A Systematic Review of the Topical Drugs for Post Hemorrhoidectomy Pain

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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, sulfanilamide 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 of GTN, CCBs, metronidazole, local anesthetics, sulfanilamide 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 (Moursy 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 (Moursey 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; Mirkazaeeian 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 (Keshkikaran et al., 2011; Holzheier, 2004). The spasm of internal anal sphincter seems to be the main reason for post hemorrhoidectomy pain (Roe et al., 1987). Various invasive and non-invasive 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

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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
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<tr>
<td>Aloe vera cream (n = 24) vs. placebo cream (n = 25)</td>
<td>3 g 3 times daily</td>
<td>Prospective, randomized, double-blind, placebo-controlled</td>
<td>Open</td>
<td>ND</td>
<td>Less postoperative pain at h 12, 24 and 48 h and at 2 weeks, i; pain after evacuation in 24 and 48 h post surgery (p&lt;0.001), better wound healing at the end of the second postoperative week (p&lt;0.001) and fewer analgesic requirement (p&lt;0.001) in Aloe group compared with placebo</td>
<td>Esghii et al. (2010)</td>
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<td>Botulinum toxin (intramuscular injection) (n = 24) vs. normal saline (n = 25)</td>
<td>0.4 mL (20 units) vs. 0.4 mL</td>
<td>Double-blind, randomized</td>
<td>Milligan-Morgan</td>
<td>Cocodormal (codeine phosphate, paracetamol)</td>
<td>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</td>
<td>Davies et al. (2003)</td>
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<td>Botulinum toxin (intramuscular injection) (n = 15) vs. normal saline (n = 15)</td>
<td>0.4 mL (20 units) vs. 0.4 mL</td>
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<td>Nimesulide</td>
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<td>Bupivacain injection 0.5% (n = 72) vs. control (n = 70)</td>
<td>1-3 mL 10 min before operation</td>
<td>Prospective randomized</td>
<td>ND</td>
<td>Morphine, pethidine, tramadol or paracetamol</td>
<td>Longer pain free period in bupi group vs. control (p&lt;0.001); greater number of patients with no pain after surgery in bupi group vs. placebo (p&lt;0.001); less analgesic requirement in bupi group (p&lt;0.001)</td>
<td>Jirasrittham et al. (2004)</td>
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<td>Bupivacain depofoam injection (n = 95) vs. sodium chloride 0.9% (n = 94)</td>
<td>30 mg/30 mL vs. 30 mL at the end of surgery</td>
<td>Randomized, double-blind, parallel-group, placebo-controlled</td>
<td>Milligan-Morgan</td>
<td>Morphine</td>
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<td>Diltiazem 2% ointment (n = 9) vs. vaseline ointment (n = 9)</td>
<td>3 times per day for 7 days</td>
<td>Randomized, prospective, double-blind, placebo-controlled</td>
<td>Ferguson</td>
<td>Hydrocodone</td>
<td>Lower postoperative pain (p&lt;0.001) and higher overall benefit (p&lt;0.001) with 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 rash; no difference in morbidity between two groups</td>
<td>Silverman et al. (2005)</td>
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<td>Diltiazem 2% ointment (n = 16) vs. vaseline ointment (n = 17)</td>
<td>1 g 3 times per day for 7 days</td>
<td>Prospective, randomized, double-blind, placebo-controlled</td>
<td>Milligan-Morgan</td>
<td>Acetaminophen codeine</td>
<td>Less pain on postoperative days 2-7 in diltiazem group (p=0.0001), fewer patients using analgesic in diltiazem group (p=0.0001)</td>
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<td>EMLA cream (lidocaine 2.5% and prilocaine 2.5%) (n = 15) vs. neomycin ointment (n = 15)</td>
<td>5 g</td>
<td>Double-blind, randomized</td>
<td>Ferguson</td>
<td>Meperidine injection</td>
<td>Lower postoperative pain (p=0.05), i; analgesic use (p = 0.04); i; 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</td>
<td>Shiau et al. (2008)</td>
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<td>EMLA cream/local lidocaine injection</td>
<td>5 g/10 mL</td>
<td>Randomized</td>
<td>Ferguson</td>
<td>Paracetamol, diclofenac</td>
<td>Lower postoperative pain (p &lt; 0.001), analgesic use g = 0.05 and better patient-reported analgesia satisfaction score (p &lt; 0.01) in EMLA cream at 6 hours after surgery</td>
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<td>EMLA cream (n = 30) vs diclofenac suppository (n = 40) vs placebo (n = 40)</td>
<td>5 g vs. 150 mg</td>
<td>Randomized</td>
<td>Ferguson</td>
<td>Paracetamol, diclofenac</td>
<td>Lower postoperative pain (p &lt; 0.001), analgesic use g = 0.05 and better patient-reported analgesia satisfaction score (p &lt; 0.01) in EMLA cream at 6 hours after surgery</td>
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<td>GTN ointment (n = 20)</td>
<td>0.2%</td>
<td>Randomized</td>
<td>Double-blind</td>
<td>Hydromorphone</td>
<td>No difference between groups (p = 0.03) in pain scores, lower analgesic use (p = 0.03), and no difference in patient satisfaction scores (p = 0.05)</td>
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<td>GTN ointment (n = 20) vs placebo ointment (n = 20)</td>
<td>0.2% vs. 0.1%</td>
<td>Randomized</td>
<td>Double-blind</td>
<td>Hydromorphone</td>
<td>No difference between groups (p = 0.03) in pain scores, lower analgesic use (p = 0.03), and no difference in patient satisfaction scores (p = 0.05)</td>
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- **EMLA cream/local lidocaine injection**: Lower postoperative pain (p < 0.001), analgesic use g = 0.05 and better patient-reported analgesia satisfaction score (p < 0.01) in EMLA cream at 6 hours after surgery.
- **EMLA cream vs diclofenac suppository**: Lower postoperative pain (p < 0.001), analgesic use g = 0.05 and better patient-reported analgesia satisfaction score (p < 0.01) in EMLA cream at 6 hours after surgery.
- **GTN ointment**: No difference between groups (p = 0.03) in pain scores, lower analgesic use (p = 0.03), and no difference in patient satisfaction scores (p = 0.05).
- **GTN ointment vs placebo ointment**: No difference between groups (p = 0.03) in pain scores, lower analgesic use (p = 0.03), and no difference in patient satisfaction scores (p = 0.05).
- **GTN ointment vs placebo**: No difference between groups (p = 0.03) in pain scores, lower analgesic use (p = 0.03), and no difference in patient satisfaction scores (p = 0.05).
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<td>GTN ointment 0.2% (n = 30) vs. petroleum ointment (n = 30)</td>
<td>1g twice per day for 2 weeks</td>
<td>Prospective, randomized, double-blind, placebo-controlled</td>
<td>Ferguson</td>
<td>Naproxen, paracetamol, metamizole</td>
<td>Overall lower pain in GTN group (p&lt;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</td>
<td>Karanlik et al. (2009)</td>
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<td>Metronidazole 10% cream (n = 10) vs. petrolatum cream (n = 10)</td>
<td>2.5 mL 3 times daily</td>
<td>Prospective, randomized, single-blind</td>
<td>Harmonic scalpel</td>
<td>Hydrocodone</td>
<td>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</td>
<td>Nicholson and Armstrong (2004)</td>
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<td>Metronidazole 10/5 ointment (n = 25) vs. petrolatum ointment (n = 22)</td>
<td>1.5-2 cm 3 times daily</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Open</td>
<td>ND</td>
<td>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 post surgery in metronidazole group (p&lt;0.05); No significant complications or allergic reactions</td>
<td>Als et al. (2008)</td>
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<tr>
<td>0.3% nifedipine+1.5% lidocaine ointment vs. lidocaine ointment</td>
<td>3 g twice daily for 2 weeks</td>
<td>Prospective, randomized, double-blind</td>
<td>Milligan-Morgan</td>
<td>Ketoprofen</td>
<td>No significant difference in postoperative pain and analgesic use between two groups</td>
<td>Perrotti et al. (2010)</td>
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<td>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)</td>
<td>At the end of procedure and removed 12 h later</td>
<td>Double-blind prospective randomized placebo-controlled</td>
<td>Milligan-Morgan</td>
<td>ND</td>
<td>Increase in time elapsing from the end of the surgical procedure to the request for analgesic (p&lt;0.001) in Morphin group vs. placebo; higher mean time to voiding in vehicle vs. morphine and oxycodone (p&lt;0.001); secondary bleeding in 3 patients (2 from morphine and 1 from the oxycodone groups)</td>
<td>Tegon et al. (2009)</td>
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<td>Sulphafate 7% cream (n = 54) vs. petrolatum cream (n = 56)</td>
<td>3 g 3 times daily</td>
<td>Double-blind, prospective, randomized</td>
<td>Milligan-Morgan</td>
<td>Tramadol, paracetamol</td>
<td>Less postoperative pain at Day 7 (p&lt;0.002) and Day 14 (p&lt;0.01) in sulphasalazine; more patients with wound healing at week 4 in sulphasalazine (p&lt;0.02), fewer days for complete wound healing in sulphasalazine (p&lt;0.01); no difference in analgesic use between 2 groups; no complications recorded</td>
<td>Gupta et al. (2008)</td>
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<td>Trimebutine suppository (120 mg trimebutine+10 mg ruscogenin) (n = 80) vs. no treatment (n = 80)</td>
<td>Single dose after hemorrhoidectomy</td>
<td>Randomized controlled</td>
<td>Standard diathermy excision</td>
<td>Ketoprofen, pethidine</td>
<td>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</td>
<td>Ho et al. (1997)</td>
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GTN: Glycerol 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 (Jimisintham 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 postsurgical 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 (Candioti, 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 (Fiornamonti 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, it’s 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 analgesics 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 (Gyu 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 hoped 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 tramadol 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.

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