



International Journal of Pharmacology

ISSN 1811-7775

science
alert

ansinet
Asian Network for Scientific Information

A Systematic Review of the Topical Drugs for Post Hemorrhoidectomy Pain

¹Roja Rahimi and ²Mohammad Abdollahi

¹Faculty of Traditional Medicine and Pharmaceutical Sciences Research Center,
Tehran University of Medical Sciences, Tehran, 1417614411, Iran

²Faculty of Pharmacy and Pharmaceutical Sciences Research Center and Endocrinology and Metabolism
Research Institute, Tehran University of Medical Sciences, Tehran, 1417614411, Iran

Abstract: The purpose of this study is to review all of these preparations and evaluate their efficacy and safety. Electronic databases were searched to obtain studies about the efficacy of locally used medications in the management of post-hemorrhoidectomy complications. Data were collected for the years 1966 to 2012 (up to September). Finally 24 relevant studies were included. The topical preparations used include botulinum toxin, Calcium Channel Blockers (CCBs), Glyceryl Trinitrate (GTN), local anesthetics, metronidazole, opioids, sucralfate and one herbal cream mainly consist of Aloe vera. Overall, topical preparations showed encouraging results in reducing pain and analgesic use and improving wound after hemorrhoidectomy. Because of better bioavailability and lower incidence of adverse events compared with other dosage forms, it is suggested to use topical preparations especially those with confirmed efficacy in the following order o GTN, CCBs, metronidazole, local anesthetics, sucralfate and botulinum toxin.

Key words: Hemorrhoidectomy, post-hemorrhoidectomy pain, wound healing, analgesic use, systematic review

INTRODUCTION

Hemorrhoidectomy is the most effective treatment to reduce recurrent symptoms in patients with grade 3 or 4 hemorrhoids (Mounsey *et al.*, 2011). Hemorrhoids are defined as the symptomatic enlargement and distal displacement of the normal anal cushions and dysregulation of the vascular tone and vascular hyperplasia seems playing important role in hemorrhoidal development and could be a potential target for medical treatment (Lohsiriwat, 2012). Several anorectal conditions may cause symptoms similar to those associated with hemorrhoids such as colorectal and anal cancers and inflammatory bowel disease (Mounsey *et al.*, 2011) which should be managed differently (Cellini and Valentini, 2012; Van Cutsem *et al.*, 2008; Nikfar *et al.*, 2009; Rahimi *et al.*, 2006, 2007a-c). Indications for hemorrhoidectomy include failure of non-operative management, acute complicated hemorrhoids such as strangulation or thrombosis, patient preference and concomitant anorectal conditions such as anal fissure or fistula-in-ano which require surgery (Lohsiriwat, 2012; Mirfazaelian *et al.*, 2012).

In clinical practice, the third-degree or fourth-degree internal hemorrhoids are the main indications for hemorrhoidectomy (Lohsiriwat, 2012). The major complications of hemorrhoidectomy are pain, infection,

inflammation, hemorrhage, fecal incontinence, unhealed wound and urinary retention (Keshtkaran *et al.*, 2011; Holzheimer, 2004). The spasm of internal anal sphincter seems to be the main reason for post hemorrhoidectomy pain (Roe *et al.*, 1987). Various invasive and noninvasive methods, including sphincterotomy, anal dilation, application of topical preparations, flavonoids and oral or parenteral analgesics have been suggested to relieve internal sphincter spasm to resolve post hemorrhoidectomy pain. Topical preparations are preferred because of better bioavailability and fewer incidence of adverse events compared with other dosage forms. In this study, management of post hemorrhoidectomy complications by different topical preparations has been evaluated in details.

MATERIALS AND METHODS

Electronic databases including PubMed, Scopus and Cochrane library were searched to obtain studies about the efficacy of locally used medications in the management of post hemorrhoidectomy complications. Data were collected for the years 1966 to 2012 (up to September). The search terms were: “hemorrhoidectomy” or “post hemorrhoidectomy” and “complication” or “pain”. Reference lists of the retrieved articles were also reviewed for additional applicable studies. The title and

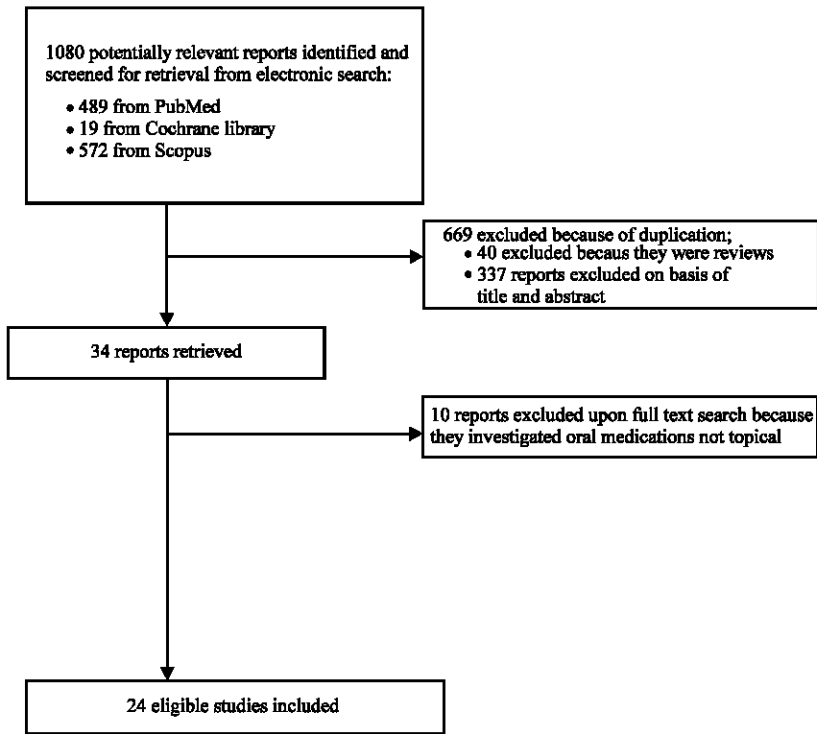


Fig. 1: Flow diagram of the study selection process

abstract of each article were examined to eliminate duplicates, reviews, studies examining parenteral or oral medications other than topical or local. Figure 1 shows a flow diagram of the study selection process. As shown in Table 1, 1080 articles were found, from that 1056 were excluded and finally 24 of them included.

LOCALLY USED MEDICATIONS FOR POST HEMORRHOIDECTOMY COMPLICATIONS

Botulinum toxin: Botulinum toxin has shown efficacy in a large spectrum of human pain disorders. Botulinum toxin exhibits its analgesic effect by inhibiting the release of a number of neurotransmitters from presynaptic vesicles via deactivation of specific proteins located at, or in proximity of, the vesicular membrane. Of the seven distinct serotypes of botulinum toxin (A to G), types A and B are currently used in clinical practice (Jabbari and Machado, 2011). The first study on the use of botulinum toxin after hemorrhoidectomy showed lower daily average and maximal post-operative pain in botulinum group compared to placebo throughout the study period. But there was no significant difference in morphine requirements in the first 24 h and analgesic requirement during 7 days after surgery (Davies *et al.*, 2003). Intrasphincteric injection of botulinum toxin after hemorrhoidectomy in another study reduced maximum

resting pressure of the anal canal, accelerated wound healing, decreased postoperative pain on resting and during defecation and reduced analgesics use in patients with hemorrhoids of third and fourth degree in absence of complications or side effects (Patti *et al.*, 2005a).

Calcium channel blockers: Calcium Channel Blockers (CCBs) block calcium uptake in the myocytes thereby decreasing contraction of internal anal sphincter and relaxation of anal sphincter smooth muscle (Cook *et al.*, 1999). Perianal application of topical diltiazem 2% after hemorrhoidectomy significantly reduced post-operative pain and analgesic demand with no increase in related morbidity (Amoli *et al.*, 2011; Silverman *et al.*, 2005). A trial compared the efficacy of 0.3% nifedipine and 1.5% lidocaine ointment versus 1.5% lidocaine ointment alone after hemorrhoidectomy and showed no difference between groups for time of administration of analgesic after open hemorrhoidectomy. The patients' assessment of pain showed that the use of topical nifedipine with lidocaine may provide a slight significant difference in favor of the study group at 6 hours and at day 7 after surgery (Perrotti *et al.*, 2010).

Glyceryl trinitrate (GTN): Recent evidence suggests that nitric oxide (NO) is an inhibitory neurotransmitter in the internal anal sphincter and causes relaxation of this

Table 1: Studies on the use of various topical preparations for the management of post-hemorrhoidectomy complications

Interventions	Dosage	Design	Surgical technique	Analgesics	Results	References
Aloe vera cream (n = 24) vs. placebo cream (n = 25)	3 g 3 times daily	Prospective, randomized, Double-blind, placebo-controlled	Open	ND	Less postoperative pain at h 12, 24 and 48 h and at 2 weeks, ↓ pain after defecation in 24 and 48 h postsurgery (p<0.001), better wound healing at the end of the second postoperative week (p<0.001) and fewer analgesic requirement (p<0.001) in Aloe group compared with placebo	Eshghi <i>et al.</i> (2010)
Botulinum toxin (intrasphincter injection) (n = 24) vs. normal saline (n = 25)	0.4 mL (20 units) vs. 0.4 mL	Double-blind, randomized	Milligan-Morgan	Cocodornal (codeine phosphate, paracetamol)	Lower postoperative pain which is significant on Day 6 (p = 0.02) and Day 7 (p = 0.04) in botulinum vs. placebo; No significant difference in analgesic requirement; No complications or adverse events	Davies <i>et al.</i> (2003)
Botulinum toxin (intrasphincter injection) (n = 15) vs. normal saline (n = 15)	0.4 mL (20 units) vs. 0.4 mL	Double-blind, randomized	Milligan-Morgan	Nimesulide	↓ Max resting pressure at day 5 in botulinum group vs. preoperative (p<0.01); ↓ max resting pressure at day 5 in placebo group vs. preoperative (p<0.05); ↓ time of healing (p<0.05), lower postoperative pain on resting and during defecation (p<0.0001), ↓ oral analgesic use (p<0.05) in botulinum vs. placebo; no complication or side effect	Patti <i>et al.</i> (2005a)
Bupivacain injection 0.5% (n = 72) vs. control (n = 70)	1-3 mL 10 min before operation	Prospective randomized	ND	Morphine, pethidine, tramadol or paracetamol	Longer pain free period in bupi group vs. control (p<0.001); greater number of patients with no pain after surgery in bupi group vs. placebo (p<0.001); less analgesic requirement in bupi group (p<0.001)	Jirasiritham <i>et al.</i> (2004)
Bupivacain depofoam injection (n = 95) vs. sodium chloride 0.9% (n = 94)	30 mg/30 mL vs. 30 mL at the end of surgery	Randomized, Double-blind, parallel-group, placebo-controlled	Milligan-Morgan	Morphine	↓ Pain intensity scores in bupi group vs. placebo (p<0.0001); More opioid free Patients during 72 h after surgery in bupi vs. placebo (p<0.0008); ↓ mean total amount of opioids consumed through 72 h in bupi vs. placebo (p = 0.0006); longer median time to first opioid use in bupi group vs. placebo (p<0.0001); greater proportion of patients satisfied with their postsurgical analgesia in bupi group vs. placebo (p = 0.0007)	Gorfine <i>et al.</i> (2011)
Diltiazem 2% ointment (n = 9) vs. vaseline ointment (n = 9)	3 times per day for 7 days	Randomized, prospective, double-blind, placebo-controlled	Ferguson	Hydrocodone	Lower postoperative pain (p<0.001) and higher overall benefit (p<0.001) in diltiazem vs. placebo; greater number of analgesic use in placebo vs. diltiazem but not significant; one patient in diltiazem group dropped out on day 2 due to development of a rash; no difference in morbidity between two groups	Silverman <i>et al.</i> (2005)
Diltiazem 2% ointment (n = 16) vs. vaseline ointment (n = 17)	1 g 3 times per day for 7 days	Prospective, randomized, controlled	Milligan-Morgan	Acetaminophen codeine	Less pain on postoperative days 2-7 in diltiazem group (p<0.0001); fewer patients using analgesic in diltiazem group (p<0.0001)	Amoli <i>et al.</i> (2011)
EMLA cream (lidocaine 2.5% and prilocaine 2.5%) (n = 15) vs. neomycin ointment (n = 15)	5 g	Double-blind, Randomized	Ferguson	Meperidine injection	Lower postoperative pain (p<0.05), ↓ analgesic use (p = 0.04), ↓ voiding time (p = 0.03), less single urinary catheterizations (p = 0.04) and better patient-reported satisfaction score (P<0.01) in EMLA vs. placebo; no systemic complications	Shiau <i>et al.</i> (2008)

Table 1: Continue

Interventions	Dosage	Design	Surgical technique	Analgesics	Results	References
EMLA cream+local lidocain injection 1% (n = 30) vs. neomycin ointment (n = 30)	5 g+ 10 mL	Randomized	Ferguson	Meperidine injection	Lower postoperative pain (p<0.05), 1 analgesic use (p< 0.05) and better patient-reported analgesia satisfaction score (p<0.01) in EMLA vs. placebo; no difference in voiding time and single urinary catheterizations; no systemic complications	Shiau <i>et al.</i> (2007)
EMLA cream (n = 30) vs. diclofenac suppository (n = 30) vs. petrolatum ointment (n = 30)	5 g vs. 100 mg vs. 5 g	Randomized	Ferguson	Pethidine injection	The lowest pain on transfer to recovery and at 2 h after surgery in EMLA group (p<0.05); The lowest pain in the evening and the morning after surgery (p<0.05) and fewest requests for analgesic (p = 0.0001) in diclofenac group	Rahimi and Abdollahi (2012)
GTN ointment 0.2% (n = 19) vs. vaseline ointment (n = 20)	1 g 3 times per day for 7 days	Randomized, prospective, double-blind, placebo-controlled	Ferguson	Hydrocodone	Lower postoperative pain in GTN group but not significant for each of the seven days; significantly lower use of analgesic in GTN only in day 2 after surgery (p<0.05); higher morbidity in GTN vs. placebo (p<0.001)	Wasvary <i>et al.</i> (2001)
GTN ointment 0.2% (n = 10) vs. placebo ointment (n = 10)	Twice daily for 6 weeks	Randomized, Double-blind, placebo-controlled	-	-	No difference in pain scores between both groups; 20% of patients in each group complained that the ointment caused headache Nitroderm	Elton <i>et al.</i> (2001)
TTS® 5 band (adhesive bandage contains 25 mg of nitroglycerin on lactose in a viscous silicone fluid under semipermeable membrane) vs. nothing	Placing in to anal canal after surgery vs. nothing placed in anal canal	ND	Standard three-column hemorrhoid excision	Pethidine	Lower postoperative pain in Nitroderm group (p = 0.0001); less patients requiring analgesics in Nitroderm group (p<0.05)	Coskun <i>et al.</i> (2001)
GTN ointment 0.2% (n = 55) vs. placebo ointment (n = 55)	1 g 3 times per day for 3 weeks	Randomized, prospective, Double-blind, placebo-controlled	Modified Milligan-Morgan	Pethidine, ketorolac, amfenac	Lower postoperative pain in GTN (p<0.001); lower but not significant amount of analgesic use in GTN; higher proportion of complete wound healing in GTN (p = 0.002); no difference in morbidity between two groups	Hwang <i>et al.</i> (2003)
GTN ointment 0.2% (n = 40) vs. placebo ointment (n = 42)	ND*	Randomized, placebo-controlled	Milligan-Morgan	ND*	! Max resting pressure in GTN group and increased in the placebo group after 5 days; reduction in Postoperative pain both at rest and during defecation and the time to healing were significantly reduced in GTN; no difference in analgesic consumption; more incidence of headache in GTN group	Patti <i>et al.</i> (2005b)
GTN ointment 0.2% (n = 40) vs. petrolatum ointment (n = 42)	330 mg 3 times per day for 2 weeks	Randomized prospective Double-blind placebo-controlled	Open diathermy	Paracetamol, diclofenac	No difference in mean pain score and mean use of analgesic; more patients in the GTN group had completely epithelialized wounds compared with placebo (p = 0.021); no difference in complications between 2 groups	Tan <i>et al.</i> (2006)
GTN ointment 0.2% (n = 15) vs. butolinum toxin (n = 15)	300 mg 3 times daily for 30 days vs. single 0.4 mL (20 U) injection	Randomized	Milligan-Morgan	Nimesulide	More reduction of pain at rest in the Tox group compared with the GTN group (P = 0.01); No difference in pain during defecation and time of wound healing; more analgesic use in GTN compared with tox (p<0.05); more adverse drug reactions in GTN compared with Tox (p<0.03)	Patti <i>et al.</i> (2006)

Table 1: Continue

Interventions	Dosage	Design	Surgical technique	Analgesics	Results	References
GTN ointment 0.2% (n = 30) vs. petrolatum ointment (n = 30)	1g twice per day for 2 weeks	Prospective, randomized, Double-blind, placebo-controlled	Ferguson	Naproxen, paracetamol, metamizole	Overall lower pain in GTN group (p<0.0001), lower amount of analgesic use in GTN (p = 0.006); higher number of patients with complete wound healing after 3 weeks in GTN (p = 0.02); no difference in the number of patients with complications	Karamlik <i>et al.</i> (2009)
Metronidazole 1.0% cream (n = 10) vs. petrolatum cream (n = 10)	2.5 mL 3 times daily	Prospective, randomized, single-blind	Harmonic scalpel	Hydrocodone	Less postoperative pain at day 7 (p = 0.002) and day 14 (p = 0.02) and better score of overall wound healing (p = 0.03) in metronidazole group; no difference in analgesic use	Nicholson and Armstrong (2004)
Metronidazole 10/5 ointment (n = 25) vs. petrolatum ointment (n = 22)	1.5-2 cm 3 times daily	Randomized, double blind, prospective, placebo-controlled	Open	ND	Lower Pain on defecation on day 2 (p = 0.02) in metronidazole group but no significant difference was observed at day 7 and day 14, lower use of analgesic at 12 h and on days 2 and 7 postsurgery in metronidazole group (P<0.05); No significant complications or allergic reactions	Ala <i>et al.</i> (2008)
0.3% nifedipine+1.5% lidocaine ointment vs.	3 g twice daily for 2 weeks	Prospective, randomized, double-blind	Milligan-Morgan	Ketoprofen	No significant difference in postoperative pain and analgesic use between two groups	Perrotti <i>et al.</i> (2010)
A sponge cotton gauze dressing embedded 1.5% lidocaine with 1 mg of morphine (n = 51) vs. 1 mg oxycodone (n = 45) ointment vs. 2 mL of vehicle (n = 39)	At the end of procedure and removed 12 h later	Double-blind prospective randomized placebo-controlled	Milligan-Morgan	ND	Increase in time elapsing from the end of the surgical procedure to the request for analgesic (p<0.001) in Morphine group vs. placebo; higher mean time to voiding in vehicle vs. morphine and oxycodone (p<0.001); secondary bleeding in 3 patients (2 from morphine and 1 from the oxycodone groups)	Tegon <i>et al.</i> (2009)
Sucralfate 7% cream (n = 54) vs. petrolatum cream (n = 56)	3 g 3 times daily	Double-blind, prospective, randomized	Milligan-Morgan	Tramadol, paracetamol	Less postoperative pain at Day 7 (P<0.002) and Day 14 (p<0.01) in sucralfate; more patients with wound healing at week 4 in sucralfate (p<0.02), fewer days for complete wound healing in sucralfate (p<0.01); no difference in analgesic use between 2 groups; no complications recorded	Gupta <i>et al.</i> (2008)
Trimebutine suppository (120 mg trimebutine+10 mg nuscogenins) (n = 80) vs. no treatment (n = 80)	Single dose after hemorrhoidectomy	Randomized controlled	Standard diathermy excision	Ketoprofen, pethidine	No differences in the pain score at 4 h after surgery, maximum pain during the first 24 h, maximum pain during the second postoperative day and analgesic requirement between two groups	Ho <i>et al.</i> (1997)

GTN: Glyceryl trinitrate; vs.: Versus ; ND: not determined; *Only abstract evaluated

smooth muscle (Rattan and Chakder, 1992). Organic nitrates, such as GTN are degraded by cellular metabolism, liberating NO. Moreover, GTN increases the anodermal blood flow and therefore it seems to increase wound healing rate (Kua *et al.*, 2001). There are conflicting results about the use of topical GTN for post hemorrhoidectomy complications. Some shows lower post-operative pain following the use of these preparations (Coskun *et al.*, 2001; Hwang *et al.*, 2003; Patti *et al.*, 2005b; Karanlik *et al.*, 2009) but no significant reduction in pain score was seen in some other studies (Wasvary *et al.*, 2001; Elton *et al.*, 2001; Tan *et al.*, 2006). Significantly lower amount of analgesic use was reported in several studies (Coskun *et al.*, 2001; Karanlik *et al.*, 2009), but this reduction was not significant in some other ones (Hwang *et al.*, 2003; Patti *et al.*, 2005a; Tan *et al.*, 2006). Some studies demonstrated significantly higher morbidity in GTN group compared with placebo. The most reported adverse event was headache (Wasvary *et al.*, 2001; Elton *et al.*, 2001; Patti *et al.*, 2005b). Other studies reported no difference in morbidity between GTN and placebo (Hwang *et al.*, 2003; Tan *et al.*, 2006). GTN caused better improvement in wound healing (Hwang *et al.*, 2003; Patti *et al.*, 2005b; Tan *et al.*, 2006; Karanlik *et al.*, 2009).

Local anesthetics: Topical EMLA™ cream (lidocaine 2.5% and prilocaine 2.5%) decreased post hemorrhoidectomy pain and dosage of analgesic injections compared to control group who received neomycin ointment. The voiding time was significantly later in the control group and the frequency of single catheterization was significantly lower in the EMLA group. Patient satisfaction with post-operative pain control was significantly higher in the EMLA group. No systemic complications were observed (Shiau *et al.*, 2008). Combination of topical EMLA cream with local injection of lidocaine caused more decrease in pain score and analgesic use than that of control group who received combination of neomycin ointment with local injection of lidocaine. Patient satisfaction with post-operative pain control was also significantly higher in EMLA group. There was no significant difference in voiding time and the frequency of single catheterization between two groups. No systemic complications occurred (Shiau *et al.*, 2007). A comparison between EMLA cream and diclofenac suppository showed better short-term pain control by EMLA following hemorrhoidectomy, but more sustainable pain control by diclofenac (Rahimi *et al.*, 2012).

Bupivacaine is a local anesthetic used via infiltration to the surgical site for reducing post hemorrhoidectomy pain. Better post-operative pain relief could be induced by

bupivacaine infiltration after general anesthesia. Pain severity in bupivacaine group was mainly none or mild degree while in control group it was moderate or severe (Jirasiritham *et al.*, 2004). Although effective, its duration of action is relatively short, which usually leads to the use of other agents, such as opioids, for effective post-surgical pain control in most patients. Liposomal bupivacaine contains a product delivery platform to release drug slowly over 96 h after infiltration at the surgical site (Candiotti, 2012). This extended-release formulation established a statistically significant reduction in pain through 72 h, decreased opioid requirements, delayed time to first opioid use and improved patient satisfaction compared with placebo after hemorrhoidectomy (Gorfine *et al.*, 2011). Liposomal formulation resulted in significantly reduced postsurgical pain and analgesic use compared with bupivacaine (Haas *et al.*, 2012).

Metronidazole: Topical 10% metronidazole has significantly reduced post hemorrhoidectomy discomfort at days 7 and 14 post-operatively. Post-operative edema was reduced and overall healing was improved, compared with that of carrier controls (Nicholson and Armstrong, 2004). In another trial, topical 10% metronidazole significantly reduced post hemorrhoidectomy discomfort and post-operative defecation pain compared with that of the placebo control group (Ala *et al.*, 2008). The pain relieving activity of metronidazole may be the result of its antibacterial and anti-inflammatory properties (Guy and Seow-Choen, 2003).

Opioids: The local administration of very low doses of κ -opioid agonists including morphine and oxycodone decreased hemorrhoidectomy postoperative pain through the interaction with specific opioid receptors located on anal mucosa (Tegon *et al.*, 2009).

Trimebutine was originally considered to be an opiate compound because of its effect on intestinal motility in dogs was reversed by naloxone. It was subsequently classified as a weak opioid receptor agonist, mainly acting at the μ receptor. Trimebutine has been found effective against hyperalgesia to rectal distension induced by inflammation or stress. Trimebutine interacts with sensory neurons of the dorsal root ganglia and has local anesthetic activity which is 17 times more potent than that of lidocaine (Fioramonti and Bueno, 2002). Although trimebutine suppository has the ability to reduce mean resting anal pressure at 4 h after application, it could not reduce the pain score and analgesic requirement after hemorrhoidectomy compared with control group (Ho *et al.*, 1997).

Sucralfate: Sucralfate, a common antiulcer medication, is a basic aluminum salt of sucrose octasulfate. It has been shown to act as a mechanical barrier because of a strong electrostatic interaction of the drug with proteins at the ulcer site (Rees, 1991). Moreover, sucralfate has shown antibacterial activity (Bragman *et al.*, 1995). Topical sucralfate can reduce pain at days 7 and 14 after hemorrhoidectomy and promote faster wound healing when compared with placebo. No significant difference in analgesic use between two groups was observed (Gupta *et al.*, 2008).

Aloe vera: Aloe vera is a medicinal plant with different pharmacological activities. On the basis of its wound healing property, Aloe cream has been examined in patients after hemorrhoidectomy and has been effective in reducing postoperative pain both on resting and during defecation, healing time and analgesic requirements in comparison to placebo in patients undergoing hemorrhoidectomy (Eshghi *et al.*, 2010).

DISCUSSION

The most important challenge after hemorrhoidectomy is management of postoperative pain. This pain seems to be multifactorial and dependent on individual tolerance, mode of anesthesia, post-operative analgesia regimen and surgical technique. Other than the spasm of internal anal sphincter, the two major factors responsible for post-operative pain comprise discomfort from the surgical wound in the sensitive anoderm and perianal skin and edema from tissue inflammation around the wound (Nicholson and Armstrong, 2004). Thus, any agent that causes relaxation of internal anal sphincter may have wound healing and anti-inflammatory effects that will lead to reduction of post hemorrhoidectomy pain. In this paper, topical agents used for this purpose have been elaborated. Data show that most of studies have been done on topical GTN preparations while the achieved results were conflicting. Results from a meta-analysis on the use of GTN ointment after hemorrhoidectomy revealed that GTN ointment reduces pain on day 3 and 7 more than that of placebo. However, GTN was not effective in day 1 post surgery. Furthermore, its wound healing effect was apparent after 3 weeks. Side effect of headache was not statistically significant (Ratnasingham *et al.*, 2010). Botulinum toxin is another topical agent that is used by intrasphincteric injection. Comparison between GTN and botulinum showed that a single intrasphincteric injection of botulinum toxin was more effective in reducing early post-operative pain at rest but not during defecation. Moreover, the use of analgesic was lower in botulinum

group compared with GTN group. Incidence of adverse reactions was significantly higher in GTN compared with botulinum (Patti *et al.*, 2006). Topical preparations from CCBs including nifedipine and diltiazem were also used for post hemorrhoidectomy complications. Their mechanism of action is similar to GTN but they are safer and have lower incidence of headache.

Another drug used for post hemorrhoidectomy pain is metronidazole. Although the exact mechanism of action is unknown, antibacterial and anti-inflammatory properties of metronidazole may be responsible for its pain relieving activity. Metronidazole can interfere with bacterial colonization through its antibacterial activity during the days after hemorrhoidectomy; though, the role of bacterial colonization in post hemorrhoidectomy pain is unknown (Guy and Seow-Choen, 2003). Metronidazole reduces pain by its anti-inflammatory activity and results in lower edema around the wound. The results from local anesthetics including bupivacaine injection and EMLA cream were hopeful and seem to be appropriate choice for reducing post-operative pain and analgesic use. Among different opioids used topically for post hemorrhoidectomy pain, only morphine showed benefit but others including oxycodone and trimebutine did not demonstrate significant effect.

Sucralfate is another drug that is administered topically for post hemorrhoidectomy complications. In one study, its wound healing properties and pain relieving activity was proved. The pain relieving properties of sucralfate seems mediated through its antiulcer activity which help wound to repair faster while its antibacterial activity should not be forgotten. Only one topical herbal preparation was examined for post hemorrhoidectomy complications and it was a cream prepared from Aloe vera gel. There are many other medicinal herbs with analgesic and wound healing activities (Rahimi *et al.*, 2009, 2010; Rahimi and Abdollahi, 2012) that can be used alone or in combination for post-hemorrhoidectomy complications.

Among all of preparations studied, botulinum toxin and bupivacaine are administered via local infiltration to surgical site in single dose by physician and thus it seems to be more feasible and compatible in comparison to other topical preparations that should be used several times per day.

Overall, topical preparations showed encouraging results in reducing pain and analgesic use and improving wound after hemorrhoidectomy. Because of better bioavailability and lower incidence of adverse events compared with other dosage forms, it is suggested to use topical preparations especially those with confirmed efficacy such as GTN, CCBs, metronidazole, local anesthetics, sucralfate and botulinum toxin.

ACKNOWLEDGMENT

This study is the outcome of an in-house financially non-supported study.

REFERENCES

- Ala, S., M. Saeedi, F. Eshghi and P. Mirzabeygi, 2008. Topical metronidazole can reduce pain after surgery and pain on defecation in postoperative hemorrhoidectomy. *Dis. Colon Rectum*, 51: 235-238.
- Amoli, H.A., A.Y. Notash, F.J. Shahandashti, A.Y. Kenari and H. Ashraf, 2011. A randomized, prospective, double-blind, placebo-controlled trial of the effect of topical diltiazem on posthaemorrhoidectomy pain. *Colorectal Dis.*, 13: 328-332.
- Bragman S.G., C.L. Pankhurst and M.W. Casewell, 1995. Activity of sucralfate (sucrose octa-sulphate), an anti-ulcer agent, against opportunistic gram-negative bacilli. *J. Antimicrob. Chemother.*, 36: 703-706.
- Candiotti, K., 2012. Liposomal bupivacaine: An innovative nonopioid local analgesic for the management of postsurgical pain. *Pharmacotherapy: J. Hum. Pharmacol. Drug Ther.*, 32: 19S-26S.
- Cellini, F. and V. Valentini, 2012. Current perspectives on preoperative integrated treatments for locally advanced rectal cancer: A review of agreement and controversies. *Oncology*, 26: 730-735.
- Cook, T.A., A.F. Brading and N.J. Mortensen, 1999. Differences in contractile properties of anorectal smooth muscle and the effects of calcium channel blockade. *Br. J. Surg.*, 86: 70-75.
- Coskun, A., S.A. Duzgun, A. Uzunkoy, M. Bozer, O. Aslan and B. Canbeyli, 2001. Nitroderm TTS® band application for pain after hemorrhoidectomy. *Dis. Colon Rectum*, 44: 680-685.
- Davies, J., D. Duffy, N. Boyt, A. Aghahoseini, D. Alexander and S. Leveson, 2003. Botulinum toxin (botox) reduces pain after hemorrhoidectomy result of a double-blind, randomized study. *Dis. Colon Rectum*, 46: 1097-1102.
- Elton, C., P. Sen and A.C. Montgomery, 2001. Initial study to assess the effects of topical glyceryl trinitrate for pain after haemorrhoidectomy. *Int. J. Surg. Invest.*, 2: 353-357.
- Eshghi F., S.J. Hosseini, N. Rahmani, M. Khademloo, M.S. Norozi and O. Hojati, 2010. Effects of Aloe vera Cream on Posthemorrhoidectomy Pain and Wound Healing: Results of a Randomized, Blind, Placebo-Control Study. *J. Altern. Complementary Med.*, 16: 647-650.
- Fioramonti, J. and L. Bueno, 2002. Centrally acting agents and visceral sensitivity. *Gut*, 51: i91-i95.
- Gorfine, S.R., E. Onel, G. Patou and Z.V. Krivokapic, 2011. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: A multicenter, randomized, double-blind, placebo-controlled trial. *Dis. Colon Rectum*, 54: 1552-1559.
- Gupta, P.J., P.S. Heda, S. Kalaskar and V.P. Tamaskar, 2008. Topical sucralfate decreases pain after hemorrhoidectomy and improves healing: A randomized, blinded, controlled study. *Dis. Colon Rectum*, 51: 231-234.
- Guy, R.J. and F. Seow-Choen, 2003. Septic complications after treatment of haemorrhoids. *Br. J. Surg.*, 90: 147-156.
- Haas, E., E. Onel, H. Miller, M. Ragupathi and P.F. White, 2012. A double-blind, randomized, active-controlled study for post-hemorrhoidectomy pain management with liposome bupivacaine, a novel local analgesic formulation. *Am. Surg.*, 78: 574-581.
- Ho, Y.H., F. Seow-Choen, J.Y. Low, M. Tan and A.P. Leong, 1997. Randomized controlled trial of trimebutine (anal sphincter relaxant) for pain after haemorrhoidectomy. *Br. J. Surg.*, 84: 377-379.
- Holzheimer, R.G., 2004. Hemorrhoidectomy: Indications and risks. *Eur. J. Med. Res.*, 9: 18-36.
- Hwang, D.Y., S. Yoon, H.S. Kim, J.K. Lee and K.Y. Kim, 2003. Effect of 0.2% glyceryl trinitrate ointment on wound healing after a hemorrhoidectomy results of a randomized prospective double-blind placebo controlled trial. *Dis. Colon Rectum*, 46: 950-954.
- Jabbari, B. and D. Machado, 2011. Treatment of refractory pain with botulinum toxins: An evidence-based review. *Pain Med.*, 12: 1594-1606.
- Jirasiritham, S., K. Tantivitayatan and S. Jirasiritham, 2004. Perianal blockage with 0.5% bupivacaine for postoperative pain relief in hemorrhoidectomy. *J. Med. Assoc. Thai.*, 87: 660-664.
- Karanlik, H., R. Akturk, H. Camlica and O. Asoglu, 2009. The effect of glyceryl trinitrate ointment on posthemorrhoidectomy pain and wound healing: Results of a randomized, double-blind, placebo-controlled study. *Dis. Colon Rectum.*, 52: 280-285.
- Keshtkaran, A., S.V. Hosseini and L. Mohammadinia, 2011. Short-term complications of hemorrhoidectomy in outpatient and inpatient operations in Shiraz, Southern Iran. *Iran. Red Crescent Med. J.*, 13: 267-271.
- Kua, K.B., H.M. Kocher, A. Kelkar and A.G. Patel, 2001. Effect of topical glyceryl trinitrate on anodermal blood flow in patients with chronic anal fissures. *Anz. J. Surg.*, 71: 548-550.

- Lohsiriwat, V., 2012. Hemorrhoids: From basic pathophysiology to clinical management. *World J. Gastroenterol.*, 18: 2009-2017.
- Mirfazaelian, H., S. Nikfar, S. Derakhshani and M. Abdollahi, 2012. Efficacy and incontinence rate of biomaterials (fibrin glue and fibrin plug) in comparison to surgical interventions in the treatment of perianal fistula: A systematic review and meta-analysis of randomized, controlled trials. *Int. J. Pharmacol.*, DoI: 10.3923/ijp.2012
- Mounsey, A.L., J. Halladay and T.S. Sadiq, 2011. Hemorrhoids. *Am. Family Physician*, 84: 204-210.
- Nicholson, T.J. and D. Armstrong, 2004. Topical metronidazole (10%) decreases posthemorrhoidectomy pain and improves healing. *Dis. Colon Rectum*, 47: 711-716.
- Nikfar, S., R. Rahimi, A. Rezaie and M. Abdollahi, 2009. A Meta-Analysis of the efficacy of sulfasalazine in comparison with 5-aminosalicylates in the induction of improvement and maintenance of remission in patients with ulcerative colitis. *Dig. Dis. Sci.*, 54: 1157-1170.
- Patti, R., A.P. Luigi, A. Matteo, S. Sergio, R. Pietro, F. Calogero and D.V. Gaetano, 2006. Botulinum toxin vs. topical glyceryl trinitrate ointment for pain control in patients undergoing hemorrhoidectomy: A randomized trial. *Dis. Colon Rectum*, 49: 1741-1748.
- Patti, R., M. Arcara, D. Padronaggio, S. Bonventre and M. Angileri *et al.*, 2005a. Efficacy of topical use of 0.2% glyceryl trinitrate in reducing post-haemorrhoidectomy pain and improving wound healing. *Chirurgia Italiana*, 57: 77-85.
- Patti, R., P.L. Almasio, V.M.R. Muggeo, S. Buscemi, M. Arcara, S. Matranga and G. Di Vita, 2005b. Improvement of wound healing after hemorrhoidectomy: A double-blind, randomized study of botulinum toxin injection. *Dis. Colon Rectum*, 48: 2173-2179.
- Perrotti, P., P. Dominici, E. Grossi, R. Cerutti and C. Antropoli, 2010. Topical nifedipine with lidocaine ointment versus active control for pain after hemorrhoidectomy: Results of a multicentre, prospective, randomized, double-blind study. *Can. J. Surg.*, 53: 17-24.
- Rahimi, R., S. Nikfar, A. Rezaie and M. Abdollahi, 2006. A meta-analysis of broad spectrum antibiotic therapy in patients with active Crohn's disease. *Clin. Therapeutics*, 28: 1983-1988.
- Rahimi, R., S. Nikfar and M. Abdollahi, 2007a. Do anti-tumor necrosis factors induce response and remission in patients with acute refractory Crohn's disease? A systematic meta-analysis of controlled clinical trials. *Biomed. Pharmacother.*, 61: 75-80.
- Rahimi, R., S. Nikfar and M. Abdollahi, 2007b. Meta-analysis technique confirms the effectiveness of anti-TNF-alpha in the management of active ulcerative colitis when administered in combination with corticosteroids. *Med. Sci. Monit.*, 13: 13-18.
- Rahimi, R., S. Nikfar, A. Rezaie and M. Abdollahi, 2007c. A meta-analysis of antibiotic therapy for active ulcerative colitis. *Dig. Dis. Sci.*, 52: 2920-2925.
- Rahimi, R., S. Mozaffari and M. Abdollahi, 2009. On the use of herbal medicines in management of inflammatory bowel diseases: A systematic review of animal and human studies. *Dig. Dis. Sci.*, 54: 471-480.
- Rahimi, R., M.R. Shams-Ardekani and M. Abdollahi, 2010. A review of the efficacy of traditional Iranian medicine for inflammatory bowel disease. *World J. Gastroenterol.*, 16: 4504-4514.
- Rahimi, R. and M. Abdollahi, 2012. Herbal medicines for the management of irritable bowel syndrome: A comprehensive review. *World J. Gastroenterol.*, 18: 589-600.
- Rahimi, M., A.R. Kazemeini, N. Pourtabatabaei and A.R. Honarmand, 2012. Comparison of topical anesthetic cream (EMLA) and diclofenac suppository for pain relief after hemorrhoidectomy: A randomized clinical trial. *Surg. Today*, (In Press). 10.1007/s00595-012-0222-9
- Ratnasingham, K., M. Uzzaman, S.M. Andreani, D. Light and B. Patel, 2010. Meta-analysis of the use of glyceryl trinitrate ointment after haemorrhoidectomy as an analgesic and in promoting wound healing. *Int. J. Surg.*, 8: 606-611.
- Rattan, S. and S. Chakder, 1992. Role of nitric oxide as a mediator of internal anal sphincter relaxation. *Am. J. Physiol.*, 262: G107-G112.
- Rees, W.D.W., 1991. Mechanisms of gastroduodenal protection by sucralfate. *Am. J. Med.*, 91: 58S-63S.
- Roe, A.M., D.C. Bartolo, K.D. Vellacott, J. Locke-Edmunds and N.J. Mortensen, 1987. Submucosal versus ligation excision haemorrhoidectomy: A comparison of anal sensation anal sphincter manometry and postoperative pain and function. *Br. J. Surg.*, 74: 948-951.
- Shiau, J.M., K.C. Hung, H.H. Chen, W.H. Chen, Y.H. Wu and C.C. Tseng, 2007. Combination of topical EMLA with local injection of lidocaine: Superior pain relief after Ferguson hemorrhoidectomy. *Clin. J. Pain*, 23: 586-590.
- Shiau, J.M., H.P. Su, H.S. Chen, K.C. Hung, S.E. Lin and C.C. Tseng, 2008. Use of a topical anesthetic cream (EMLA) to reduce pain after hemorrhoidectomy. *Reg. Anesthesia Pain Med.*, 33: 30-35.

- Silverman, R., P.J. Bendick and H.J. Wasvary, 2005. A randomized, prospective, double-blind, placebo-controlled trial of the effect of a calcium channel blocker ointment on pain after hemorrhoidectomy. *Dis. Colon Rectum*, 48: 1913-1916.
- Tan, K.Y., K.K. Sng, K.H. Tay, J.H. Lai and K.W. Eu, 2006. Randomized clinical trial of 0.2% glyceryl trinitrate ointment for wound healing and pain reduction after open diathermy haemorrhoidectomy. *Br. J. Surg.*, 93: 1464-1468.
- Tegon, G., L. Pulzato, L. Passarella, D. Guidolin, M. Zusso and P. Giusti, 2009. Randomized placebo-controlled trial on local applications of opioids after hemorrhoidectomy. *Tech. Coloproctol.*, 13: 219-224.
- Van Cutsem, E., M. Dicato, K. Haustermans, N. Arber and J.F. Bosset *et al.*, 2008. The diagnosis and management of rectal cancer: expert discussion and recommendations derived from the 9th World Congress on Gastrointestinal Cancer, Barcelona, 2007. *Ann. Oncol.*, 19: 1-8.
- Wasvary, H.J., J. Hain, M. Mosed-Vogel, P. Bendick and S.N. Klein, 2001. Randomized, prospective, double blind, placebo-controlled trial of effect of nitroglycerin ointment on pain after hemorrhoidectomy. *Dis. Colon Rectum*, 44: 1069-1073.