Study Protocol and Statistical Analysis Plan

Cover Page

Official Title: A Randomized, Double-Blind, Placebo-Controlled Study of Nitroglycerin Ointment for Postoperative Pain Relief After Endoscopic Rubber Band Ligation of Internal Hemorrhoids

NCT Number: *to be assigned*

Document Type: Study Protocol and Statistical Analysis Plan

Document Date: 2025.12.13

1. Background and Rationale

Endoscopic rubber band ligation (ERBL) is a widely used minimally invasive treatment for internal hemorrhoids. Despite its effectiveness, postoperative anal pain remains a common complication and may significantly affect patient comfort, daily activities, and recovery. Nitroglycerin ointment, a nitric oxide donor, has been shown to reduce anal sphincter pressure and improve local blood flow, suggesting potential benefit in postoperative pain control.

This study aims to evaluate the efficacy and safety of topical nitroglycerin ointment in reducing postoperative pain following ERBL for internal hemorrhoids.

2. Study Objectives

Primary Objective

To compare the proportion of participants requiring rescue analgesic medication within 72 hours after ERBL between the nitroglycerin ointment group and the placebo group.

Secondary Objectives

- To compare postoperative pain intensity at predefined time points
- To evaluate time to complete pain relief (VAS = 0)
- To assess postoperative complications
- To evaluate treatment-related adverse events
- To assess overall treatment effectiveness at 30 days after the procedure

3. Study Design

This is a single-center, randomized, double-blind, placebo-controlled clinical trial. Eligible participants will be randomly assigned in a 1:1 ratio to receive either nitroglycerin ointment or placebo ointment following ERBL.

4. Study Population

Inclusion Criteria

- Adults aged 18–75 years
- Diagnosed with grade I–III internal hemorrhoids
- Scheduled for ERBL
- Able to provide written informed consent

Exclusion Criteria

- Inability to understand study procedures or assessments
- Current use of oral nitrates or calcium channel blockers
- Known allergy to nitroglycerin or study-related medications
- Pregnant or breastfeeding women
- Severe cardiovascular, respiratory, neurological, or psychiatric disorders
- Inability to tolerate ERBL or bowel preparation

5. Interventions

Experimental Group

Participants will receive topical nitroglycerin ointment applied to the intrarectal wound area starting after ERBL, three times daily, approximately 1–1.5 cm per application, for 2 weeks.

Control Group

Participants will receive a placebo ointment identical in appearance and application schedule to the study drug.

All participants will receive standardized perioperative management. Rescue analgesia with oral loxoprofen sodium will be permitted when clinically indicated.

6. Outcome Measures

Primary Outcome

- Use of rescue analgesic medication (loxoprofen sodium) at least once within 72 hours after ERBL

Secondary Outcomes

- Visual Analog Scale (VAS) pain scores at postoperative 3 hours, days 1, 3, 5, 7, and 14
- Time to first achievement of VAS = 0
- Incidence of postoperative complications
- Incidence of treatment-related adverse events
- Treatment effectiveness at postoperative day 30

7. Sample Size Calculation

Based on previous randomized controlled studies, the expected incidence of rescue analgesic use is 25% in the nitroglycerin group and 70% in the placebo group. With a two-sided alpha of 0.05 and 80% power, the minimum required sample size is 19 participants per group. Considering covariate adjustment and potential dropout, a total of 68 participants (34 per group) will be enrolled.

8. Statistical Analysis Plan

Analysis Sets

- **Full Analysis Set (FAS):** All randomized participants who received at least one dose of study medication and had at least one efficacy assessment
- **Safety Set (SS):** All participants who received at least one dose of study medication
- **Per Protocol Set (PPS):** Participants without major protocol deviations

Primary Outcome Analysis

The proportion of participants requiring rescue analgesia within 72 hours will be compared between groups using the chi-square test or Fisher's exact test. Logistic regression will be performed to adjust for baseline pain score and age, with results reported as adjusted odds ratios and 95% confidence intervals.

Secondary Outcome Analysis

- VAS scores will be summarized as mean ± standard deviation and compared using t-tests or Mann–Whitney U tests as appropriate
- Time to pain relief will be analyzed using Kaplan–Meier methods and compared using the log-rank test
- Complication and adverse event rates will be compared using chi-square or Fisher's exact tests
- Treatment effectiveness will be analyzed using Wilcoxon rank-sum tests and categorical comparisons

A two-sided p-value < 0.05 will be considered statistically significant.

9. Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki and applicable regulatory requirements. Written informed consent will be obtained from all participants prior to enrollment.

10. Study Timeline

- Patient recruitment and treatment: December 2025 – November 2026
- Follow-up and data analysis: December 2026 – November 2027
- Manuscript preparation: December 2027 – November 2028