International Surgery Journal
Alkhateep Y et al. Int Surg J. 2017 Dec;4(12):3822-3826
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: http://dx.doi.org/10.18203/2349-2902.isj20175111

Original Research Article

Double blinded randomized placebo-controlled comparative study between sucralfate ointment and lidocaine ointment after Milligan Morgan hemorrhoidectomy

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Received: 27 September 2017
Accepted: 04 October 2017

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ABSTRACT

Background: Post haemorrhoidectomy pain and delayed wound healing are the most annoying drawbacks to the patients and the surgeons. Topical application of sucralfate or lidocaine may help in reducing postoperative pain and promoting wound healing after Milligan Morgan hemorrhoidectomy.
Methods: This study was designed as a single-center double blinded randomized placebo controlled trial at the Department of general Surgery Menoufia University, immediately after Milligan Morgan Hemorrhoidectomy, a total of 150 patients were randomly assigned to receive either 10% Sucralfate ointment, 5% lidocaine ointment or placebo ointment (control group). The primary outcome measure was pain intensity measured by a visual analogue scale at different time points after hemorrhoidectomy and the secondary outcome measure was wound healing.
Results: There was no significant difference in age, gender, and number of excised hemorrhoid piles between the two groups. At the 1st ,3rd and 7th days after surgery pain intensity was significantly lower in sucralfate group (4.18±0.82, 3.92±0.72, 3.56±0.67) when compared to lidocaine group (5.06±1.11, 4.70±0.84, 3.93±0.75) and placebo group (6.17±1.26, 5.42±0.98, 4.55±0.84). At the 21st and 28th days no significant difference in pain intensity between groups ($p > 0.05$) with better wound healing in sucralfate group ($P<0.05$).
Conclusions: sucralfate was able to reduce the acute postoperative pain and improve wound healing after Hemorrhoidectomy, local anaesthetic lidocaine could help in pain control but without effect on healing.

Keywords: Hemorrhoidectomy, Lidocaine, Pain, Sucralfate, Wound healing

INTRODUCTION

Hemorrhoids are symptomatic enlargement and distal displacement of the normal anal cushions with dysregulation of the vascular tone and vascular hyperplasia.[1] Symptoms from hemorrhoids include bleeding, pain, prolapse and perianal itch with prevalence rates of up to 4.4% within the general population.[2]

Given the prevalence of the condition, the management of hemorrhoidal disease continues to have considerable workload and costs implications for the National Health Service (NHS), with approximately 25,000 hemorrhoidal procedures being performed yearly in U.K.[3]

Treatment of hemorrhoids depends mainly on the stage and symptoms of the disorder. Haemorrhoidectomy is considered an effective method for 3rd and 4th degree symptomatic hemorrhoids. Many surgical techniques have been proposed; however, open haemorrhoidectomy is still the most common performed operation for haemorrhoids.[4]

Post haemorrhoidectomy pain and delayed wound healing are the most annoying drawbacks to the patients and the surgeons, Pain may be explained by presence of surgical wound in the sensitive anoderm and perianal skin and the edema from tissue inflammation around the wound.[5,6] Various topical applications were used to reduce pain following open haemorrhoidectomy e.g. botulinum toxin, Calcium Channel Blockers (CCBs), Glyceryl Trinitrate (GTN), local anesthetics, metronidazole, opioids, sucralfate, one herbal cream mainly consist of Aloe vera and other formulations with variable outcomes.[7]

Sucralfate is the aluminium hydroxide salt of the disaccharide sucrose octasulfate. For more than three decades, sucralfate has been used as a cytoprotective agent for treatment of gastrointestinal ulcer diseases. This drug has antimicrobial and antioxidant activity, stimulates the secretion of prostaglandin E2 (PGE2) with subsequent increased blood flow and mucus formation, and enhances the production of epidermal growth factor (EGF) which can lead to increased angiogenesis.[8]

Topical anesthetics represent important components of multimodal analgesic regimens for surgical wound and proved efficacy and tolerability when administered appropriately.[9] Respecting the role and effectiveness of open haemorrhoidectomy and on trial to minimize complications associated with this procedure, two topical ointment formulations (sucralfate 10% and lidocaine 5%) were investigated and compared in this study for their efficacy on postoperative pain and wound healing following open haemorrhoidectomy.

METHODS

This study was designed as a single-center double blinded randomized placebo controlled trial at the Department of General Surgery Menoufia University, with prior approval from our Institution's Ethics Review Board.

Inclusion criteria

After a written informed consent, patients suffering from 3rd or 4th degree haemorrhoids and indicated for open haemorrhoidectomy were enrolled in this study.

Exclusion criteria

It was concomitant anal or rectal pathologies (e.g. abscess, fistulae, prolapse, etc.), age younger than 18, previous anal surgery, poorly controlled diabetes mellitus, recent history of chemotherapy and active cancer patients. Patients with severe anemia, hypoalbuminemia or immunocompromised patients were also excluded.

Preparation of the ointments: 10% Sucralfate ointment was prepared using liquid paraffin as levigating agent in a petrolatum base. The placebo ointment was prepared by the same method from liquid paraffin and petrolatum. The physicochemical stability of the ointment was evaluated at 50, 60, 70 and 80 C. Microbiological limit tests were performed for the preparation and no evidence of microbial growth was found. Both preparations were filled in identical tubes each containing 30 g of the ointment. Commercially available lidocaine ointment of the same tube size was prepared as well.

All tubes of the three ointments were masked by non-removable adhesive tape and packaged, each package contain 5 tubes of the same ointment and each package was labeled by computerized random labels of letters and digits. The package label was considered as the patient I.D during the study.

All surgeries were performed out by the same surgeon and followed the same anaesthesia protocol in order to abolish any interpersonal variation. After end of surgery, patients were randomly assigned into one of the three treatment groups using closed envelope containing a label of one of the ointment packages. The treatment groups received either 10% Sucralfate ointment, 5% lidocaine ointment or placebo ointment. Neither the surgeon nor the patients were aware of the type of ointment applied to the patient until the end of the study.

The ointment was applied immediately after end of surgery and patients were instructed to apply it every 6 hours thereafter. The patients were hospitalized for one day after resection and received single intramuscular injection diclofenac sodium 75 mg after end of surgery then oral analgesic in form of diclofenac sodium 50 mg tablets every 12 hours for seven days. Stool softeners were also advised to be taken (lactulose 30 ml twice daily) from the 1st post-operative day until complete wound healing. Patients were evaluated on days 1, 3, 7, 14, 21, 28 post-haemorrhoidectomy for pain and wound healing. Intensity of pain was evaluated immediately before the time of the next analgesic dose.

The primary outcome measure was pain intensity based on the patients' subjective use of a visual analogue scale (VAS), with zero denoting the absence of pain and 10 denoting the worst possible pain. The secondary outcome measure was wound healing, the wounds were inspected during the clinic visits and the amount of mucosal covering of the wound at each visit was recorded. Wounds that were fully epithelialized with no discharge were judged to be completely healed.

Statistical analysis

Statistical analysis performed using SPSS v. 24.0. (IBM Corp., USA). Discrete variables presented as numbers (counts) and percent. Continuous variables presented as mean and standard deviation (SD). Difference in categorical data was compared using a chi-square test. One-way ANOVA (Analysis of Variance) with post-hoc Tukey HSD (Honestly Significant Difference) Test was used for intergroup comparisons to test the significance

of difference between the different variables. P < 0.05 was considered statistically significant.

RESULTS

From March 2016 to July 2017, one hundred and fifty patients were eligible to participate in this study; they were randomly assigned into 3 groups each containing 50 patients. Two patients of lidocaine group removed the masking tape from the ointment tube and lost their blindness about the treatment and were excluded from follow up statistics along with 5 patients from control group (four missed the follow up visits and one used other local medications on his wound).

Table 1: The base line characteristics.

	Sucralfate group	Lidocaine group	Placebo group	P value
Age (mean±SD)	43.35±8.3	40.91±7.62	41.42±7.1	0.14
Male/female	26/24	31/19	22/28	0.19
Piles grade III/IV ratio	35/15	39/11	41/9	0.35
No. of piles removed (mean±SD)	2.57±0.49	2.65±0.47	2.48±0.50	0.12

Table 2: Average pain scores on a visual analogue scale (VAS) at different time points after Hemorrhoidectomy (mean ± SD).

Pain	Sucralfate group N= 50	Lidocaine group N=48	Placebo group N=45	F statistic	P value
1st day	4.18±0.82	5.06±1.11	6.17±1.26	40.70	0.0001
	Sucralfate compared to Lidocaine				0.001
	Sucralfate compared to Placebo				0.001
	Lidocaine compared to Placebo				0.001
3rd day	3.92±0.72	4.70±0.84	5.42±0.98	36.60	0.0001
	Sucralfate compared to Lidocaine				0.001
	Sucralfate compared to Placebo				0.001
	Lidocaine compared to Placebo				0.001
7th day	3.56±0.67	3.93±0.75	4.55±0.84	20.72	0.0001
	Sucralfate compared to Lidocaine				0.039
	Sucralfate compared to Placebo				0.001
	Lidocaine compared to Placebo				0.001
14th day	3.18±0.74	3.41 ±0.79	3.93±0.91	10.36	0.001
	Sucralfate compared to Lidocaine				0.32
	Sucralfate compared to Placebo				0.001
	Lidocaine compared to Placebo				0.007
21st day	2.81±0.56	2.95±0.69	3.12±0.87	2.24	0.11
28th day	1.97±0.45	2.04±0.53	2.19±0.60	2.12	0.12

The base line characteristics including age, gender, piles grade and number of piles removed were homogenous in the three groups as shown in Table 1. Pain scores in treatment groups based on the VAS at different time points after haemorrhoidectomy are tabulated in Table 2.

Significant differences in pain score was detected between the treatment groups at the 1, 3 and 7 days post-operative visits (P<0.05), pain intensity was significantly lower in sucralfate group (4.18±0.82, 3.92 ±0.72, 3.56±0.67) when compared to lidocaine group (5.06±1.11, 4.70±0.84, 3.93±0.75) and placebo group (6.17±1.26, 5.42±0.98, 4.55±0.84), and when comparing lidocaine to placebo; lidocaine had a lower pain intensity (P<0.05).

Pain intensity 14 days post haemorrhoidectomy was similar in sucralfate and lidocaine groups (P>0.05) and both were significantly lower than placebo (P<0.05). Later on, visits showed no significant difference regarding pain intensity between all groups.

Wound healing was evaluated at 21st and 28th days as shown in Table 3, sucralfate significantly improved wound healing (62% and 88%) when compared to lidocaine (39.5% and 66.6%) and placebo (37.7% and

64.4%) (P<0.05). Lidocaine had no superiority regarding wound healing over placebo (P >0.05).

Table 3: Wound healing in treatment groups.

Wound healing	Sucralfate group N= 50	Lidocaine group N=48	Placebo group N=45	P value
21st day	31(62%)	19 (39.5%)	17 (37.7%)	0.028
	Sucralfate compared to Lidocaine			0.042
	Sucralfate compared to Placebo			0.024
	Lidocaine compared to Placebo			1.00
28th day	44 (88%)	32 (66.6%)	29 (64.4%)	0.014
	Sucralfate compared to Lidocaine			0.015
	Sucralfate compared to Placebo			0.007
	Lidocaine compared to Placebo			0.83

There were no significant differences in the frequencies of postoperative complications (anal pruritus, wound infection, early or delayed bleeding) between the three groups; fecal incontinence was not reported in all groups.

DISCUSSION

Despite concerted efforts for improvement, the burden and severity of postoperative pain continue to contribute to negative post hemorrhoidectomy outcomes. Pain seems to be multifactorial and dependent on individual tolerance, mode of anesthesia, post-operative analgesia regimen and surgical technique. Surgical wound in the sensitive anoderm and perianal skin and edema from tissue inflammation around the wound causes reflex spasm of internal anal sphincter and all lead to more worsening of post-operative pain.[10] From topical drugs used to control pain after hemorrhoidectomy, sucralfate ointment and lidocaine ointment had been investigated in this study. By adding a control group and double blinding the study we had tried to evaluated efficacy of both treatments and if there is any superiority of one of them in pain management and wound healing.

The level of post-operation pain was measured based self-report visual analogue scale (VAS) at 6 times during the experiment. When compared to placebo both sucralfate and lidocaine had significant efficacy in relieving post haemorrhoidectomy pain during the first two weeks (P<0.05). On the other hand, sucralfate showed superiority in pain control over lidocaine during early postoperative period (P<0.05), by the end of 2nd week both sucralfate and lidocaine had comparable effect on pain intensity (P>0.05), but both still superior to placebo. At the end of the 3rd week and later on both drugs had no significant superiority to placebo regarding post-operative pain control (P>0.05).

Regarding wound healing, Sucralfate showed significant improvement in wound healing when compared to lidocaine or placebo at 21 and 28 days post-surgery (P<0.05), while lidocaine had no effect better than placebo on wound healing (P>0.05).

Role of sucralfate in treatment of gastrointestinal ulcer diseases is well known, recently few studies evaluated its effect on skin ulcers and surgical wounds, in a study published by Tumino et al, sucralfate improved healing of chronic venous ulceration.[11] In a randomized controlled study by Gupta et al on 116 patients, topical sucralfate reduced pain at days 7 and 14 after hemorrhoidectomy but later on had no effect more than placebo, They also reported better overall wound healing when compared with placebo. Unlike Gupta study we evaluated pain intensity at the 1st and 3rd days which give more data about early effect of the drugs.[12]

In present study, sucralfate had significant effect on pain intensity even in the first post-operative day but against this, study by Mirani et al. showed that topical sucralfate ointment (10%) has a significant analgesic effect and can reduce both acute and chronic pain after hemorrhoidectomy but its analgesic effect is not obvious before 24 hours. This difference me be explained by the frequency of application of the treatment as in Mirani study patients applied the ointment every 12 hours only unlike every 6 hours in our study, we think that more frequent application gives better effect.[13] In another work by Ala et al, topical sucralfate did decreased post-hemorrhoidectomy pain in the first 24 h after surgery, by thorough revision of the methods and results of this study and Mirani study; we had found high cross matching between them which may raise doubts about plagiarism.[14] Sucralfate also had been tried in post anal fistulotomy wound and proved to be effective regarding pain control and wound healing.[15]

Despite being inferior to sucralfate; local anesthetic lidocaine ointment did reduced pain intensity post hemorrhoidectomy when compared to placebo group. In a study by Shiau et al, local anesthetic cream, EMLA cream was used for post hemorrhoidectomy pain and showed a better pain control and Patient satisfaction than

control group.[16] Rahimi et al, also reported that EMLA showed better short-term pain control following hemorrhoidectomy, while more sustainable pain control was provided by diclofenac suppository.[17]

CONCLUSION

It could be inferred from the above data that sucralfate was able to reduce the acute postoperative pain and improve wound healing after hemorrhoidectomy; local anesthetic lidocaine could help in pain control but without effect on healing.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Alkhateep Y, Fareed A. Double blinded randomized placebo-controlled comparative study between sucralfate ointment and lidocaine ointment after Milligan Morgan hemorrhoidectomy. Int Surg J 2017;4:3822-6.