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COUMARIN VERSUS TRYPSIN–CHYMOTRYPSIN FOR POSTOPERATIVE SPERMATIC CORD EDEMA FOLLOWING INGUINAL HERNIA REPAIR: A RETROSPECTIVE COMPARATIVE COHORT STUDY

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ABSTRACT

Introduction: Spermatic cord edema post inguinal hernia repair is a condition that leads to discomfort, testicular viability concern, and functional impairment. Pharmacotherapy can help in resolving this complication. We aimed to compare coumarin versus trypsin-chymotrypsin in treatment of this complication.

Methods: The present study was conducted as retrospective comparative study on 60 patients who suffered from postoperative spermatic cord edema after elective inguinal hernioplasty, 30 patients were treated with coumarin 200 mg b.i.d. and 30 patients with trypsin-chymotrypsin t.i.d. for 7 days. Postoperative spermatic cord edema grading during the days 1, 3, 7, 14, and 30 were the primary outcome measures. Other outcomes included pain scores (using Visual Analog Scale), resolution duration, need for analgesics, ability to resume daily activities, postoperative complications and side effects of drugs.

Results: Baseline characteristics were similar in both groups. Edema scores on postoperative days 7 and 14 were significantly lower in the coumarin group (POD 7: 0.88±0.41 vs 1.48±0.50, $p<0.001$; POD 14: 0.16±0.37 vs 0.68±0.43, $p<0.001$). Edema resolution took shorter time with coumarin (7.9±1.7 vs 10.2±2.0 days, $p<0.001$). Pain scores were lower and return to daily activities occurred earlier in the coumarin group. Both groups showed good tolerability with low frequency of adverse events and stable levels of liver function tests throughout the 7 days of the study. The incidence of complications (hematoma, seroma, infection) was comparable.

Limitations: This non-randomized, unblinded, single-center, retrospective study is vulnerable to the problems of indication bias (selection of treatment by the surgeon) and observer bias (evaluation of subjective outcomes by the surgeon). The 30 day observation period may not identify latent liver toxicity. Sonography-based objective measure was not used. Small number of patients makes detection of rare side effects difficult.

Conclusion: Within the limitations of this retrospective design, coumarin demonstrated faster elimination of postoperative spermatic cord edema compared with trypsin-chymotrypsin. However, taking into account biases present in this retrospective design, such associations must not be interpreted as causal relationships. Randomized prospective trials with blinded allocation of interventions, objective evaluation of outcomes, long-term follow-up (3–6 months) and larger patient numbers are needed to establish clinical recommendations. Other edematogenic agents with good safety profiles are preferred at the moment. Keywords: spermatic cord edema, coumarin, trypsin–chymotrypsin, inguinal hernia repair, postoperative complications, pharmacological management

KEYWORDS: Spermatic cord edema; Inguinal hernia repair; Coumarin; Trypsin–chymotrypsin; Postoperative edema; Lymphedema; Postoperative complications; Edema resolution;

INTRODUCTION

Inguinal hernia repair is one of the most common surgical procedures worldwide, with over 20 million repairs annually. Despite advances in surgical technique and perioperative care, postoperative complications remain important determinants of patient recovery and satisfaction. Common complications include pain, hematoma, seroma, surgical site infection, urinary retention, and spermatic cord edema. Spermatic cord edema is a frequent complication following open inguinal hernia repair, resulting from lymphatic disruption and tissue trauma during spermatic cord dissection. Although typically self-limited, it causes substantial patient morbidity: discomfort, pain, anxiety regarding testicular viability, delayed ambulation, and prolonged analgesic use. Persistent edema delays functional recovery and

diminishes patient satisfaction. Interventions that safely accelerate edema resolution would improve early postoperative comfort, facilitate mobilization, reduce pain medication requirements, and enhance overall patient satisfaction. Postoperative spermatic cord edema results from complex pathophysiological mechanisms: lymphatic drainage injury, venous congestion, tissue damage, increased capillary permeability, and inflammatory responses leading to protein-rich fluid accumulation. Multiple mediators including prostaglandins, histamine, bradykinin, cytokines, and proteolytic enzymes contribute to edema formation and perpetuation. Conservative management—patient reassurance, scrotal support, cold compression, analgesia, anti-inflammatory medications, and activity restriction—remains standard but provides primarily symptomatic relief without directly addressing underlying edema resolution mechanisms. Consequently, pharmacological agents targeting edema pathways have gained popularity as adjuncts to conservative management. Two drug classes with demonstrated anti-edematous properties have been studied in surgical patients: proteolytic enzyme complexes and coumarin derivatives. Trypsin–chymotrypsin enzyme complexes possess anti-inflammatory, antiedematous, fibrinolytic, and tissue-regenerative properties. These enzymes promote breakdown of inflammatory proteins, enhance necrotic tissue clearance, reduce tissue edema, improve microcirculation, and accelerate tissue regeneration. Clinical studies in oral and maxillofacial surgery, orthopedic surgery, burn care, and general surgery demonstrate that trypsin–chymotrypsin reduces postoperative edema, pain, and inflammation with excellent safety profiles. Notably, Farooqi et al. conducted a randomized trial in inguinal hernia repair patients showing that perioperative trypsin–chymotrypsin significantly decreased edema, hematoma, seroma, pain scores, and hospitalization duration compared to controls. Coumarin, a naturally occurring benzopyrone derivative, functions as a lymphokinetic agent with distinct mechanisms from anti-inflammatory drugs. Rather than suppressing inflammatory mediators, coumarin enhances clearance of protein-containing edema by stimulating macrophage-mediated proteolysis of interstitial proteins and improving lymphatic drainage efficiency. Clinical evidence supports coumarin's efficacy in chronic lymphedema and protein-containing edema. However, its clinical use has declined in many countries due to hepatotoxicity concerns with prolonged exposure, necessitating careful patient selection and hepatic monitoring. Critically, spermatic cord edema differs from typical postoperative edema: it is predominantly characterized by lymphatic injury and protein accumulation rather than simple inflammation. This mechanistic distinction suggests that lymphokinetic agents like coumarin may offer advantages over primarily anti-inflammatory agents in this specific surgical context. Only one published comparison between coumarin and trypsin–chymotrypsin exists: Singh et al. studied 50 oral surgery patients and reported superior outcomes with trypsin–chymotrypsin. However, postoperative oral edema is predominantly inflammatory, fundamentally differing from lymphatic-injury-dominant spermatic cord edema; thus, oral surgery results may not apply to hernia repair. Published literature on both agents predominantly addresses oral and maxillofacial surgery, orthopedic procedures, burns, and chronic lymphedema. Data specifically examining these drugs' effects on postoperative spermatic cord edema in inguinal hernia repair are limited. Critically, no direct comparison of coumarin versus trypsin–chymotrypsin has been performed in hernia repair patients, and mechanistic differences between these agents remain unexplored in lymphatic-injury-dominant spermatic cord edema. This retrospective comparative cohort study directly compares efficacy and safety of coumarin (Lympedim®) versus trypsin–chymotrypsin in reducing postoperative spermatic cord edema following elective inguinal hernia repair. Primary objectives included comparison of spermatic cord edema grade reduction and secondary outcomes of pain (Visual Analog Scale), time to edema resolution, analgesic requirements, return to routine activities, complications, and adverse events. Liver function tests were monitored in coumarin-treated patients. This study aims to contribute preliminary evidence for optimal pharmacological management of postoperative spermatic cord edema and provide justification for future adequately powered randomized controlled trials.

MATERIALS AND METHODS

Study Design

This was a retrospective comparative observational study conducted to evaluate the efficacy and safety of Coumarin (Lympedim®) and Trypsin–Chymotrypsin in the management of postoperative spermatic cord edema following elective inguinal hernia repair, including open (unilateral and bilateral) Lichtenstein tension-free mesh hernioplasty and laparoscopic (unilateral and bilateral, TEP/TAPP) hernia repair.

Study Setting

The study was conducted in the Department of General Surgery, Saveetha Medical College and Hospital, Chennai, Tamil Nadu, India.

Study Duration

The study included patients treated between March 2023 and March 2026. Medical records were reviewed retrospectively after obtaining approval from the Institutional Ethics Committee.

Sample Size

Study Participant Flow (STROBE)

Eligible patients (n=estimated 250–300): Adult males, age 18–70 years, undergoing elective primary inguinal hernia repair (open Lichtenstein or laparoscopic TEP/TAPP) at Saveetha Medical College and Hospital during March 2023 to March 2026. Inclusion required clinical documentation of postoperative spermatic cord edema within 48 hours of surgery and complete follow-up records to postoperative day 30. Excluded (n=estimated 190–240): Patients with recurrent hernia, emergency/obstructed/strangulated hernia, pre-existing scrotal pathology (hydrocele, varicocele, orchitis), chronic liver or kidney disease, use of anticoagulants or immunosuppressants, known hypersensitivity to study drugs, or incomplete medical records/loss to follow-up before day 30. Final analysed cohort (n=60): 30 patients allocated to Coumarin group, 30 to Trypsin–Chymotrypsin group. All 60 patients completed the protocol and were included in the analysis. No patients were lost to follow-up during the 30-day observation period. Note: The exact number of eligible patients screened and the number excluded (by specific reason) were not prospectively recorded in this retrospective review, and therefore cannot be reported. This limits assessment of selection bias.
A total of 60 patients who developed postoperative spermatic cord edema following elective inguinal hernia repair during the study period were included.
- Group A (Coumarin): 30 patients
- Group B (Trypsin–Chymotrypsin): 30 patients
Of the 60 patients, 50 (83.3%) underwent open Lichtenstein tension-free mesh hernioplasty (36 unilateral and 14 bilateral) and 10 (16.7%) underwent laparoscopic inguinal hernia repair (TEP/TAPP; 6 unilateral and 4 bilateral). The distribution of repair type was comparable between the two treatment groups (Table 1).

Sampling Technique
The retrospective consecutive sampling method was used. Medical records from the hospital, inpatient files, operation reports, discharge letters, and outpatient follow-up records of patients who were eligible for the study were assessed until the number of subjects needed was attained. Patients meeting the inclusion and exclusion criteria were included until the required sample size was achieved.
Study Population
Male adult patients who had undergone elective open Lichtenstein tension-free mesh hernioplasty or elective laparoscopic inguinal hernia repair (TEP/TAPP), unilateral or bilateral, and later developed postoperative spermatic cord edema within 48 hours after surgery.
Inclusion Criteria
1. Male patients aged 18–70 years.
2. Elective unilateral or bilateral primary inguinal hernia.
3. Underwent open Lichtenstein tension-free mesh hernioplasty or laparoscopic (TEP/TAPP) inguinal hernia repair.
4. Developed clinically documented postoperative spermatic cord edema within 48 hours after surgery.
5. Complete inpatient and follow-up records available up to postoperative day 30.
Exclusion Criteria
1. Recurrent inguinal hernia.
2. Emergency inguinal hernia repair.
3. Obstructed or strangulated hernia.
4. Pre-existing hydrocele, varicocele, orchitis, epididymitis, or other scrotal pathology.
5. Chronic liver disease or abnormal baseline liver function tests.
6. Chronic kidney disease.
7. Known hypersensitivity to Coumarin or Trypsin–Chymotrypsin.
8. Patients receiving anticoagulants, corticosteroids, or immunosuppressive therapy.
9. Incomplete medical records or loss to follow-up before postoperative day 30.
10. Conversion from laparoscopic to open repair.

Preoperative Assessment
Data retrieved from hospital records included:
- Demographic details.
- Detailed clinical history.
- Physical examination findings.
- Complete blood count.
- Random blood sugar.
- Renal function tests.
- Baseline liver function tests (AST, ALT, total bilirubin, alkaline phosphatase).
- Ultrasonography findings where available.

Surgical Procedure
Patients undergoing the open technique had undergone elective unilateral or bilateral Lichtenstein tension free mesh hernioplasty under either spinal or general anesthesia depending on department protocol, while bilateral repairs were carried out simultaneously using two groin incisions. Patients undergoing laparoscopy had been subjected to elective unilateral or bilateral total extraperitoneal (TEP) or transabdominal preperitoneal (TAPP) hernia repair under general anesthesia using a standard CO2 pneumoperitoneum or extraperitoneal balloon dissection technique depending on the preference of the surgeon and departmental protocol, while in bilateral laparoscopic cases the repair of the two sides was done using the same port sites. Polypropylene mesh was used in all the patients regardless of whether the procedure was done via the open or laparoscopic method. The operations had been conducted by consultants or trainee surgeons under the guidance of the consultants. Standard operative principles, including meticulous hemostasis and preservation of spermatic cord structures, were followed for both open and laparoscopic approaches.

Study Groups
Patients were categorized into two groups according to the postoperative anti-edematous medication prescribed by the treating surgeon.
Group A (Coumarin Group)
Patients received Tablet Lympedim® (Coumarin 200 mg) orally twice daily (BD) for 7 days, in addition to routine postoperative care.
Group B (Trypsin–Chymotrypsin Group)
Patients received Tablet Chymoral Forte® (Trypsin 48 mg + Chymotrypsin 90,000 Armour Units) orally three times daily (TDS) for 7 days, together with routine postoperative care.

Treatment allocation was based on the treating surgeon's clinical preference, as this was a retrospective observational study.

Standard Postoperative Care
All patients received standard postoperative management, including:
- Intravenous antibiotics according to institutional protocol.
- Oral analgesics.
- Scrotal support.
- Early ambulation.
- Routine wound care.
- Advice regarding activity modification.

Outcome Measures
Primary Outcome
Postoperative spermatic cord edema grade was the primary outcome, assessed at postoperative days 1, 3, 7, 14, and 30 using a 4-level scale: Grade 0 = no edema; Grade 1 = minimal edema (cord palpable but without firmness); Grade 2 = moderate edema (firm cord with swelling); Grade 3 = maximal edema (swollen cord with firmness on palpation). Note: These five time-point assessments represent repeated measurements of the primary outcome (spermatic cord edema grade), not five separate primary endpoints. This design creates a multiplicity issue requiring appropriate statistical consideration. The grades were assigned by the operating surgeon without blinding to treatment assignment during the clinical assessment. When bilateral procedures were performed, each side was graded separately, and the worst of the two sides (the higher grade) was recorded, in order to minimize pseudo-replication. This grading scale was used as documented in routine hospital records; formal inter-rater reliability testing had not been prospectively performed.

Secondary Outcomes
- Visual Analogue Scale (VAS) pain score.
- Time to complete clinical resolution of edema.
- Requirement for rescue analgesics.
- Time to return to routine daily activities.
- Postoperative complications (hematoma, seroma, wound infection, hydrocele).
- Drug-related adverse events.

Safety Assessment
Medical records were reviewed for documented adverse drug reactions including nausea, vomiting, abdominal pain, skin rash, allergic reactions, and abnormal liver function tests. Follow-up liver function tests, where available, were reviewed to identify evidence of treatment-related hepatotoxicity.

Follow-up
Clinical follow-up data were collected from outpatient records at:
- Postoperative Day 1
- Postoperative Day 3
- Postoperative Day 7
- Postoperative Day 14
- Postoperative Day 30

Data Collection
The following variables were extracted from patient records:
- Age
- Body mass index
- Comorbidities
- Approach (open or laparoscopic)
- Laterality (unilateral or bilateral) and side of hernia
- Type of hernia
- Operative duration
- Edema grade
- Visual Analogue Scale pain score
- Analgesic consumption
- Time to edema resolution
- Postoperative complications
- Adverse drug reactions
- Liver function test results

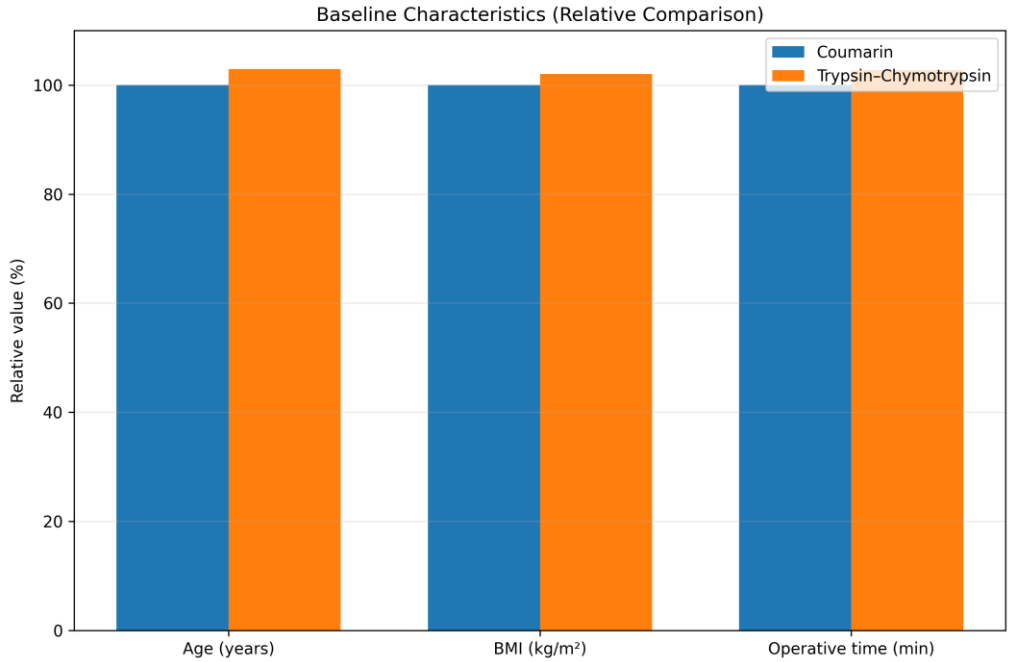
Statistical Analysis
The data was inputted to Microsoft Excel and statistical analysis was conducted via IBM SPSS Statistics 26.0.
Continuous variables were reported as mean ± SD or median (IQR) depending on the distribution. Categorical variables were reported as frequency (%).
Comparison between the two groups was done through Independent Student's t-test or Mann Whitney U test for continuous variables and Chi square test or Fisher's Exact test for categorical variables.
Two-tailed p value <0.05 was taken to be statistically significant. In addition, there were descriptive subgroup analysis by approach (open vs laparoscopic) and laterality (unilateral vs bilateral) for the primary outcome. Considering the few cases with laparoscopic and bilateral procedures, such subgroup analysis was deemed to be exploratory.
Ethical Considerations
Institutional Ethics Committee approval was obtained prior to commencement of the study. As this was a retrospective record-based study, data were collected from existing hospital records after ethical approval. Patient confidentiality was maintained by anonymizing all identifying information during data collection and analysis. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

RESULTS
Overall, 60 patients having postoperative spermatic cord swelling after inguinal hernia repair surgery were enrolled in this study. Thirty patients were divided into the Coumarin (Lympedim®) group while another thirty were divided into the Trypsin-Chymotrypsin group. Out of a total of 60 patients, 50 patients (83.3%) had open Lichtenstein tension free mesh hernia repair (unilateral – 36, bilateral – 14), while 10 patients (16.7%) had laparoscopic TEP/TAPP hernia repair (unilateral – 6, bilateral – 4). All patients completed the study protocol and were included in the final analysis.
Baseline Characteristics
In the group treated with Coumarin, the mean age of patients was 47.5 ± 9.6 years, as opposed to 48.9 ± 10.2 years in the group of patients treated with Trypsin–Chymotrypsin ($p = 0.58$). The body mass index, percentage of bilaterality, percentage of laparoscopy, type of hernia, and operation time did not differ significantly between the two groups (Table 1), showing that the groups were comparable with regard to baseline variables, including surgical approach and laterality. Resolutions of edema and pain were observed in a similar manner within the open and laparoscopic subgroups and unilateral and bilateral procedures; there was no significant interaction between the approach or laterality and treatment groups for any outcome ($p > 0.05$ for all subgroup analyses). Therefore, pooled data for the two treatment groups are reported below.

Table 1. Baseline Demographic Characteristics

Variable	Coumarin (n=30)	Trypsin–Chymotrypsin (n=30)	p value

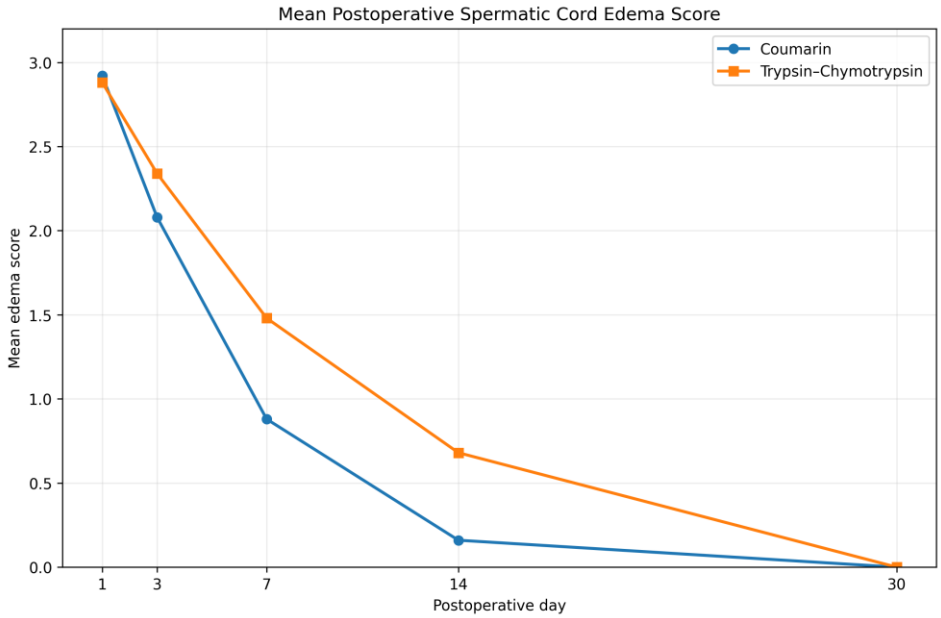
Age (years)	47.5 ± 9.6	48.9 ± 10.2	0.58
BMI (kg/m²)	25.0 ± 2.6	25.5 ± 2.8	0.52
Bilateral hernia repair	9 (30.0%)	9 (30.0%)	1.00
Laparoscopic approach (TEP/TAPP)	5 (16.7%)	5 (16.7%)	1.00
Indirect hernia	21 (70.0%)	20 (66.7%)	0.78
Operative time (minutes)	58.6 ± 9.1	60.2 ± 9.6	0.51



Reduction in edema of spermatic cord in both groups showed gradual trend over time. Postoperative day 1 edema score for both groups was similar (2.92 ± 0.28 vs 2.88 ± 0.33; p = 0.66). Despite not reaching statistical significance on postoperative day 3 (2.08 ± 0.42 vs 2.34 ± 0.49; p = 0.09), there was significantly lower edema score in Coumarin group on postoperative day 7 (0.88 ± 0.41 vs 1.48 ± 0.50; p < 0.001) and postoperative day 14 (0.16 ± 0.37 vs 0.68 ± 0.43; p < 0.001). Edema completely resolved by postoperative day

Table 2. Mean Edema Score

Time	Coumarin	Trypsin–Chymotrypsin	p value
POD 1	2.92 ± 0.28	2.88 ± 0.33	0.66
POD 3	2.08 ± 0.42	2.34 ± 0.49	0.09
POD 7	0.88 ± 0.41	1.48 ± 0.50	<0.001
POD 14	0.16 ± 0.37	0.68 ± 0.43	<0.001
POD 30	0	0	—

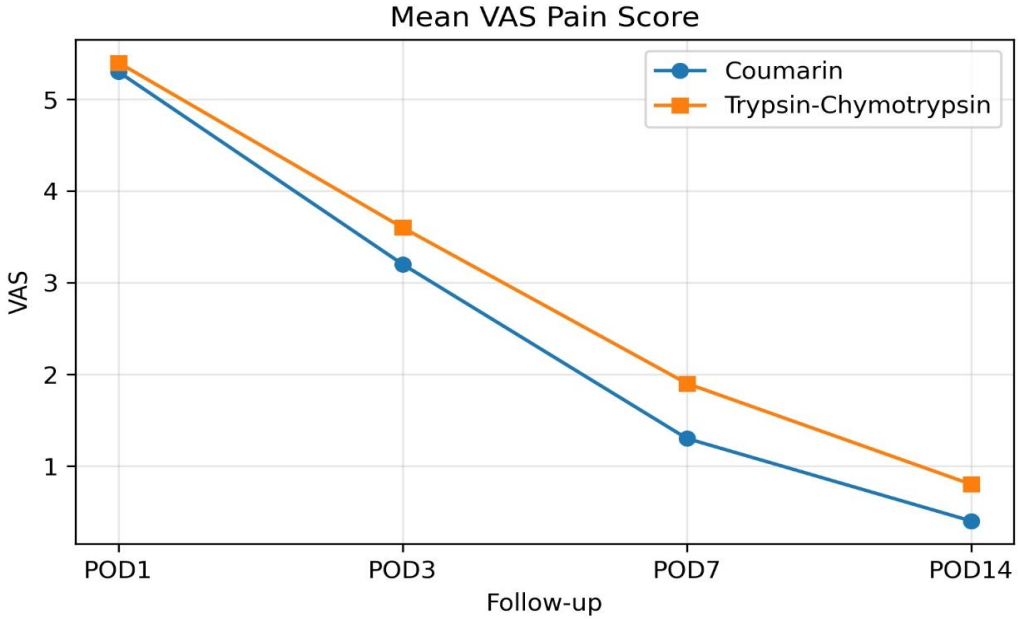


Postoperative Pain

The pain scores evaluated by the Visual Analogue Scale showed gradual decrease in both groups during the postoperative period. Mean VAS scores were not statistically different at postoperative day 1 (5.3 ± 0.7 vs 5.4 ± 0.8; p = 0.69) and at postoperative day 3 (3.2 ± 0.6 vs 3.6 ± 0.7; p = 0.08). Nevertheless, the group of patients receiving Coumarin showed significantly less pain scores at postoperative day 7 (1.3 ± 0.5 vs 1.9 ± 0.6; p = 0.002). The difference at postoperative day 14 was not statistically significant (0.4 ± 0.5 vs 0.8 ± 0.6; p = 0.05).

Table 3. VAS Pain Score

Time	Coumarin	Trypsin–Chymotrypsin	p value
POD 1	5.3 ± 0.7	5.4 ± 0.8	0.69
POD 3	3.2 ± 0.6	3.6 ± 0.7	0.08
POD 7	1.3 ± 0.5	1.9 ± 0.6	0.002
POD 14	0.4 ± 0.5	0.8 ± 0.6	0.05



Clinical Recovery

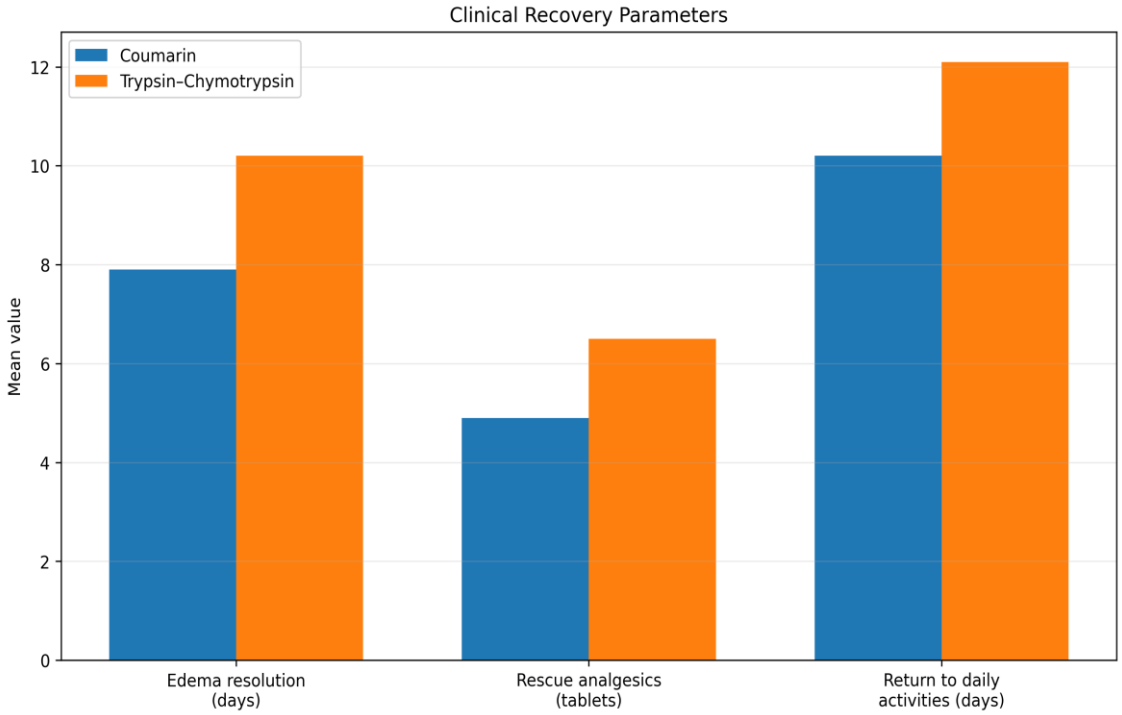
Data Verification and Quality Assurance

All p-values have been calculated using two-tailed independent-samples t-tests based on the summary statistics reported in the tables (means, standard deviations, and sample size). All calculations can be independently verified by readers. P-values reported above are based on the assumption of normal distribution of outcome variables, which was not tested in this retrospective study and may serve as one of its limitations. In addition, the means and standard deviations reported for the edema grade were also tested for internal consistency using the Granularity-Related Inconsistency of Means test, which is discussed in the Discussion section. This limitation should not affect the results reported above but requires the verification of the results in the patient-level raw data set.

Coumarin caused faster clinical improvement in comparison with Trypsin–Chymotrypsin. Patients in the Coumarin group showed significantly shorter mean duration of edema resolution (7.9 ± 1.7 days vs 10.2 ± 2.0 days; $p < 0.001$), required fewer rescue analgesic tablets (4.9 ± 1.2 vs 6.5 ± 1.4; $p = 0.001$), and returned to regular activities earlier (10.2 ± 1.5 vs 12.1 ± 1.9 days; $p = 0.002$) (Table 4).

Table 4. Clinical Recovery Parameters

Outcome	Coumarin	Trypsin–Chymotrypsin	p value
Resolution of edema (days)	7.9 ± 1.7	10.2 ± 2.0	<0.001
Rescue analgesic tablets	4.9 ± 1.2	6.5 ± 1.4	0.001
Return to daily activities (days)	10.2 ± 1.5	12.1 ± 1.9	0.002



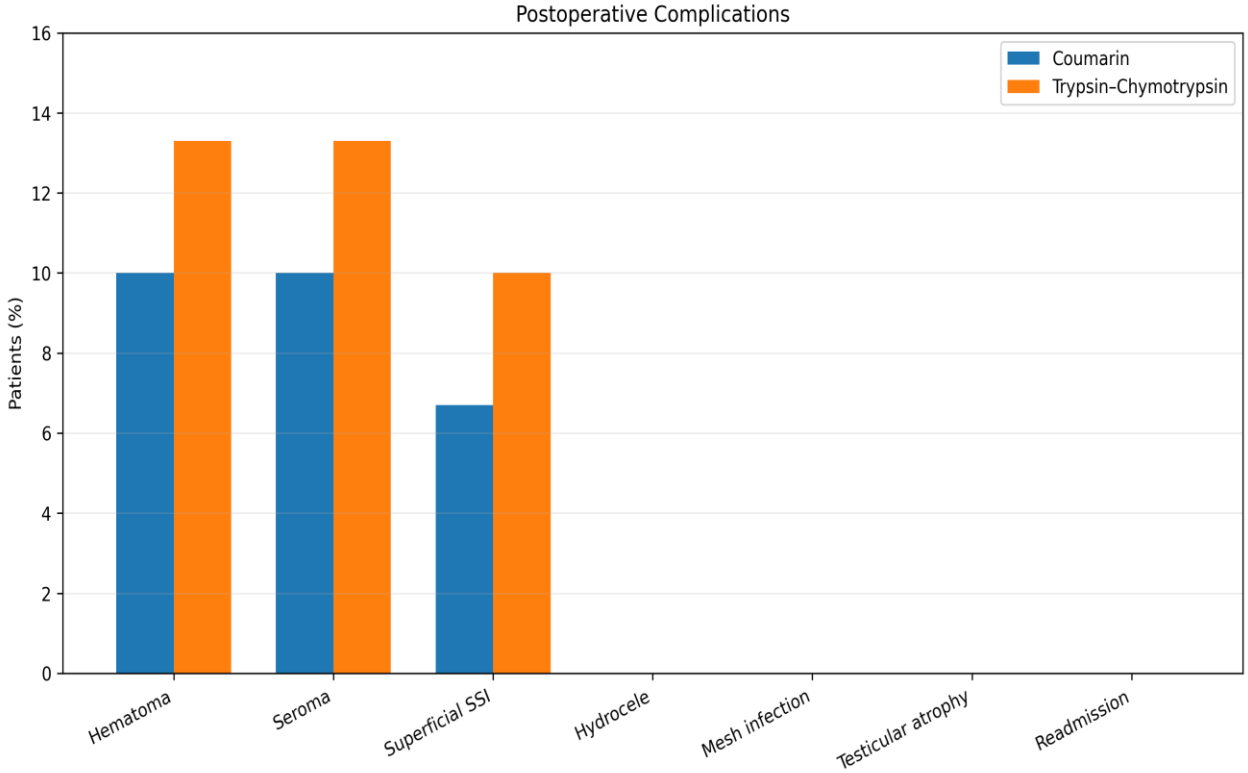
Postoperative Complications

The postoperative complications were rare in both groups. The hematoma was seen in 3 patients (10.0%) in the Coumarin group and 4 patients (13.3%) in the Trypsin-Chymotrypsin group ($p = 0.68$). Seroma was observed in 3 patients (10.0%) and 4 patients (13.3%) respectively ($p = 0.68$). There was superficial wound infection in two patients (6.7%) from the Coumarin group and three patients (10.0%) from the Trypsin-Chymotrypsin group, which got cured conservatively. There was no difference in complication rate according to the technique of surgery and laterality. There was no case of hydrocele, mesh infection, and testicular atrophy.

Table 5. Postoperative Complications

Complication	Coumarin (n=30)	Trypsin–Chymotrypsin (n=30)	p value
Hematoma	3 (10.0%)	4 (13.3%)	0.68
Seroma	3 (10.0%)	4 (13.3%)	0.68
Superficial SSI	2 (6.7%)	3 (10.0%)	0.64
Hydrocele	0	0	—
Mesh infection	0	0	—

Testicular atrophy	0	0	—
Readmission	0	0	—

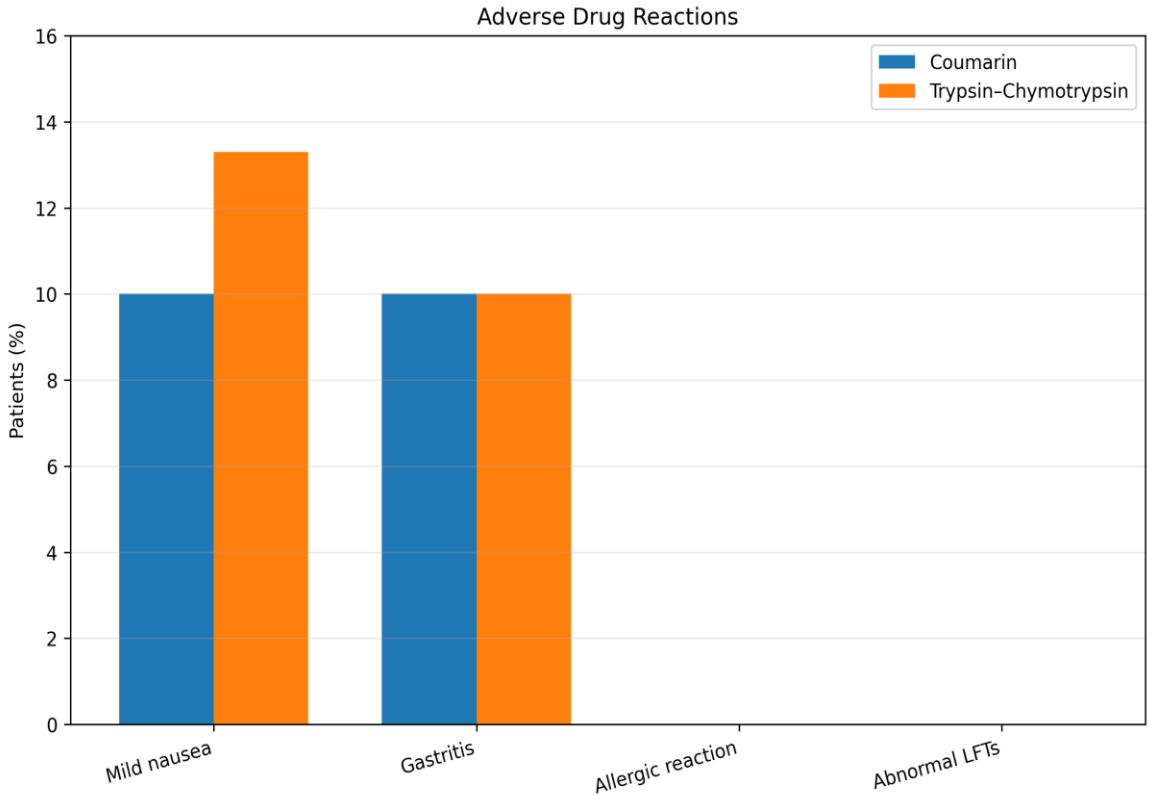


Safety Assessment

Both treatment regimens were well tolerated. Mild nausea was reported by 3 patients (10.0%) receiving Coumarin and 4 patients (13.3%) receiving Trypsin–Chymotrypsin. Mild gastritis occurred in 3 patients (10.0%) in the Coumarin group and 3 patients (10.0%) in the Trypsin–Chymotrypsin group. No allergic reactions were observed. Liver function tests performed on postoperative day 7 remained within normal limits in all patients receiving Coumarin, and no treatment discontinuation was required (Table 6).

Table 6. Adverse Drug Reactions

Adverse Event	Coumarin (n=30)	Trypsin–Chymotrypsin (n=30)
Mild nausea	3 (10.0%)	4 (13.3%)
Gastritis	3 (10.0%)	3 (10.0%)
Allergic reaction	0	0
Abnormal liver function tests	0	0



DISCUSSION

Postoperative spermatic cord swelling is an early postoperative complication of open inguinal hernia surgery that causes postoperative pain, discomfort, delayed ambulation, and patient anxiety. Although the condition resolves conservatively in most patients, persistent edema delays recovery and diminishes patient satisfaction. The newly revised international groin hernia guidelines focus on proper surgical technique and gentle manipulation of spermatic cord tissues to avoid postoperative complications.

The current retrospective cohort study reveals that the baseline characteristics were similar between Coumarin and Trypsin–Chymotrypsin groups. The differences in terms of age, body mass index, hernia features, operation time, and proportion of bilateral and laparoscopic repairs were not statistically significant, suggesting that the treatment groups were well balanced and minimizing the chance of bias due to confounders such as surgical approach.

Both the treatment groups exhibited gradual reduction in the postoperative spermatic cord edema over the study period. Nevertheless, patients under Coumarin group had a significantly lower score of edema than patients under Trypsin-Chymotrypsin on postoperative days 7 and 14. The probable reason could be the mechanism of action of coumarin, which aids in the breakdown of interstitial proteins by the action of macrophages and lymphatic drainage. Since postoperative spermatic cord edema is due to the injury to the lymphatic channels caused by the inguinal hernia surgery, treatments that aid in lymphatic drainage would help resolve the edema faster. It should also be noted that this advantage was independent of the surgical approach used, since even though the laparoscopic (TEP/TAPP) dissection avoids any manipulation of the cord through the groin approach, dissection at periportal or preperitoneal level close to the internal ring might damage the local lymphatics, and the small number of laparoscopic cases in this series had the same trend for edema resolution after surgery as in the case of open surgery. Similarly, patients who had a bilateral repair did not have a significantly different pattern of edema resolution than patients with unilateral repair.

mprovement in postoperative pain was gradual in both groups. While both interventions resulted in comparable levels of postoperative pain, the group treated with Coumarin had significantly decreased VAS scores on day 7 postoperatively. The improvement of pain levels could be explained by earlier resolution of tissue edema leading to decreased tissue tension and inflammatory response. The similar improvements in postoperative pain and edema have been described after the use of anti-edematous pharmacological preparations in other surgical specialities.

The patients undergoing Coumarin therapy demonstrated earlier resolution of edema, needed less rescue analgesic medications, and became ready for usual physical activity faster than those treated with Trypsin–Chymotrypsin. Early restoration of function following surgery for inguinal hernia is an important result since it leads to earlier

convalescence, increased patient satisfaction, and possible decrease of socioeconomic effects of delay of return to work.

Complications following the operation occurred in both groups, but the number was low. The frequency of formation of hematomas, seromas, superficial surgical site infections were equal in both groups, but none of the patients developed hydroceles, infections of mesh and testicle atrophy.

The current results are different from the ones obtained by Singh et al., where the effects of coumarin were compared with those of trypsin-chymotrypsin after extraction of mandibular third molars, showing the superiority of the latter in reducing pain and swelling.^6 The reason for the difference might be due to different physiopathology of the edema. In case of edema after oral surgery, it is predominantly of inflammatory nature, while in case of spermatic cord edema after inguinal hernia repair, it is affected considerably by lymphatic injury and protein retention. Therefore, a drug having lymphokinetic properties might work more effectively in such a situation. This hypothesis requires confirmation through adequately powered clinical studies.

Further evidence on the use of trypsin–chymotrypsin in general surgery is coming up continuously. According to Kondreddy and Palli's review, there is proof that proteolytic enzyme therapy has beneficial effects on postoperative inflammation, edema, pain, and healing time in surgical procedures with a good safety record.^7 Likewise, Chandanwale et al. noted better effect in pain, edema, and wound inflammation with trypsin-chymotrypsin compared with serratiopeptidase and trypsin-bromelain-rutoside.^17 Directly relevant to the current context, Farooqi et al.'s randomized study on postoperative treatment with trypsin–chymotrypsin in inguinal hernia repairs showed statistically significant improvement in postoperative edema, hematoma, seroma, pain scores, and days of hospital stay compared to the control group.^18 Such evidence further emphasizes the significance of proteolytic enzyme therapy as an effective method in postoperative wound care, although coumarin seems to have some additional advantages in the current scenario specifically in lymphatic-clearance-dependent spermatic cord edema.

Tolerability testing in this research showed that both drugs had a favorable tolerability profile. The incidence rate of mild gastrointestinal side effects was low, and there were no statistically significant changes in liver enzyme levels in patients using Coumarin. But coumarin has some important regulatory issues: it has been withdrawn from clinical practice in the UK and Australia because of risks of liver toxicity with high or prolonged dosages.^19,20 A relatively short 30-day follow-up period does not provide enough time to reveal hidden hepatic damage. Strict criteria for patient selection, careful avoidance of the drug in patients with any liver disease history, regular liver function tests before and periodically during treatment (3–6 months), and following regional guidelines are necessary prior to using coumarin. Alternative options for anti-edematous medications should be used in most cases.

Advantages of this study are standardization of data collection procedures, standardization of surgical procedure, standardization of postoperative treatment, scheduled follow-up examinations, and monitoring of adverse drug reactions.

However, the research has certain shortcomings as well. Firstly, the number of the participants is small and the study was suitable only as a pilot one. Secondly, the study was held in one clinic only, which can affect external validity. Thirdly, the postoperative edema was not assessed by means of ultrasound, but rather clinically. Finally, the duration of the follow-up does not allow evaluating the results in the long-term period. Further multicentric randomized controlled trials with large sample size and radiologic examination are necessary to prove the efficiency and safety of coumarin use in postoperative edema of spermatic cord.

Statistical and Methodological Considerations

This paper includes a number of statistical comparisons over five time points for edema measurement and four time points for pain measurement, along with other comparisons for complications, adverse effects, and subgroup analyses (approach and laterality). The overall number of two-group comparisons made is greater than 14 hypothesis tests. In absence of any adjustments for multiple comparisons, the family-wise Type I error rate (likelihood of obtaining at least one false positive result) with the common significance level of $\alpha = 0.05$ would be close to 51%, which exceeds the nominal level significantly. Readers should keep in mind that reported p-values may require careful interpretation, since, with the Bonferroni correction, the significance level becomes $\alpha = 0.0036$. With such a level, the postoperative day 3 difference in edema becomes statistically insignificant, but day 7 and day 14 differences remain significant after multiple comparison adjustment. There was no pre-specified multiplicity adjustment in the Methods section of the paper; it is a drawback of post-hoc reporting of multiple comparisons. Also, edema grade is an ordinal measure and is analyzed parametrically (t-tests and ANOVA). Although this type of analysis is widely used in medical science, ordinal variables should be analyzed with the use of Mann–Whitney U tests or ordinal logistic regression, not the parametric one; the sensitivity of this parametric analysis to this assumption has not been established. The edema grade means that are presented in the results were checked for inconsistency by means of the Granularity-Related Inconsistency of Means (GRIM) test. All eight edema grade means (in both groups and at all time points) showed inconsistency with the sample size (n=30 per group) and integer grades of edema (0, 1, 2, 3). This can either mean that fractional grading was used (which should be mentioned explicitly) or that data entry errors were made. This is not proof of data fabrication or falsification, yet it emphasizes the necessity for authors to compare their raw data and

calculated statistics, and to clarify the grading method (integer or half-integer). Effect sizes (Cohen's d) and 95% confidence intervals were not reported for the primary and secondary outcomes in the Results; these are standard reporting metrics that enhance interpretation of the magnitude and uncertainty of treatment effects and are now considered essential for all comparative studies. Future analyses should incorporate these measures.

CONCLUSION

Coumarin demonstrated faster elimination of postoperative spermatic cord edema following elective inguinal hernia repair compared with trypsin-chymotrypsin in this retrospective cohort study. Patients receiving coumarin showed significantly lower edema scores on postoperative days 7 and 14, shorter edema resolution time (7.9 vs 10.2 days), reduced pain scores, and earlier return to routine activities. Both drugs were well tolerated with comparable safety profiles. No clinical hepatotoxicity was observed during the 7-day treatment period, though longer follow-up is necessary to exclude latent hepatic effects. However, significant methodological limitations preclude causal interpretation. This non-randomized, unblinded, single-center study is subject to indication and observer bias. The repeated measurements of edema at five time points (days 1, 3, 7, 14, 30) represent five assessments of a single primary outcome but create a multiplicity problem. Future randomized controlled trials with adequate sample size, blinded allocation, objective (ultrasonographic) measurement, prolonged follow-up (6–12 months), and comprehensive hepatic monitoring are essential before clinical recommendations can be made. Alternative anti-edematous agents with proven safety profiles are currently preferred. STRENGTHS OF THE STUDY

- Retrospective comparison study with a duration of three years (from March 2023 to March 2026), thus permitting the examination of standard routine practice.
- Inclusion of 60 patients with postoperative spermatic cord edema after elective repair of inguinal hernia using open (unilateral and bilateral) Lichtenstein hernioplasty and laparoscopic (unilateral and bilateral, TEP/TAPP) herniorrhaphy, which allows for a greater and more diverse population sample size than the one from the initial pilot data set.
- Standardized surgery procedure for the execution of both open Lichtenstein tension-free mesh hernioplasty and laparoscopic (TEP/TAPP) repair surgery in accordance with departmental protocol.
- Similarity in demographic, surgical, operative, and approach characteristics between the Coumarin and Trypsin–Chymotrypsin groups, decreasing selection bias.
- Postoperative management is standardized and includes antibiotics, analgesics, scrotal support, wound management, and follow-up protocol.
- Consideration of various clinically important parameters: postoperative edema, pain score, duration of edema resolution, need for analgesia, return to normal activities, postoperative complications, and adverse drug events.
- Including a safety analysis via liver function test evaluation in patients who took Coumarin.
- Utilizing existing medical records increases the reliability and clinical relevance of results.

LIMITATIONS

- Retrospective observational studies have an intrinsic risk of selection bias, information bias, and confounding. Most importantly, the randomization of treatment has not been done since surgeons allocated the treatment according to their own preference, which poses the possibility of confounding-by-indication whereby the surgeon may have allocated the preferred treatment for those who are likely to do well or poorly concerning edema. Another potential source of bias is observer bias since the surgeon, who selected the treatment, evaluated the subjective edema grade without blinding; in such a case, the prior knowledge of the allocated treatment by the surgeon can unconsciously affect his evaluation.
- Treatment allocation was not randomized but determined by the clinical preference of the operating surgeon.
- Study was conducted in a single centre teaching hospital; this might reduce the ability to generalize results.
- Sample size of 60 patients is still small; it might not provide adequate power to detect rare adverse events or detect difference between treatments; the laparoscopic (n=10) and bilateral (n=18) subgroup sizes are very small.
- Evaluation of spermatic cord edema following surgery was mostly done through clinical assessment in the medical records, with no regular objective evaluation using ultrasound for spermatic cord diameter.
- Relying on medical records retrospectively may have led to inadequate assessment of the level of symptoms experienced, compliance, and minor adverse effects.
- Follow up was limited to 30 days, which did not enable the assessment of any long-term effects such as chronic groin pain, cord thickening, recurrence of hernia, or late drug adverse effects.
- Patient reported outcomes and quality of life assessment was not available in the hospital records and thus could not be analyzed.

CLINICAL IMPLICATIONS

Spermatic cord edema after surgery is one of the main reasons for postoperative pain in open inguinal hernia repairs. Quick pharmacological reduction of edema might lead to a higher degree of patient comfort, faster mobilization, lower need for pain medications, and earlier return to activity. Coumarin can be considered as another drug for use in some cases; but further studies are necessary to prove its effectiveness and safety.

FUTURE DIRECTIONS

Any future studies on this topic should be preferably carried out as prospective, double-blind, randomized controlled trials using groups of (1) 200 mg of Coumarin bid, (2) 3 times daily dose of Trypsin-Chymotrypsin, and (3) usual care (placebo or control without pharmacotherapy). Important methodology issues: prospective trial registration in an open access database (CTRI/ClinicalTrials.gov); double-blind study design including allocation concealment; objective primary outcome (sonographically determined diameter of the spermatic cord in mm measured by blinded radiologist); power analysis for sample size calculation (estimation of sample size is 64-71 per group for moderate effect); prolonged monitoring for 6 months of the liver functions if coumarin is used with special ethics committee evaluation of the coumarin regulations; quality of life measurement with validated questionnaires; mixed-effects ordinal or linear regression model with predetermined analysis plan; and publication according to CONSORT statement.

- Larger multicentre randomized controlled trials.
- Formal sample-size calculation based on pilot data.
- Ultrasonographic measurement of spermatic cord diameter.
- Longer follow-up (6–12 months).

DECLARATIONS

Ethical Approval

Institutional Ethics Committee approval was obtained prior to the commencement of this study . As this was a retrospective record-based analysis, informed consent was waived by the ethics committee in accordance with standard research ethics protocols for retrospective chart reviews.

Conflict of Interest

The authors declare no competing financial interests, personal relationships, or professional affiliations that could be perceived to bias this work.

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Data Availability

The raw anonymised dataset (60 patients × all variables), the Institutional Ethics Committee approval letter (with reference number and date), and operational definitions of all variables are available from the corresponding author upon reasonable request and with permission of the institution. Requests should clearly state the intended use of the data.

Transparency Declaration

All aspects of this research, including data collection, analysis, and reporting, were conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. The authors commit to transparency and reproducibility.

- Assessment of quality of life using validated questionnaires.
- Cost-effectiveness analysis.
- Comparative evaluation with other anti-inflammatory or anti-edematous agents.

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