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Original Research Article

# Serratiopeptidase with diclofenac sodium for the management of post-operative pain and inflammation in a day care obstetric and gynaecological surgeries

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ABSTRACT

**Background:** Management of acute post-operative pain and swelling after the obstetric and gynaecological (OBG) surgeries is crucial part of patient care. Reduction or complete elimination of post-operative pain & swelling, without excessive sedation is the most preferred treatment strategy helping patient's recovery in terms of rapid mobilization and return to independence. Serratiopeptidase a proteolytic enzyme used for its anti-inflammatory properties. Diclofenac Sodium is commonly used to treat the pain and swelling.

**Objective:** This study aimed to evaluate the effectiveness and tolerability of the fixed dose combination (FDC) of Serratiopeptidase (10 mg) with Diclofenac Sodium (50 mg) gastro-resistant tablets in day care OBG surgery.

**Materials and Methods:** This was a single centre, retrospective, observational data collection in real-life scenario. Data of adult women who had undergone day care OBG surgery and received a FDC of Serratiopeptidase (10 mg) with Diclofenac Sodium (50 mg) gastro-resistant tablets TID for period of 24 hours was retrieved and analysed. VAS (Visual Analogue Scale) data on post-operative pain at rest and pain on movement as well as post-operative swelling were analyzed in conjunction with monitoring for adverse events.

**Result:** Among 61 patient's data included in the study, 40 (65.57%) had undergone Minimally Invasive Vaginal Hysterectomy (MIVH), 4 (6.56%) had MIVH with Bilateral Salpingo-oophorectomy, and 17 (27.87%) had other OBG surgeries. The average VAS scores for pain at rest (VAS), pain on movement (VAS) and swelling were significantly reduced compared to baseline at all-time points ($p>0.001$). Clinical global impression of efficacy and safety for 95% physician's and 93.3% patients was good to very good. FDC was found to be well tolerated without any serious adverse reaction.

**Conclusion:** The results of this clinical study confirms the effectiveness and tolerability of FDC of Serratiopeptidase and Diclofenac sodium in day care OBG surgeries in the early post-operative period.



## 1. Introduction

Postoperative pain is a major complication after surgery which can affect functional recovery and also diminish patients' overall quality of life. Gerbershagen et al. conducted a study regarding pain intensity on the first day post-surgery, it was revealed that several routine minor to moderate surgical procedures, including certain laparoscopic techniques, showed higher-than-anticipated postoperative pain levels.[1] According to this study, patients from the Departments of Obstetrics and Gynaecology reported higher pain scores compared to patients from the other surgical departments.

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Inflammation plays critical role in the postoperative pain pathophysiology. Due to surgical procedures tissue damages and inflammatory cells proliferate at the surgical site, generating inflammatory mediators that induce tissue inflammation.[2] Analgesic or anaesthetic measures are used to inhibit the potential transition from acute to chronic postoperative pain. These measures reduce the frequency and intensity of acute pain during and immediately after surgery.[3] Current treatment strategies in the postoperative pain management includes the usage of systemic non-opioid and opioid pain relievers, along with analgesics, peripheral nerve blockers, and, as per the need, the utilization of additional pharmaceutical agents to alleviate pain.[4]

The attention of surgeons has been focused on the elements of patient care that can be improved in the light of the modern emphasis on managed care and shorter hospital stays. Reducing or even eliminating post-operative pain, without introducing excessive sedation, promotes rapid mobilization and return to autonomy. Targeted multimodal pain management can reduce postoperative ileus and other adverse reactions to analgesics.[5]

One proteolytic enzyme that has been used to lessen inflammation is serratiopeptidase. Because of its anti-inflammatory and anti-edema qualities, enteric coated oral formulations of this enzyme are frequently used in a variety of specialties, including surgery, orthopaedics, otolaryngology, gynecology, and dentistry.[6]

When used in conjunction with surgery, nonsteroidal anti-inflammatory drugs, or NSAIDs, have demonstrated their efficacy as analgesics, as evidenced by either a decrease in pain scores or an opioid sparing effect.[7] Diclofenac is one of the NSAIDs commonly prescribed for pain relief.[8] Although the efficacy and safety of Serratiopeptidase and Diclofenac Sodium has been proven in few randomized clinical trials, data regarding the effectiveness of this combination for relief of symptoms in clinical practice settings in obstetric and gynaecological surgeries, are scarce. Therefore, based on a retrospective pooled analysis of data in clinical practice settings, we have aimed to assess the fixed dose combination (FDC) of Serratiopeptidase (10 mg) with Diclofenac Sodium (50 mg) in day care obstetric and gynaecological surgeries in daily practice.

## 2. Material and Methods

### 2.1. Study design

This was a single centre, retrospective, open label, observational study over 4 weeks in a real-world scenario at the Bapat Hospital, Sukhliya, Indore, India. The study was carried out from 15-January 2022 to 20-March 22.

### 2.2. Patient characteristics

Data of total 61 female patients in age group of 18-65 years, who had undergone day care gynecogical surgery and patients who had hospital stays for minimum 24 hours were enrolled in this study. Patients with a medical history of impaired renal or hepatic function, patients with gastric or duodenal ulceration, patients who were on any narcotic analgesics, and patients who were pregnant were excluded from the study.

### 2.3. Study treatment

Data of all patients who received fixed dose combination (FDC) of Serratiopeptidase 10 mg [Equivalent to Enzyme activity 20,000 units] + Diclofenac Sodium 50 mg gastro resistant tablet (Emanzen-D Tablet) thrice a day orally immediately after surgery were included in this study.

### 2.4. Outcome measure

Primary outcome measure of the study was assessed for pain at rest, pain on movement and swelling on basis of visual analogue scale (VAS) at 1, 2, 4, 6, 8, 12 and 24 hours after surgery compared to baseline. Also, the proportion of patients with moderate to severe symptoms at 24 hours after surgery and proportion of patients who required the use of rescue analgesics over 24 hours after surgery was measured as secondary outcome measure. Safety was assessed with measure of incidence of adverse effects over 24 hours after surgery.

### 2.5. Ethical consideration

The investigator ensured that the study was conducted in accordance with the law of the Declaration of Helsinki, International Conference on Harmonization- Good Clinical Practice (ICH-GCP) directions, and Indian supervisory directions (Indian Council of Medical Research (ICMR), Indian GCP directions) and new drug dispassionate trial rules (March 2019) by Ministry of Health and Family Welfare. Prior approval of the Independent Ethics Committee (IEC) for the protocol, submission of any protocol amendments, consent process, the case report forms (CRFs) and all study related documents were obtained prior to initiation of study.

### 2.6. Study procedure

Patients assessment was recorded by marking the severity of pain at rest, pain on movement, and swelling during each assessment on a visual analogue scale (VAS) of 0 mm to 100 mm.

To assess the efficacy of study medication, improvement in mean VAS symptom of pain at rest, pain on movement, and swelling at 1, 2, 4, 6, 8, 12 and 24 hours were compared with baseline values. The efficacy was assessed

by comparing the improvement in mean VAS symptoms score, proportion of patients with moderate to severe symptoms after the surgery. Any adverse reaction during the course of study was also noted from the medical records. Tolerability profile of the study medication was assessed by comparing the incidence of possible drug-related adverse effects.

### 2.7. Statistical analysis

The data was analysed through unpaired T-test for mean and Chi-square test; p-value < 0.05 was considered as statistically significant.

## 3. Results

A total of 61 patients were retrospectively enrolled in the study. The mean age of the patients was 39.98 yrs. (±SD 9.12). All the patients who had undergone gynecogical surgery during the period of recruitment 15-January 2022 to 20-March 22 and who had hospital stays for minimum of 24 hours were included in this study. Patients underwent different surgeries as given in the Table 1.

**Table 1:** Types of surgeries patients underwent

| Name of surgery | No. of patients (%) |
|---|---|
| Minimally Invasive Vaginal Hysterectomy (MIVH) | 40 (65.57%) |
| MIVH with Bilateral Salpingo-oophorectomy | 04 (6.56%) |
| Caesarean section | 10 (16.39%) |
| Other Obstetric and Gynaecological Surgeries | 07 (11.48%) |

Among the total 61 patients, 40 (65.57%), 4 (6.56%), 10 (16.39%) and 7 (11.48%) had undergone Minimally Invasive Vaginal Hysterectomy (MIVH), MIVH with Bilateral Salpingo-oophorectomy, Caesarean section, and other obstetric and gynaecological surgeries respectively.

From the visual analogue scale the mean value for the pain at rest at baseline i.e. immediately after surgery was 76.97, which showed significant reduction in pain intensity within 1 hr to 67.3 (P value of <0.001). Figure 1 represents a statistically significant increase in the improvement in scores of pain at rest 2, 4, 6, 8, 12 and 24 hours after surgery compared to baseline.

Similarly, pain at movement was also analysed using visual analogue scale. A statistically significant gradual improvement in scores of pain on movement from baseline was observed.

Also, the FDC was found effective in reducing the swelling after the surgery. A statistically significant improvement in scores on swelling reduction at 1, 2, 4, 6, 8, 12 and 24 hours after surgery was observed compared to baseline.

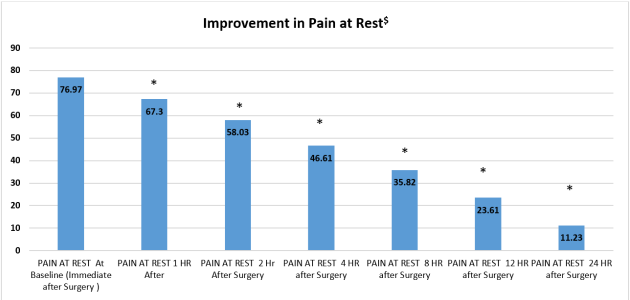


**Figure 1:** Improvement in pain at rest$
$: 0-100, 0 = No pain, 100 = Worst pain imaginable
*p<0.001 as compared to baseline

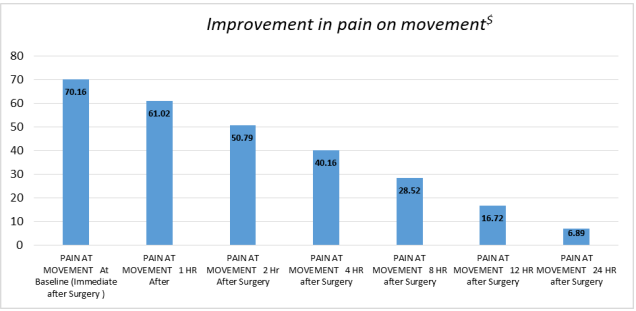


**Figure 2:** Improvement in pain on movement$
$:0-100, 0 = No pain, 100 = worst pain imaginable
$: 0-100, 0 = No pain, 100 = worst pain imaginable
*p<0.001 as compared to baseline

Swelling immediately after surgery (baseline) was compared with the swelling at various time intervals. A statistical significant decrease in the swelling was observed at various time intervals. On comparison of the mean values of swelling at baseline (Immediate after Surgery) and Swelling at 1 hr after the surgery.

Mean values of swelling at baseline i.e. Immediate after Surgery is higher with a difference of 5.016 than the mean values of swelling at 1 hour (P <0.001).

None of the patients showed moderate to severe symptoms (40-100 on VAS) at 24 hours after surgery.

Significant improvement from baseline, in pain at rest, pain on movement, and swelling at all-time points up to 24 hours after surgery (p<0.001) was noted. Physician's and patient's clinical global impression of efficacy and safety was good to very good in 95% and 93.3% of patients respectively. Nausea was the common adverse effect noted in 31.1% of patients. None of the patients reported serious adverse drug reaction.

Results of this study provides direct clinical evidence on effectiveness and safety of FDC of Serratiopeptidase and Diclofenac sodium in day care obstetric and gynaecological surgeries in reducing post-operative pain and swelling.

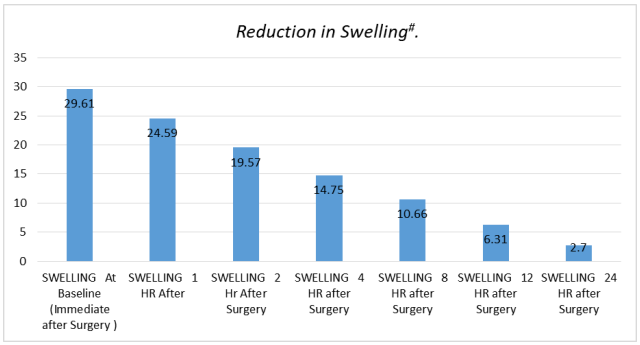


**Figure 3:** *Reduction in swelling*#
#:0 = No swelling; 100 = Extreme swelling,
*p<0.001 as compared to baseline

## 4. Discussion

Postoperative pain is the major concern in surgeries of obstetrics and gynaecology department and it is associated with the highest severity.[4] So it is highly essential to improve the postoperative pain management in minor surgeries.[1]

For certain patients, postoperative pain control still requires improvement despite advancements in pharmacology and surgical techniques. Inadequate management of pain following surgery is linked to longer hospital stays, ER visits, and readmissions.[9]

Insufficient postoperative pain control also leads to the development of chronic pain.[10] Multi-modal pain management strategy along with reduction in swelling is needed in post obstetric and gynaecological surgeries.

Serratiopeptidase is a proteolytic enzyme excreted by non-pathogenic Enterobacteria serratia isolated from intestine of silkworms Bombyx mori L Serratiopeptidase exhibits notable analgesic, anti-inflammatory, and anti-edema characteristics.[11] This enzyme was discovered to be used for pain, inflammation brought on by trauma, and surgery. It reduces inflammation in three ways: by breaking down blood coagulation-related insoluble protein byproducts, by thinned inflammation- and injury-related fluids, and by speeding up tissue repair. It lessens pain by preventing the amines that cause pain. It also aids in healing by dissolving the dead tissue that surrounds the wounded area.[12] Moreover, serratiopeptidase functions by altering adhesion molecules on the cell surface. Serratiopeptidase is not addictive and does not result in hazardous internal bleeding like NSAID painkillers do. Its application lies in its ability to suppress and eradicate hemorrhage following surgery.[13]

It was found that this enzyme is used for pain relief. It breaks down protein deposits like fibrin in the human body. This is a safe, natural substitute for NSAIDs and steroids that doesn't have any negative side effects. All non-vital tissues, such as blood clots, cysts, tissue plaques, and cellular debris, are proteolyzed by the enzyme, which also lowers the inflammatory response. Serratiopeptidase aids plasmin's fibrinolytic activity by blocking plasmin inhibitors. Extra-fibrin is broken down into tiny fragments, which helps exudates be cleared out, lessens swelling, and enhances microcirculation.[14] A FDC of an effective proteolytic enzyme, Serratiopeptidase and a potent NSAID Diclofenac, complement the action of each other by inhibiting the release of bradykinin and blocking production of prostaglandins. It is approved for use as a pharmaceutical ingredient in India to treat acute pain in conjunction with other medications.[15]

This combination not only controls inflammation but also helps in the clearance of exudates and improving microcirculation.[14]

One of the most common major surgical procedures done on female patients is a hysterectomy. When compared to open hysterectomy, the laparoscopic technique is becoming more and more popular because it is linked to lower rates of postoperative pain and morbidity, as well as earlier recovery and a shorter hospital stay. Even so, pain can still be very bad, especially in the early postoperative phase.[16]

Pain and swelling were the most frequently reported moderate, severe, and very severe symptoms in patients recovering from ambulatory minimally invasive gynecologic surgery, with 71 percent of patients reporting moderate to very severe pain after surgery, according to electronic patient-reported symptom monitoring.[17]

The combination of Diclofenac and Serratiopeptidase lead to significant reduction in pain at rest and movement at all-time points for 24 hours after surgery as compared to baseline early in the postoperative period.

The FDC also reduced the swelling at all-time points for 24 hours after surgery as compared to baseline.

These findings are critical and clinically important to strengthen the efficacy and safety of this FDC in day care obstetric and Gynaecological surgeries.

## 5. Conclusion

The use of enzymes in medical therapy has been limited. Serratiopeptidase has revealed interesting applications in the field of pain management.

Serratiopeptidase has a remarkable record of safety from decades of use by millions of users all around the world. We did not record any serious adverse events in our study either. Serratiopeptidase dosage recommendations range from 10 mg to 30 mg daily. It is commonly known that serratiopeptidase reduces pain by preventing the release of molecules that cause pain from inflammatory tissues. Enzymes have a higher affinity and specificity for their targets, which allows them to convert multiple target molecules into desired products. As a result, enzyme-specific drugs have been developed to treat a wide range of disorders.

Results of this study provides direct clinical evidence of the efficacy and safety of FDC of Serratiopeptidase and Diclofenac sodium in day care obstetric and gynaecological surgeries in reducing post-operative pain and swelling in the early post-operative period.

## 6. Sources of Funding

None.

## 7. Conflict of Interest

None.

## 8. Ethics Committee Approval

Ethics Committee approval no. & date: EMD/2021/01, 13 Jan 2022.

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