Study Protocol with Statistical Analysis Plan

Official Study Title: Role of Topical Application of Lignocaine versus 0.2% Glyceryl Trinitrate (GTN)Ointment as a Postoperative Local Analgesic in Hemorrhoidectomy in Terms of Pain Score,Wound Healing Time and Patient Satisfaction Level

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Introduction

Hemorrhoid are distension of normal hemorrhoidal venous cushions with equal incidence rate in both sexes and a prevalence rate of 4.4% with nearly 37 hemorrhoidectomies per 100,000 people per year. (1) Hemorrhoid are surgically managed most commonly by Milligan-Morgan hemorrhoidectomy. It had a major complain of post-operative pain limiting the post-operative mobility and delayed return to daily routine activities. (2)

Different modalities had been applied to reduce the post-hemorrhoidectomy pain as anal dilatation and internal sphincterotomy. However, these procedures being invasive required specialized equipment and could cause irreversible sphincter damage leading to flatus and stool incontinence. Non-steroidal anti-inflammatory drugs (NSAIDS) and opioids had beneficial effect and are required in high dose, resulting in gastrointestinal effects. Multiple topical preparations as nifedipine, botulinum toxin, metronidazole and lignocaine had been used successfully. (3)

Post-hemorrhoidectomy pain depends on various factors as surgical technique, post-operative analgesia, usage of stool softeners, adequate education and subjective pain threshold. Internal anal sphincter (IAS) is innervated by nitric oxide (NO) releasing neurons. Stimulation of these nerves result in the release of NO which then cause relaxation of the IAS by relaxing smooth muscle. The reduction of IAS spasm and reduced pressure will increase anodermal blood flow and therefore improve wound healing. Exogenous GTN ointment is an NO donor which relaxes the IAS and thus reduces pain. (4) Many studies have evaluated the analgesic efficacy of 0.2% GTN ointment on post-hemorrhoidectomy pain. (3) Lignocaine is an amide local anesthetic agent, commonly used for local and topic anesthesia. The site of action of lignocaine is at sodium ion channels on the internal surface of nerve cell membranes. (5) Kwok et.al reported that pain scores were reduced at 1 hour for the lidocaine (OR 4.15 [1.12-15.41]; p = 0.03) and compared with placebo (OR 3.85 [1.05-14.11]; p = 0.04). (6) Xu et.al reported that the post-operative use of lidocaine after the endoscopic rubber band ligation had lower VAS score as 0.80 ± 0.42 in comparison to the control group with VAS score as 4.11 ± 1.37. (7) Franceschilli et. al found that the application of 0.4% GTN after haemorrhoidectomy had a mean VAS score of 4.1 ± 1.8 lower than the control group with a mean VAS score of 7.5 ± 1.4 ($p < 0.001$). (4) Khan et.al had reported statistically significant reductions in pain scores and quantity of analgesics used from the first to the fourth post-operative days in patients using combination of 0.2% GTN and 2% lignocaine as a topical application

post-operatively in Milligan-Morgan hemorrhoidectomy. The pain scores on basis of 100 mm VAS in lignocaine group were 45.62, 26.88, 18.44 and 10.16 and in GTN group 45.9, 31.48, 15.9 and 10.16 on days 1, 2, 3, and 4 respectively. Patients had a mean healing time of 4.51 ± 0.744 weeks for 0.2% GTN group and 5.08 ± 0.762 weeks for 2% lignocaine group. The difference was highly significant between GTN and lignocaine groups ($p < 0.001$). (3) Kwok et. al reported that the topical application of lidocaine/ diltiazem after band ligation of hemorrhoids had higher satisfaction level (OR 3.82 [1.28–11.44]; $p = 0.02$). (6) When comparing lignocaine and glyceryl trinitrate (GTN) ointment as postoperative local analgesics for hemorrhoidectomy, the rationale for this study is based on the need to identify the most effective and safe pain management options for patients. Hemorrhoidectomy, while effective, often results in significant postoperative pain, which can be challenging to manage and may affect recovery and patient satisfaction. Therefore, choosing the right local analgesic can play a critical role in improving the patient experience and reducing the overall burden on healthcare resources. By exploring the relative efficacy and safety of lignocaine versus GTN ointment, this study can provide guidance for clinicians on optimizing postoperative pain management strategies in hemorrhoidectomy, potentially improving patient outcomes and enhancing the overall care experience.

Objectives

To compare the outcome of lignocaine versus 0.2% GTN ointment in post-hemorrhoidectomy patients as a local analgesic.

Hypothesis

There is a difference in the outcome of lignocaine vs 0.2% GTN in ointment post-hemorrhoidectomy patient as a local analgesic.

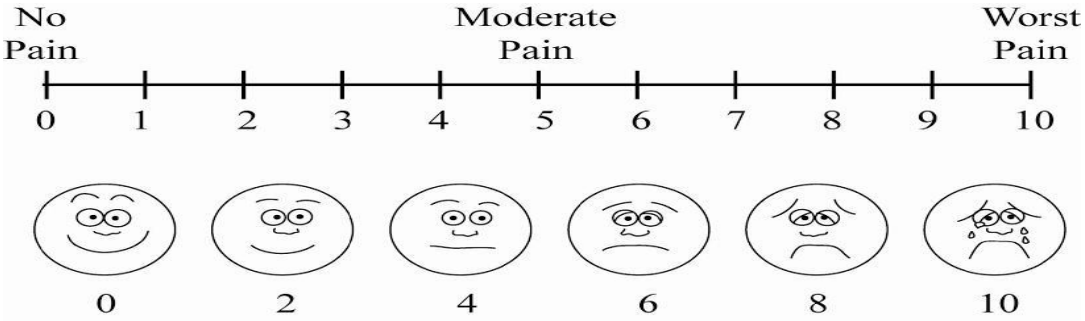
Operational Definitions

Outcomes :

will be determined in terms of

1.Mean Pain Score(VAS)

Pain in the post operative period will be assessed by VAS (visual analogue scale) on a scale of 0 to 10, with 0 showing no pain and 10 showing maximum pain. It will be used to assess the severity of pain at 6,12,24,48,72 hours and on 7^{th} , 14^{th} , 21^{st} and 28^{th} day after surgery.



2.Time to Complete Wound Healing

Complete epithelization of wound will be labelled as complete wound healing and will be measured as the time in days required for complete epithelization.

Materials and Methods

Study Design

Randomized clinical trial

Study Setting

Department of Surgery, Mayo Hospital, Lahore

Duration of Study

3-6 months after the approval of synopsis

Sampling Technique

Non Probability purposive

Sample Size Calculation

A total sample size of 64 is calculated with 32 participants in each group with the mean of healing time in group A as 5.08 ± 0.762 and the mean of healing time in group B as 4.51 ± 0.744. By using the power as 80% and 95% confidence interval. (3)

Formula

Mean of group A = 5.08 ± 0.762

Mean of group B = 4.51 ± 0.744

Type I error (α) = 0.05

Type II error (β) = 0.2

Power = 80%

Inclusion criteria

The inclusion criteria for participation includes:

- Age between 18 – 60 years
- Both genders
- Grade III and IV hemorrhoids diagnosed on the basis of history and clinical examination by consultant Surgeon.(Grade III Hemorrhoid manually reduced by patient with finger and Grade IV is prolapsed)
- ASA (American society of Anesthesia) grades I, and II

Exclusion criteria

The exclusion criteria for participation includes:

- Previously reported allergy or reaction to lignocaine and GTN
- Pregnancy or lactation
- Concomitant perianal pathology warranting surgery
- Cardiovascular disease
- Patient taking Nitrates or Calcium channel blocker

Data Collection

After ethical approval of the study from the institutional review board, the patients presenting to Department of Surgery, Mayo Hospital, Lahore with the diagnosis of hemorrhoid confirmed on history, and examination will be included in the study. Patients' information such as name, case number, age, gender, and duration of hemorrhoids will be inquired. Informed consent will be acquired from the patients. The patients will undergo hemorrhoidectomy by the consultant general surgeon or by post-graduate general surgery residents under supervision of consultants.

The participants will be divided by using the lottery method in two groups: Group A and Group B. The double blinding will be used to reduce the bias in the study. The patients in each group will undergo Milligan Morgan hemorrhoidectomy under spinal anesthesia/ saddle block/GA. Following intervention will be done:

Group A = Lignocaine cream post-operatively and then three times daily

Group B = 0.2% GTN ointment postoperatively and then three times daily

All patients will be advised to take sitz bath three times daily for 15 minutes from 1st post-operative day. They will be advised to apply the prescribed ointment with the fingertip circumferentially 1 cm in side the anal canal after sitz bath and to use stool softeners (30ml lactulose twice daily). All patients will be given injection Paracetamol 1gm intravenously 8 hourly as a standard analgesia. Injection Ketorolac 30mg intravenously stat as a rescue analgesia in first 24 hour. The patient will be discharged on 2 tablet Panadol three times a day.

The outcome will be measured by using the visual analogue score (VAS) for analgesia will be used to assess the score of pain at 6, 12, 24, 48, 72 hours and on 7th, 14th, 21st and 28th day after surgery. Time of request for 1st dose of analgesia, and amount of analgesia required as per demand of the patient will be documented within 1st 24 hours. Patients will be discharged after 24 hours with pain evaluation performa and will be followed weekly for 6 weeks to assess the level of pain and healing of wound. The level of satisfaction of patient with treatment will be assessed after 6 weeks on a 5-point Likert scale.

Data Analysis

All data will be analyzed using Statistical Package for the Social Sciences (SPSS) ver. 26. Quantitative variables as age, pain score and wound healing time will be presented as mean ± standard deviation and qualitative variables as gender and satisfaction level of patient will be displayed as frequency and percentage. Data will be stratified for age,gender,BMI,Grade of Hemorrhoids. Independent sample t-test will be applied post-stratification. A p-value < 0.05 will be considered as significant.

Performa

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Name: Age/gender:

Mr No: Address:

Date of surgical procedure: ASA Score:

Group: A/B BMI:

Grade of Hemorrhoid;

PRIMARY OUTCOMES:

Pain Score,wound Healing time is a primary outcomes

Other Variables:

- Time for request of 1st dose of analgesia:----------min/hr
- Amount of analgesia given in 24 hours:----------mg

Time after procedure	**6 hr**	**12 hr**	**24 hr**	**48 hr**	**72 hr**	**7 Day**	**14 day**	**21 day**	**28 day**
Pain Score									
Wound infection(Yes/No)									
Secretion(Yes/No)									
Itching(Yes/No)									
Bleeding(Yes/No)									
Headche(yes/No)									

Level of satisfaction of patient after 6 weeks:

- Very satisfied
- Satisfied
- Neutral
- Dissatisfied
- Very dissatisfied

Wound healing time: ----------days

References

1. Asif K, UL-HASSAN M,Muneeb Rehman P,Rasheed T,Zahid L. Compare the efficacy of 0.2% topical glyceryl trinitrate (GTN) versus placebo in prevention of wound infection in patients undergoing Milligan-Morgan hemorrhoidectomy. PJMHS. 2020;34:12-46.
2. Lashari AA, Bozdar AG, Bhellar ZH, Baker A, Shar ZA, Narejo GA. Determine the effectiveness of 0.2% topical glyceryl trinitrate in preventing postoperative wound infection after hemorrhoidectomy. Pak J Med Health Sci. 2020;14(4):1327-9.
3. Khan KI, Waqas A, Akmal M, Mahmood S, Iqbal A. Efficacy of combination of 0.2% GTN and lignocaine ointments in wound healing and pain relief after Milligan Morgan hemorrhoidectomy–a comparison with lignocaine and 0.2% GTN ointments separately. Int J Surg. 2014 ;12(4):329-33.
4. Franceschilli L, D'Ugo S, de Luca E, Cadeddu F, Milito G, Di Lorenzo N, "et al". Role of 0.4% glyceryl trinitrate ointment after haemorrhoidectomy: results of a prospective randomised study. Int J of colorectal dis. 2013;28:365-9.
5. Sekimoto K, Tobe M, Saito S. Local anesthetic toxicity: acute and chronic management. Acute Med Surg. 2017;4(2):152-160
6. Kwok AM, Smith SR, Zhao J, Carroll R, Leigh L, Draganic B. Topical Lidocaine or Lidocaine/Diltiazem Ointment Following Rubber Band Ligation of Hemorrhoids: A Prospective 3-Armed Randomized Controlled Trial. Dis Colon Rectum. 2023;66(8):1110-7.
7. Xu W, Xia G, Dong L, Zhu Y. Effect of lidocaine on postoperative analgesia of endoscopic rubber band ligation combined with injection sclerotherapy for treatment of internal hemorrhoids: A retrospective study s(with video). Arab Journal of Gastroenterology. 2024 May 1;25(2):165-9.