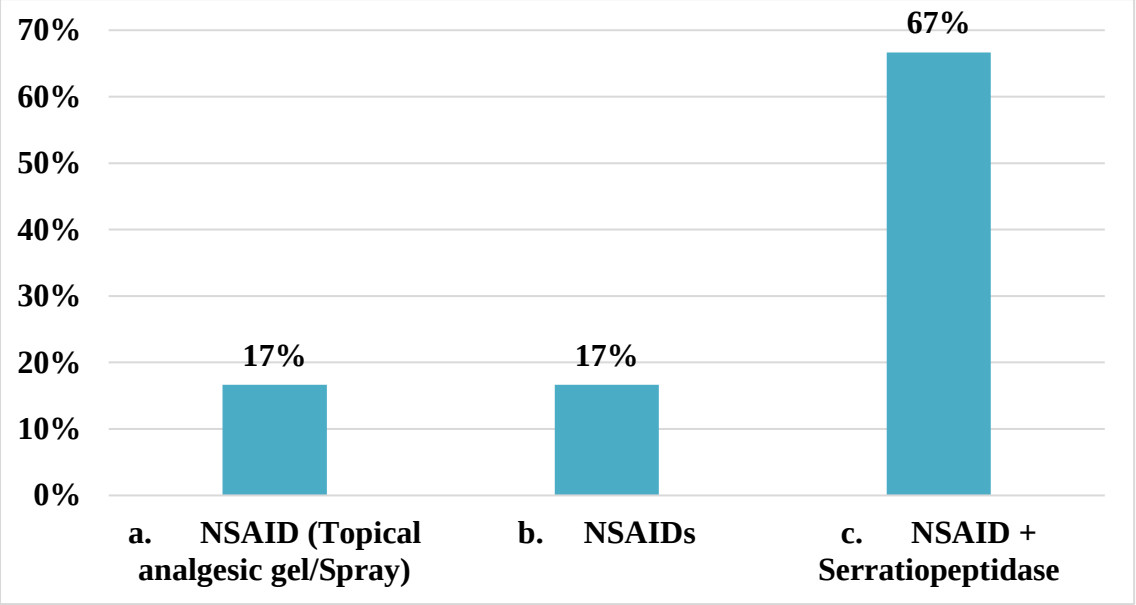
b. False



All the doctors (100%) agree that in post-operative patients, inflammation is one of the main causes of pain.

4) Which is your first choice for treatment of post-operative pain?

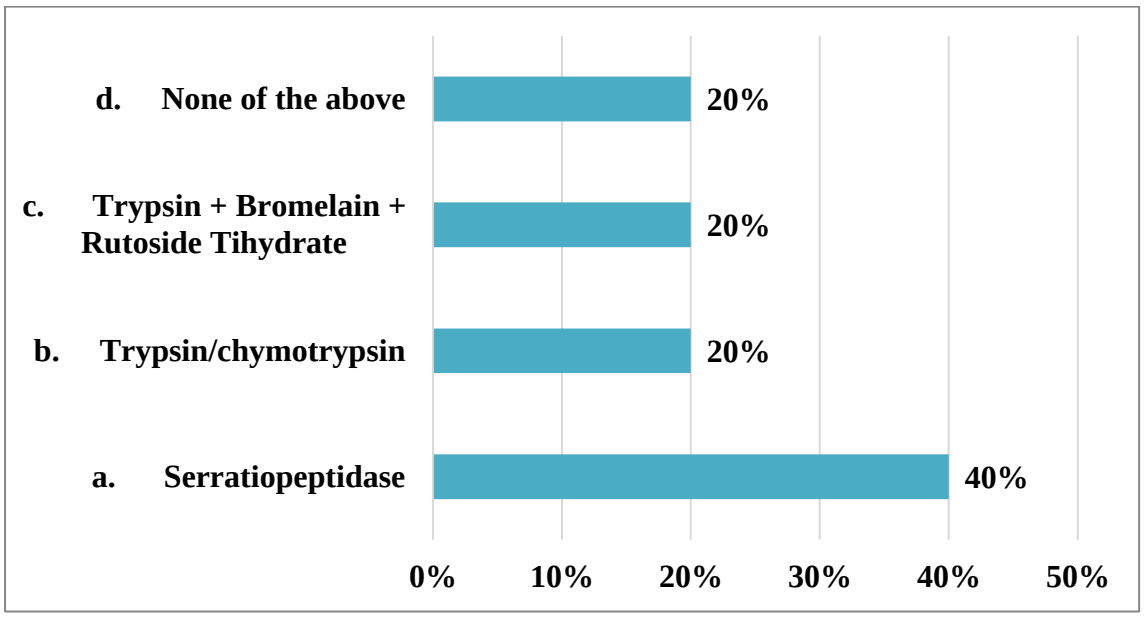
a. NSAID (Topical analgesic gel/Spray)
b. NSAIDs
c. NSAID + Serratiopeptidase



For majority of doctors, 67%, the first choice for treatment of post-operative pain is NSAID + Serratiopeptidase.

5) Which proteolytic enzymes do you prefer for wound management (Post traumatic/surgical/infection)?

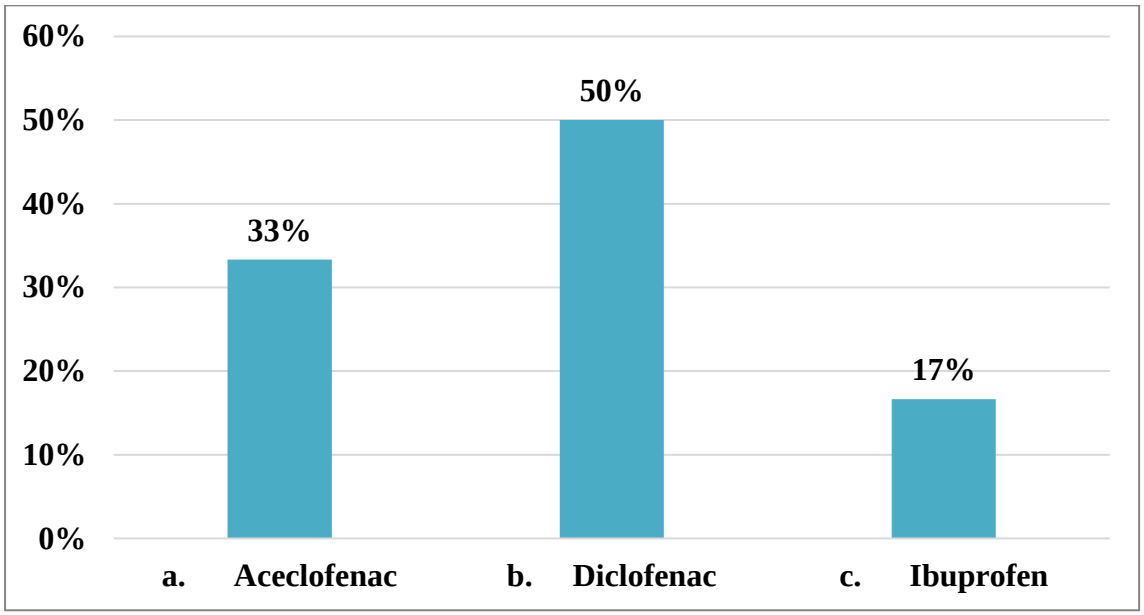
a. Serratiopeptidase
b. Trypsin/chymotrypsin
c. Trypsin + Bromelain + Rutoside Tihydrate
d. None of the above



40% of doctors prefer Serratiopeptidase proteolytic enzymes for wound management (Post traumatic/surgical/infection).

6) Which NSAID will you prefer to combine with Serratiopeptidase for wound management (Post traumatic/surgical/infection)?

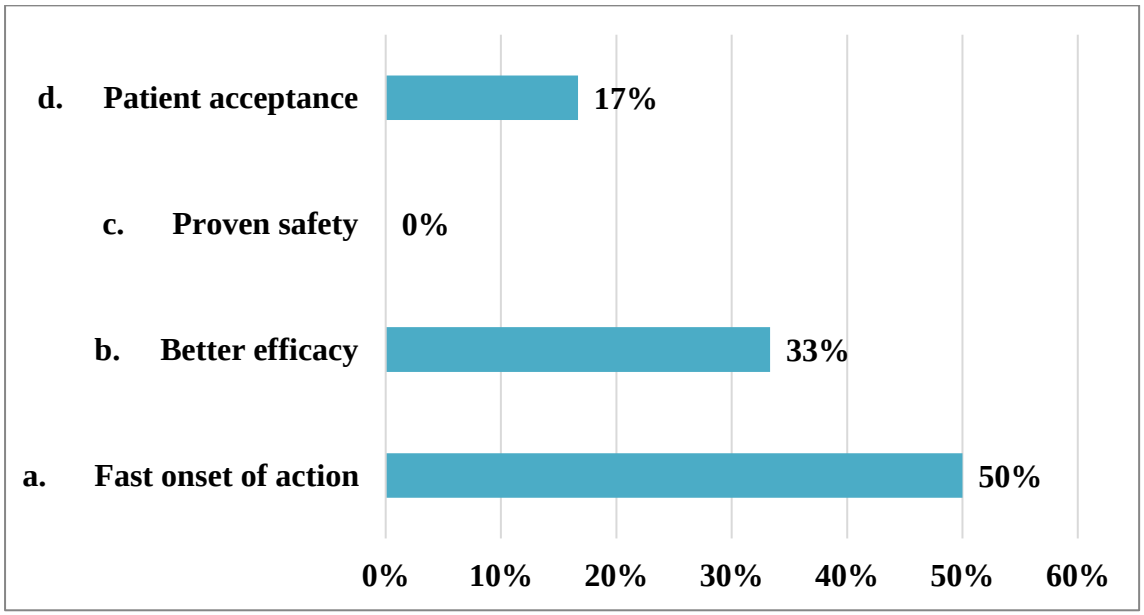
a. Aceclofenac
b. Diclofenac
c. Ibuprofen



50% of doctors would prefer Diclofenac to combine with Serratiopeptidase for wound management (Post traumatic/surgical/infection).

7) What factors influences your decision for choosing the FDC in Ques 6.?

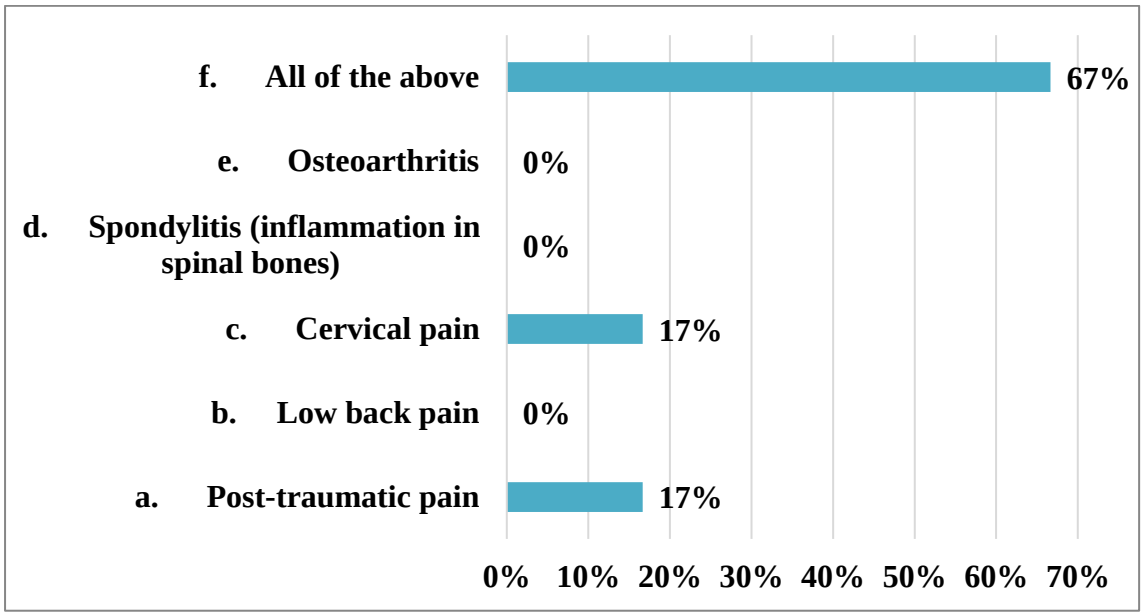
a. Fast onset of action
b. Better efficacy
c. Proven safety
d. Patient acceptance



According to 50% of doctors, fast onset of action influences their decision for choosing the FDC in Ques 6.

8) In which indications do you prescribe Serratiopeptidase?

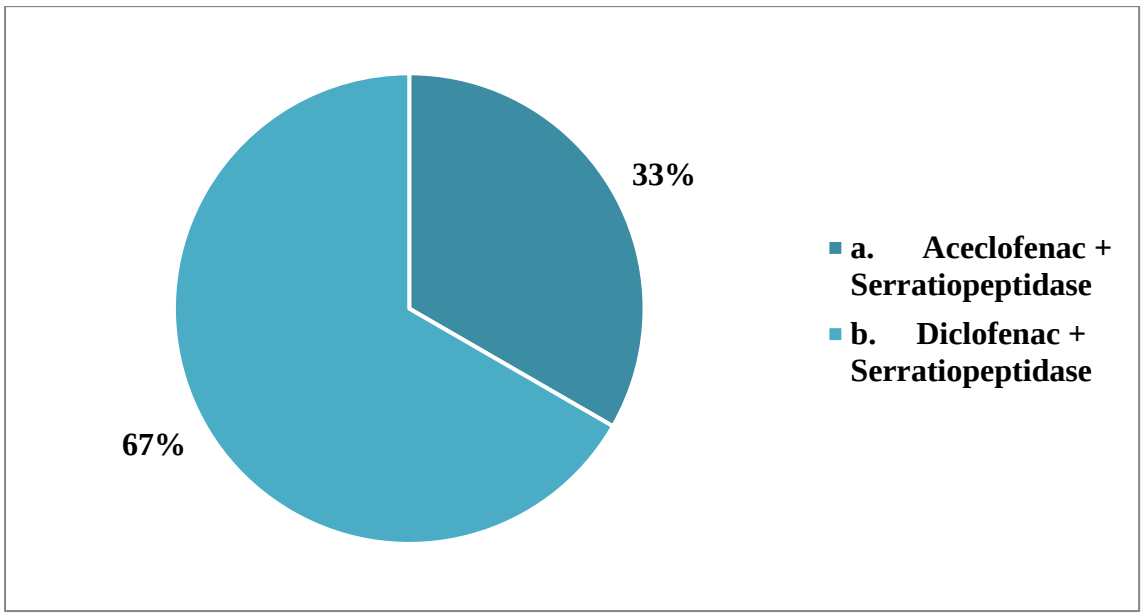
a. Post-traumatic pain
b. Low back pain
c. Cervical pain
d. Spondylitis (inflammation in spinal bones)
e. Osteoarthritis
f. All of the above



Majority of doctors prescribe Serratiopeptidase for post-traumatic pain, low back pain, cervical pain, spondylitis (inflammation in spinal bones) and osteoarthritis.

9) In your clinical experience which of the following combination provides better pain relief?

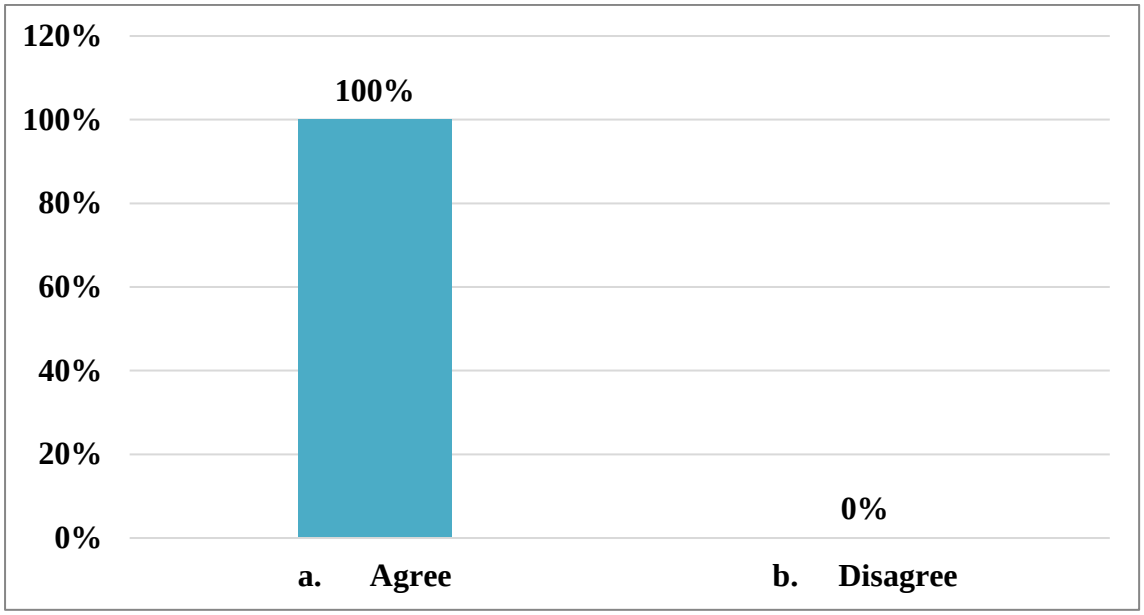
a. Aceclofenac + Serratiopeptidase
b. Diclofenac + Serratiopeptidase



In the clinical experience of 67% of doctors, the combination of Diclofenac + Serratiopeptidase provides better pain relief.

10) Serratiopeptidase enhances the action of some antibiotics.

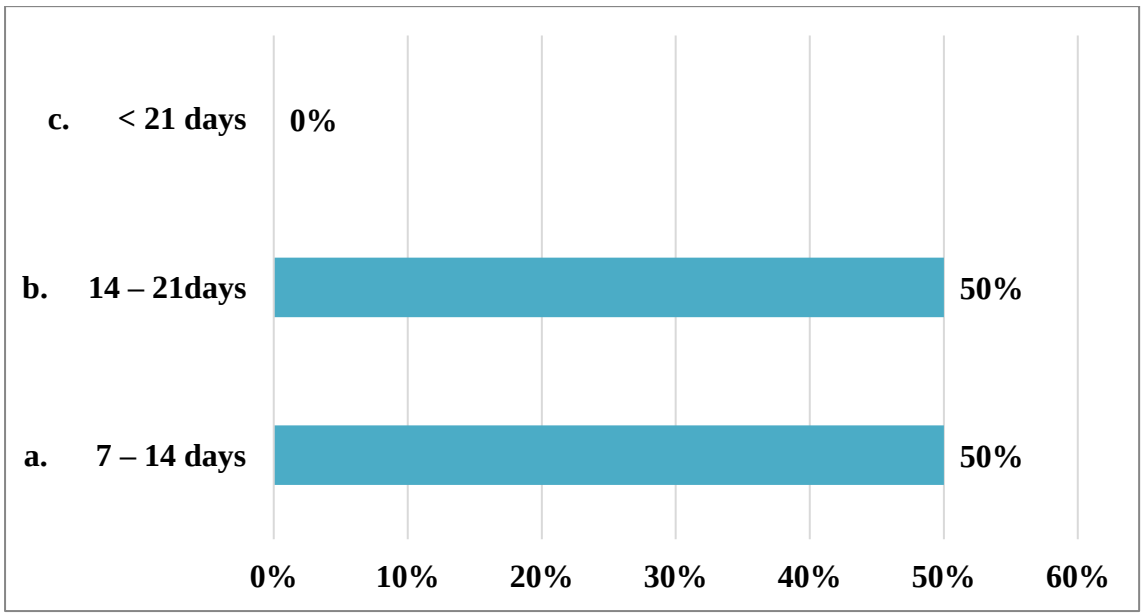
a. Agree
b. Disagree



All the doctors (100%) agree that Serratiopeptidase enhances the action of some antibiotics.

11) What is the maximum duration of treatment with above combination?

a. 7 – 14 days
b. 14 – 21days
c. < 21 days

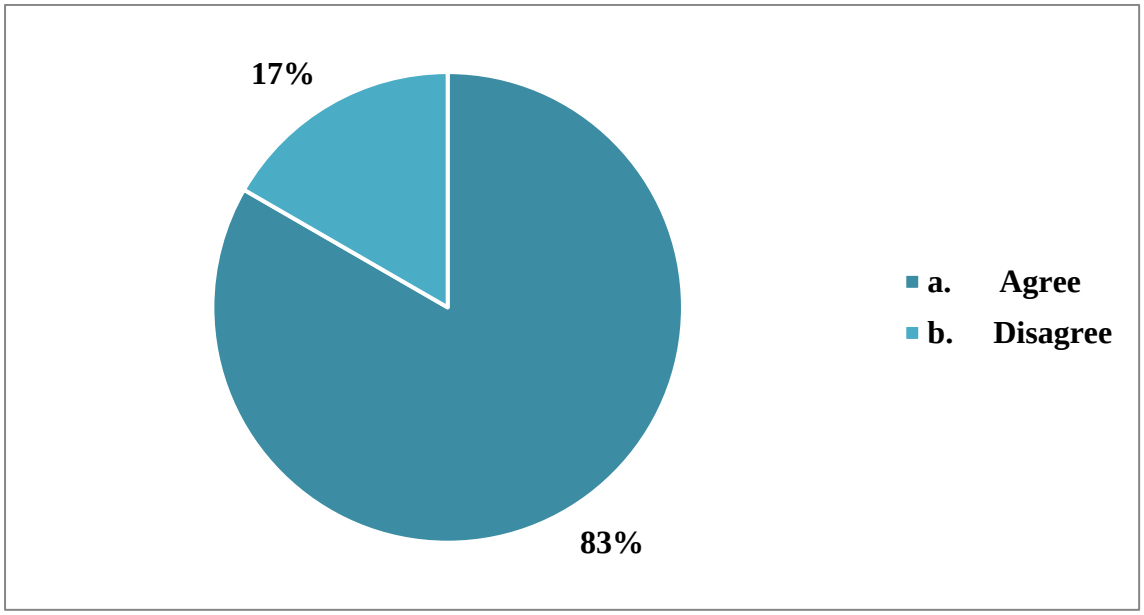


Half the doctors (50%) consider 7 – 14 days whereas other 50% of doctors consider 14 – 21 days to be the maximum duration of treatment with above combination.

12) A FDC is always better to prescribe than monotherapy.

a. Agree

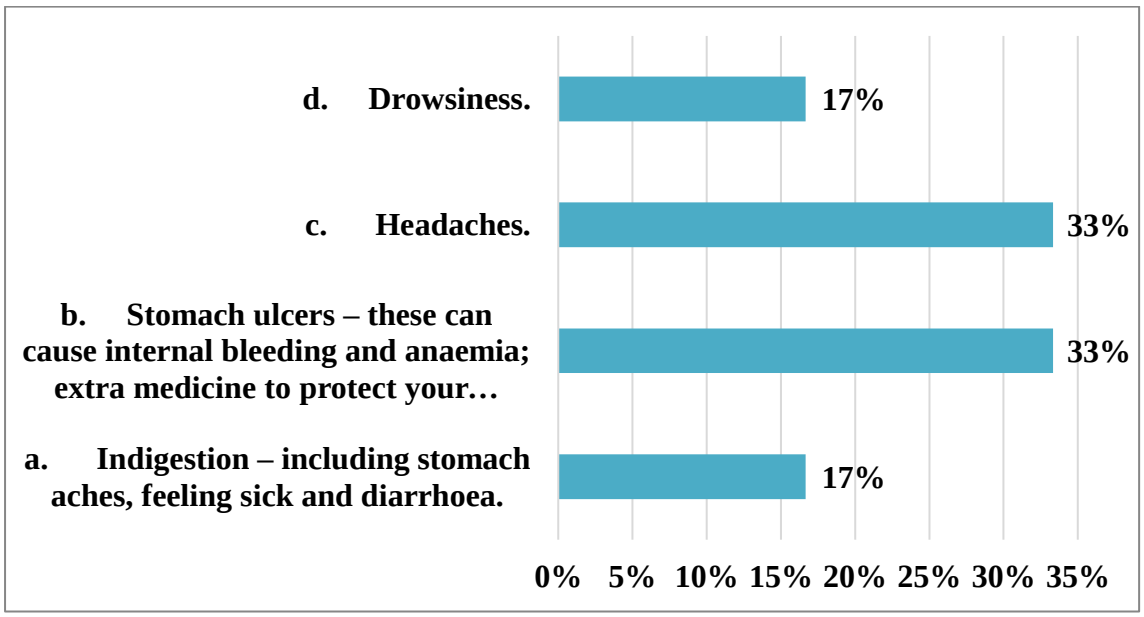
b. Disagree



Majority of doctors, 83%, agree that a FDC is always better to prescribe than monotherapy.

13) Which is the commonest side effect with NSAIDs that your patients complain of?

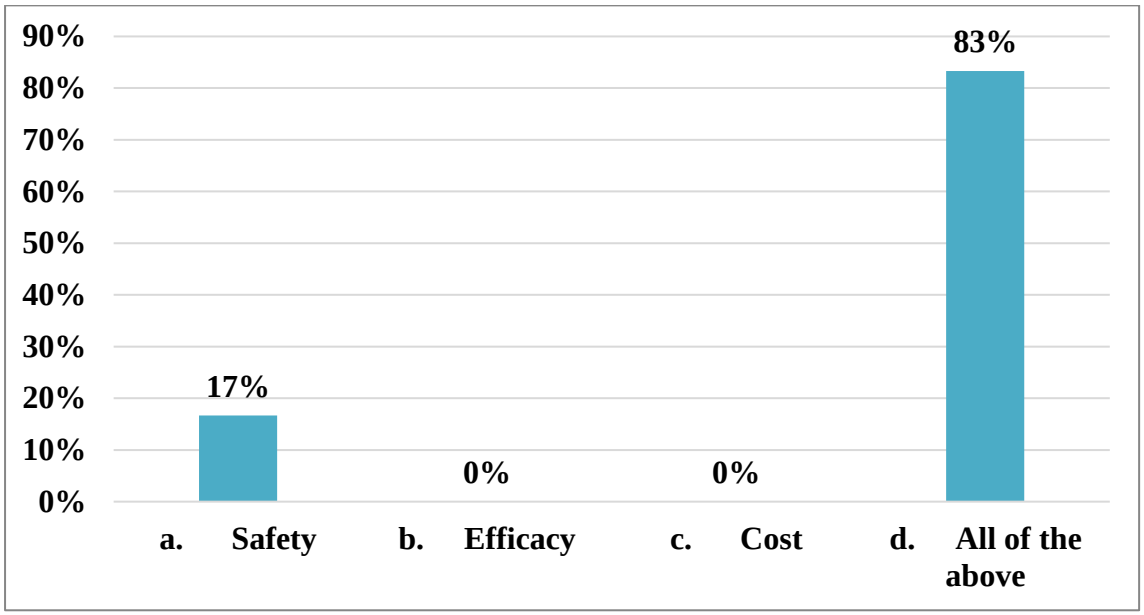
a. Indigestion – including stomach aches, feeling sick and diarrhoea.
b. Stomach ulcers – these can cause internal bleeding and anaemia; extra medicine to protect your stomach may be prescribed to help reduce this risk.
c. Headaches.
d. Drowsiness.



According 33% of doctors, the commonest side effect with NSAIDs that their patients complain of is headaches, whereas according to another 33% of doctors, the side effect is and stomach ulcers – these can cause internal bleeding and anaemia; extra medicine to protect stomach may be prescribed to help reduce this risk.

14) What attributes you keep in mind while prescribing a NSAID?

a. Safety
b. Efficacy
c. Cost
d. All of the above

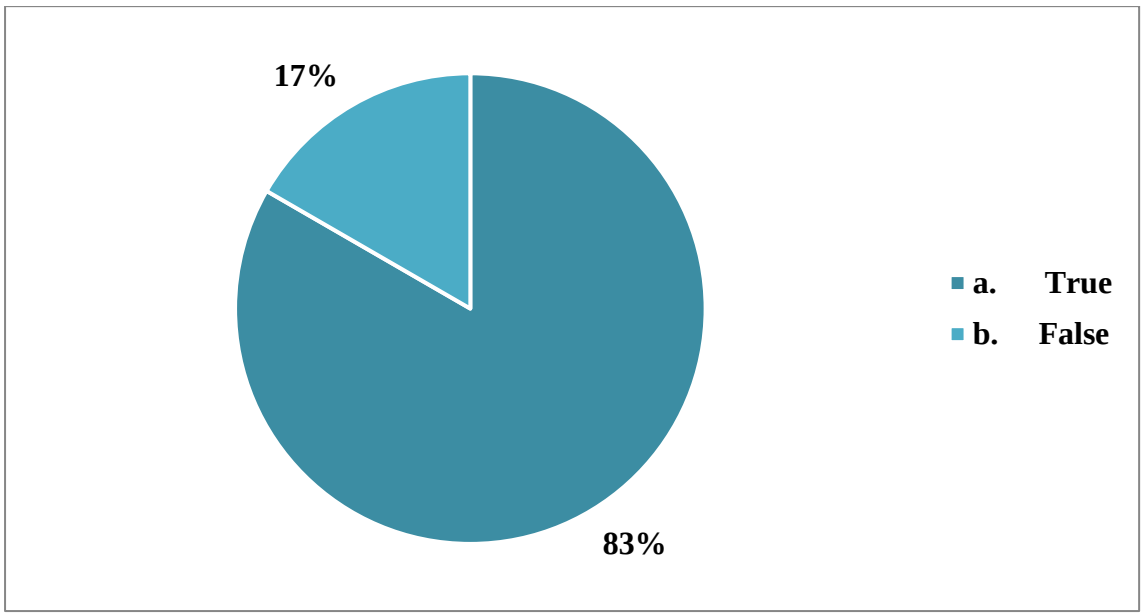


Majority of doctors, 83%, keep in mind safety, efficacy and cost while prescribing a NSAID.

15) A combination of Diclofenac and Serratiopeptidase is always better for postoperative pain management than monotherapy?

a. True

b. False



Majority of doctors, 83%, agree that a combination of Diclofenac and Serratiopeptidase is always better for postoperative pain management than monotherapy.

Summary

- 50% of doctors see > 10 patients suffering from pain in their daily practice.
- As per 33% of doctors, the most common causes of pain presenting in their daily practice is acute musculoskeletal pain, whereas for another 33% of doctors the cause is pain due to trauma.
- All the doctors (100%) agree that in post-operative patients, inflammation is one of the main causes of pain.
- For majority of doctors, 67%, the first choice for treatment of post-operative pain is NSAID + Serratiopeptidase.
- 40% of doctors prefer Serratiopeptidase proteolytic enzymes for wound management (Post traumatic/surgical/infection).
- 50% of doctors would prefer Diclofenac to combine with Serratiopeptidase for wound management (Post traumatic/surgical/infection).
- According to 50% of doctors, fast onset of action influences their decision for choosing the FDC in Ques 6.
- Majority of doctors prescribe Serratiopeptidase for post-traumatic pain, low back pain, cervical pain, spondylitis (inflammation in spinal bones) and osteoarthritis.
- In the clinical experience of 67% of doctors, the combination of Diclofenac + Serratiopeptidase provides better pain relief.
- All the doctors (100%) agree that Serratiopeptidase enhances the action of some antibiotics.
- Half the doctors (50%) consider 7 – 14 days whereas other 50% of doctors consider 14 – 21 days to be the maximum duration of treatment with above combination.
- Majority of doctors, 83%, agree that a FDC is always better to prescribe than monotherapy.
- According 33% of doctors, the commonest side effect with NSAIDs that their patients complain of is headaches, whereas according to another 33% of doctors, the side effect is and stomach ulcers – these can cause internal bleeding and anaemia; extra medicine to protect stomach may be prescribed to help reduce this risk.
- Majority of doctors, 83%, keep in mind safety, efficacy and cost while prescribing a NSAID.

- Majority of doctors, 83%, agree that a combination of Diclofenac and Serratiopeptidase is always better for postoperative pain management than monotherapy.

Consultant Opinion

Market Opportunities:

There is a significant market opportunity for pharmaceutical companies to develop fast-acting fixed-dose combinations (FDCs) of Diclofenac and Serratiopeptidase for wound management and post-operative pain. These formulations could address the need for rapid pain relief and improved patient outcomes.

Value for Healthcare Professionals:

Healthcare professionals should receive education and training on the appropriate use of NSAIDs and Serratiopeptidase in pain management, including their indications, contraindications, and potential side effects. Continuing medical education programs can help ensure that healthcare professionals make informed decisions when prescribing these medications.

Adverse Effect Management:

Healthcare professionals should closely monitor patients for common side effects associated with NSAIDs, such as headaches and gastrointestinal issues like stomach ulcers. Prophylactic measures, such as prescribing additional medication to protect the stomach lining, can help reduce the risk of adverse effects and improve patient safety.

Withdrawal Management:

Clear guidelines should be established for the duration and maximum duration of treatment with combinations of Diclofenac and Serratiopeptidase. Healthcare professionals should tailor treatment plans based on individual patient factors, such as the severity and duration of pain, to optimize outcomes and minimize the risk of adverse effects.

Market Positioning:

Pharmaceutical companies can capitalize on the benefits of combining Diclofenac and Serratiopeptidase for postoperative pain management by emphasizing the superior efficacy of FDCs compared to monotherapy. Marketing strategies should highlight the fast onset of action and enhanced pain relief provided by these combinations, positioning them as preferred options for pain management in clinical practice.

Personalized Treatment Decisions:

Healthcare professionals should consider individual patient factors, such as the type and cause of pain, when selecting the appropriate treatment regimen. Personalized treatment decisions can optimize outcomes and improve patient satisfaction by addressing the specific needs and preferences of each patient.

Improving Patient Outcomes:

Patient education is essential to ensure optimal outcomes with NSAID and Serratiopeptidase therapy. Patients should be informed about the purpose of these medications, potential side effects, and the importance of adherence to prescribed regimens. Additionally, healthcare professionals should regularly assess patient response and adjust treatment plans as needed to achieve successful pain management outcomes.

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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Developed by:

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