World J Surg (2013) 37:657–662
DOI 10.1007/s00268-012-1895-3

World Journal of Surgery

Efficacy of Cholestyramine Ointment in Reduction of Postoperative Pain and Pain during Defecation after Open Hemorrhoidectomy: Results of a Prospective, Single-center, Randomized, Double-blind, Placebo-controlled Trial

Shahram Ala · Fariborz Eshghi · Reza Enayatifard · Payam Fazel · Banafsheh Rezaei · Roja Hadianamrei

Published online: 11 December 2012

Abstract

Background The aim of the present study was to evaluate the efficacy of cholestyramine ointment (15 %) in reducing postoperative pain at rest and during defecation after open hemorrhoidectomy.

Methods A total of 91 patients with third and fourth degree hemorrhoids undergoing open hemorrhoidectomy were included in this prospective, double-blind, randomized controlled trial. The patients were randomly assigned to either cholestyramine ointment or placebo immediately after surgery, 12 h after surgery, and then every 8 h for 14 days. The primary outcomes were intensity of pain at rest and during defecation, measured with a visual analog scale, and the analgesic requirement, measured by amount of tramadol consumption.

Results The cholestyramine group had less postoperative pain than the placebo group at the 24th hour (1.84 ± 2.54 vs. 4.07 ± 3.35; $P = 0.001$) and 48th hour (0.18 ± 0.88 vs. 3.57 ± 3.45; $P < 0.001$) and less pain during defecation starting at the 48th hour (2.28 ± 2.96 vs. 4.77 ± 4.09; $P = 0.001$). Similarly, the average tramadol consumption at hours 24 and 48 was significantly lower for the cholestyramine group (5.32 ± 21.45 vs. 43.18 ± 61.56 mg at 24 h, and 4.48 ± 16.65 vs. 57.63 ± 65.47 mg at 48 h; $P < 0.001$). The only adverse event was pruritus, which had a lower frequency in the cholestyramine group but the difference was not significant until postoperative week 4 ($P < 0.001$).

Conclusions Compared with placebo, cholestyramine ointment (15 %) reduced postoperative pain at rest and on defecation, and consequently lowered the analgesic requirement after open hemorrhoidectomy.

Introduction

Treatment of hemorrhoids depends on the stage of the disorder and the symptoms. Hemorrhoidectomy is considered an effective treatment for third-degree and forth-degree symptomatic hemorrhoids. Many surgical techniques have been proposed; however, open hemorrhoidectomy is still the most commonly performed operation for hemorrhoids [1–6].

Pain is almost a constant feature after hemorrhoidectomy and is the commonest reason for delayed patient discharge. The lining of the anal canal is among the most richly innervated tissues in the digestive tract. Thus, pain after hemorrhoidectomy is certainly an expected outcome which is more intense during defecation [7].

The degree of pain experienced depends on a number of factors, including surgical technique, anesthesia used, postoperative analgesia, early defecation of soft stools, avoidance of dressings, and subjective pain threshold. Various factors are believed to be responsible for the pain after hemorrhoidectomy including spasm of the internal

S. Ala (✉) · B. Rezaei
Department of Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, 18th Kilometer Farahabad Boulevard, 48175861 Sari, Mazandaran Province, Iran
e-mail: sh204ala@yahoo.com

F. Eshghi · P. Fazel
Department of Surgery, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Mazandaran Province, Iran

R. Enayatifard · R. Hadianamrei
Department of Pharmaceutical Sciences, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Mazandaran Province, Iran

anal sphincter, inflammation of the perianal area, and bacterial colonization at the hemorrhoidectomy site [6, 8].

Opioid analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) have often been administered for pain control, but their use is confined to a short period and is associated with frequent side effects, which might lead to prolonged hospital stay [6–11]. Therefore, the management of postoperative pain after hemorrhoidectomy is crucial, both clinically and economically. Consequently, the introduction of novel methods for the control of post-hemorrhoidectomy pain is required.

Several studies have attempted to identify useful approaches to post-hemorrhoidectomy pain management. Several pharmacological agents with different mechanisms of action have all been tried for such purpose: glyceryl trinitrate; calcium channel blockers, such as diltiazem and nifedipine; metronidazole; botulinum toxin, dextromethorphan; and sucralfate [8, 12–22].

Cholestyramine, a quaternary ammonium chloride anion exchange resin, has been found to be effective in the topical form in the treatment of perianal skin irritation in a number of studies. Cholestyramine ointment has been used to treat skin irritation around enterostomies and after ileoanal anastomosis; it has also been used to treat severe perianal cutaneous lesions, as well as buttocks rash in neonates [23–28]. The effectiveness of this agent has been ascribed to its bile acid-binding activity. Bile acids secreted in the stool are considered to be a major cause of skin irritation and inflammation in the perianal area. Bile acids are powerful detergents that are able to dissolve cell membranes and produce inflammation when injected directly into the tissues [29]. Free bile acids have also been shown to produce intestinal mucosal cell damage when fed to experimental animals [30, 31]. These could be important mechanisms contributing to the inflammation and irritation of the perianal skin following hemorrhoidectomy. Thus, it seems reasonable to suppose that local application of the acid-binding agent cholestyramine might be effective in reducing postoperative pain and pain on defecation following hemorrhoidectomy. To our knowledge, the use of topical cholestyramine in the management of post-hemorrhoidectomy pain has not been reported previously.

In the present study, the efficacy of 15 % cholestyramine ointment in reducing postoperative pain at rest, pain on defecation and analgesic requirement after open hemorrhoidectomy was investigated. Our hypothesis consisted of two assumptions: (1) cholestyramine ointment (15 %) can reduce postoperative pain after open hemorrhoidectomy compared with placebo and cholestyramine ointment (15 %) can reduce pain on defecation after open hemorrhoidectomy compared with placebo; (2) cholestyramine ointment (15 %) can reduce the requirement for analgesics after open hemorrhoidectomy compared with placebo.

Materials and methods

Preparation of the ointments

The cholestyramine and placebo ointments were prepared as two indistinguishable products. From the different types of levigating agents available to prepare the ointment, almond oil was chosen for the final formula for its appropriate physicochemical properties, absence of skin irritating properties, and pleasant appearance of the preparation. The weight ratio of cholestyramine in the ointment was determined according to the clinical application (the pathological condition and the extent of the lesions) and the physical properties (appropriate appearance and smooth texture) of the ointment. In the end, 15 % w/w ointment was found to be appropriate.

Cholestyramine ointment was prepared from cholestyramine powder (15 % w/w), almond oil (21.25 % w/w), and vaseline (63.75 % w/w) by the incorporation method. Simply, the required amount of cholestyramine powder was levigated with the appropriate amount of almond oil, and the required amount of vaseline was then added to this mixture and stirred at room temperature to obtain a homogeneous ointment. The placebo ointment was prepared by mixing almond oil (25 % w/w) and vaseline (75 % w/w) by the same method. The final preparations were tested physicochemically and microbiologically and proved to be suitable for clinical use. The cholestyramine and placebo ointments were filled in identical tubes (each tube containing 30 g of ointment) and labeled with the randomization codes A and B corresponding to placebo and cholestyramine, respectively, by an individual who was not aware of the trial procedure and was not involved in it.

Patient selection

Consecutive newly diagnosed patients with hemorrhoids between 20 and 70 years of age of both sexes were screened for the purpose of enrollment in the study. Those patients with grade three or grade four hemorrhoids were scheduled for open hemorrhoidectomy and were included in the study. Subjects with a history of previous anal surgery, presence of additional anal/perianal disease (including fistula-in-ano, perianal abscess, and anal fissure), history of oral cholestyramine consumption, patients with hepatic cirrhosis, patients addicted to opioids, and pregnant women were excluded from the study.

Trial design

This study was a single-center prospective double-blind placebo-controlled randomized trial conducted in Imam

Khomeini Hospital, Sari, Iran, between March and December 2008. The study was approved by the research ethics committee of Mazandaran University of Medical Sciences and registered in the Iranian Registry of clinical trials with registration number IRCT138803091627N2 (the full trial protocol can be accessed at: http://www.irct.ir). The study was performed according to the Declaration of Helsinki, and written informed consent was obtained from all patients before their enrollment in the study. A sample size of 48 in each study arm was calculated to be appropriate with 90 % power and 5 % significance level on the basis of a power analysis. The primary outcomes were as follows: (1) postoperative pain after hemorrhoidectomy as measured by visual analogue scale (VAS) with 0 showing the absence of pain and 10 showing the worst pain imaginable; (2) pain on defecation after hemorrhoidectomy measured by VAS; (3) analgesia requirement measured by tramadol consumption in the first 48 h after hemorrhoidectomy.

Trial procedure

The patients were randomized into two groups following a simple randomization procedure using a computer-generated table of random numbers (the even numbers corresponded to code A and the odd numbers corresponded to code B). The patients were allocated to the intervention by an individual who was not aware of the randomization codes and was not involved in the subsequent therapeutic process. The patients and the investigators (health care providers, data collectors, and those assessing outcomes) were blinded to the allocation, and the randomization code was not available to either investigators or patients until the trial was completed.

All patients underwent the standard Milligan–Morgan technique of open hemorrhoidectomy [32] under general anesthesia by the same surgical team. To ensure uniformity of the surgical technique, all patients were operated on by a single surgeon (F.E.), a uniform anesthesia protocol was used for all patients, and the excision procedure was identical for both groups.

The first dose of the ointment was applied by the surgeon at completion of the surgery, followed by self-administration of the ointment under the supervision of a trained nurse to ensure proper application of the ointment. The patients were advised to apply 1.5 cm of the ointment (equal to 3 g of the ointment, which corresponds to 0.45 g of drug in the case of cholestyramine ointment) on perianal skin (but not inside the anus) 12 h after surgery and then every 8 h for 2 weeks.

All of the patients received opioid analgesic treatment (50 mg tramadol injection) at the end of the surgery and as needed thereafter, up to a maximum of 100 mg per day for a maximum of 48 h. The patients were discharged 48 h after operation and were ordered to take acetaminophen tablets (325 mg) for pain control if required every 6 h for a maximum of 7 days. The patients were visited 12, 24, and 48 h after surgery. Outpatient follow-up was conducted at the second and fourth postoperative weeks.

Statistical analysis

The statistical analysis of the data was performed with SPSS software (SPSS for windows, version 16, SPSS Inc., Chicago, IL). Student's t test was used to compare the quantitative data and the χ^2 test was used to compare the qualitative data between groups. Values of $P < 0.05$ were considered to show a statistically significant difference.

Results

Of 108 patients recruited for the study, 12 were excluded after irregular use of the ointment (forgot to use the ointment or did not use the ointment on time) and 5 were excluded because of opioid addiction that had not been diagnosed before their enrolment in the trial, leaving 91 patients (44 patients in group A and 47 patients in group B) for analysis (Fig. 1). There were no statistical differences in mean age ($P = 0.805$), gender distribution ($P = 0.34$), and degree of hemorrhoids ($P = 0.135$) between the two groups (Table 1).

The average postoperative pain scores of patients in group B were significantly lower than group A at the 24th hour ($P = 0.001$) and the 48th hour ($P < 0.001$) after hemorrhoidectomy. At the second postoperative week no pain was reported by any of the patients in group B, while a mean pain score of 0.57 ± 1.34 was reported by the patients in group A (Table 2). The average scores of pain on defecation were also lower for group B than for group A at the 48th hour ($P = 0.001$), during the second week ($P < 0.001$), and during the 4th week ($P < 0.001$) after hemorrhoidectomy (Table 3).

The average amount of tramadol consumption in group B was to a great degree lower than that in group A between the 12th and 24th hours ($P < 0.001$) and between the 24th and 48th hours ($P < 0.001$) after hemorrhoidectomy (Table 4). Furthermore, the average amount of acetaminophen consumption per day during the first postoperative week was 892 ± 89.18 mg/day for group A and 585 ± 82.94 mg/day for group B, which shows a considerable difference ($P = 0.013$, data reported as mean $\pm$ SD). No complications were recorded during the trial period except mild pruritus, which started after 48 h.

Although the frequency of pruritus was lower in group B throughout the trial period, the difference was not

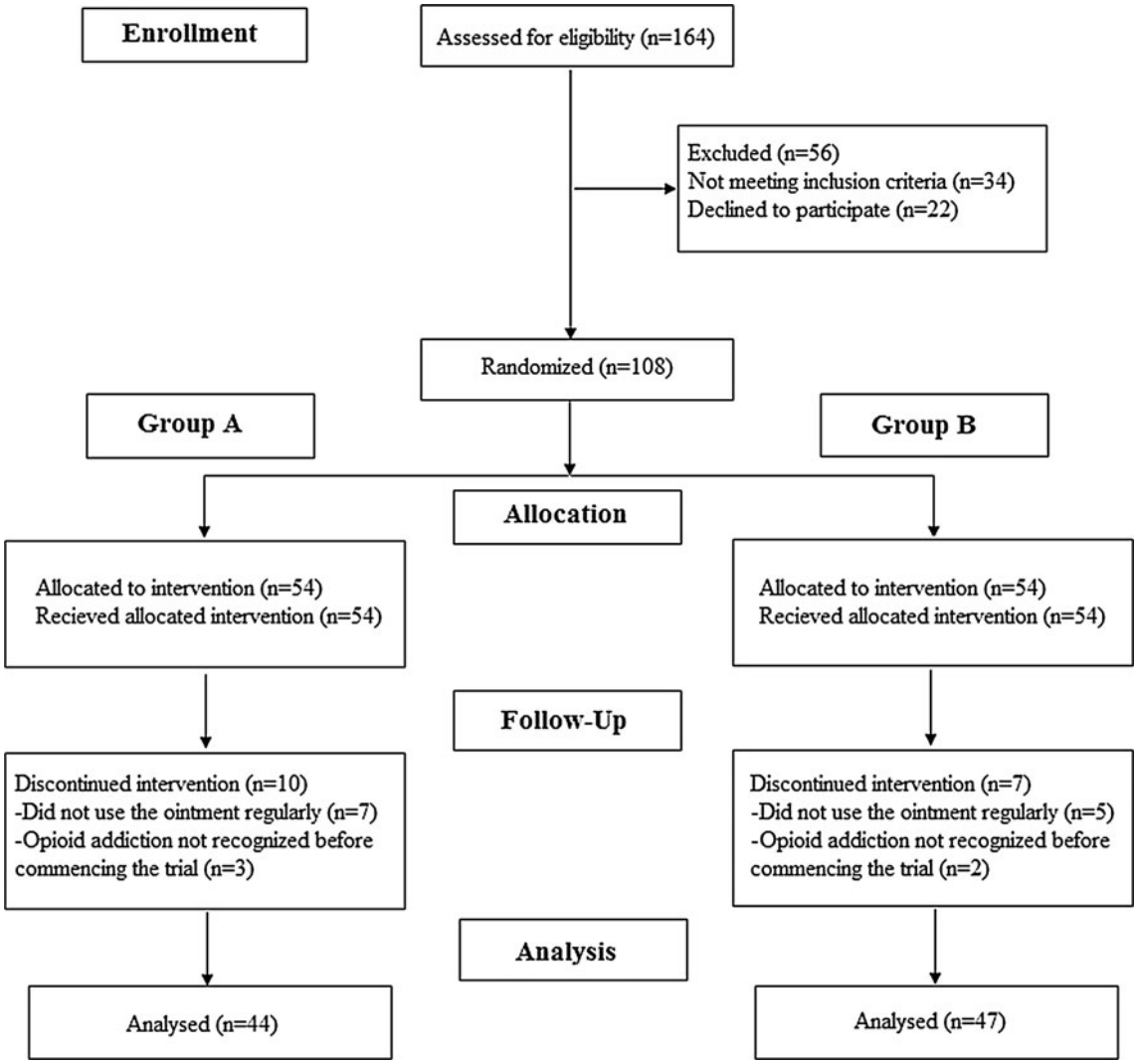

Fig. 1 Participant flow diagram (according to the CONsolidated Standards of Reporting Trials (CONSORT) 2010 guidelines)

significant until the 4th week ($P = 0.001$; Table 5). The medication was well tolerated in all patients and no patient discontinued intervention because of adverse events.

Discussion

Surgery is the most common treatment for patients with third and fourth degree hemorrhoids. Excisional hemorrhoidectomy is the most effective treatment to reduce recurrent symptoms in patients with grade 3 or 4 hemorrhoids, patients with mixed internal and external hemorrhoids, and those with recurrent hemorrhoids in whom other treatments have been ineffective [33, 34]. There are different surgical procedures for hemorrhoidectomy, but conventional open hemorrhoidectomy is still the most commonly performed operation for hemorrhoids [6].

The most commonly encountered complication after hemorrhoidectomy is postoperative pain, which is usually most intense during the first passage of stools. Pain is the commonest reason for delayed patient discharge. Studies show that, as a result of pain, patients require 4–16 days to return to normal activity. Inadequate pain control also accounts for increased opioid requirements, postoperative

Table 1 Demographic characteristics of the patients

Parameter	Group A ($n = 44$)	Group B ($n = 47$)	P value
Mean age, years[a]	45.14 ± 15.05	45.9 ± 14.07	0.805
Female/male ratio	25/19	22/25	0.340
Hemorrhoid degree (III/IV)	33/11	41/6	0.135

[a] Mean and SD

Table 2 Average postoperative pain scores[a] at different times after hemorrhoidectomy[b]

Time	Group A ($n = 44$)	Group B ($n = 47$)	P value
12 h	3.93 ± 3.85	3.63 ± 3.36	0.699
24 h	4.07 ± 3.35	1.84 ± 2.54	0.001*
48 h	3.57 ± 3.45	0.18 ± 0.88	<0.001*
2 weeks	0.57 ± 1.34	0	
4 weeks	0	0	

* Statistically significant difference

[a] Mean ± SD

[b] Pain scores were obtained from patients using a visual analog scale (VAS)

Table 3 Average scores[a] of pain during defecation (VAS) at different times after hemorrhoidectomy

Time	Group A ($n = 44$)	Group B ($n = 47$)	P value
24 h	1.39 ± 2.97	1.53 ± 2.94	0.815
48 h	4.77 ± 4.09	2.28 ± 2.96	0.001*
2 weeks	2.39 ± 2.42	0.78 ± 1.33	<0.001*
4 weeks	0.727 ± 1.06	0.10 ± 0.37	<0.001*

* Statistically significant difference

[a] Mean ± SD

Table 4 Average tramadol consumption (mg)[a] at different time intervals after hemorrhoidectomy

Time, h	Group A ($n = 44$)	Group B ($n = 47$)	P value
0–12	10.23 ± 27.66	11.70 ± 25.99	0.794
12–24	43.18 ± 61.56	5.32 ± 21.45	<0.001*
24–48	57.63 ± 65.47	4.48 ± 16.65	<0.001*

* Statistically significant difference

[a] Mean ± SD

Table 5 Number of patients having pruritus at different time points after hemorrhoidectomy

Time	Group A ($n = 44$)	Group B ($n = 47$)	P value
12 h	0	0	–
24 h	0	0	–
48 h	2	1	0.548
2 weeks	9	7	0.519
4 weeks	14	4	0.001*

* Statistically significant difference

nausea and vomiting, urinary retention, and increased readmissions [6]. As a result, the management of postoperative pain after hemorrhoidectomy is crucial, both clinically and economically. Several pharmacological agents with different mechanisms of action have been studied for postoperative pain reduction after hemorrhoidectomy. These agents include ointments of glyceryl trinitrate, diltiazem, nifedipine, metronidazole, sucralfate cream, botulinum toxin injection, and dextromethorphan injection [8, 12–22].

In the present study, we investigated the effects of 15 % cholestyramine ointment on postoperative pain, pain on defecation, and analgesic requirements after open hemorrhoidectomy. Our results showed a marked reduction in postoperative pain in the treatment group compared with the control group at the 24th hour and the 48th hour after hemorrhoidectomy and complete pain elimination by the second postoperative week (Table 2). The results of analgesic consumption in the two groups follow the same pattern (Table 4), which confirms the results obtained by VAS.

Since the action of cholestyramine in reducing pain and skin irritation is mainly through binding to bile acids excreted in the stool and inhibiting their inflammatory effects on perianal skin, the initiation of its effect is determined by the time of first defecation. Before this time no such effect could be observed. The time of first passage of stool for all of the patients in the two groups was between 12 and 24 h after hemorrhoidectomy and none of the patients defecated before this time. Thus, on the first physician visit at the 12th hour after hemorrhoidectomy, no reports of pain on defecation were recorded. There was no significant difference in pain scores on first defecation in the patients of the two groups (between the 12th and 24th postoperative hours), but comparison of the two groups showed a marked reduction in pain on defecation in the treatment group compared with control group between the 24th and 48th hours after hemorrhoidectomy (Table 3). It could be inferred from such data that the bile acid sequestering action of cholestyramine led to a considerable difference in pain on second defecation (between 24th and 48th postoperative hours) between the two groups. This pattern continued in the ensuing days, resulting in considerably less pain on defecation in the treatment group during the second and fourth postoperative weeks (Table 3).

Taking into account all the above-mentioned data, it can be concluded that cholestyramine ointment (15 %) was effective in reducing postoperative pain both at rest and during defecation, consequently decreasing the requirement for analgesic consumption after open hemorrhoidectomy compared with placebo. However, the effects of cholestyramine ointment on wound healing after hemorrhoidectomy was not investigated in this study and should be addressed by further studies.

Acknowledgments This research is recorded under trial registration number: IRCT138803091627N2. The study was funded by the Vice chancellor of research of Mazandaran University of Medical Sciences. The authors are grateful to Dr. Mohammad Reza Rouini for technical support, Dr. Nematollah Ahangar for assistance in literature review, and Drs. Mohamadpor and Maasoomeh Abolghasemi Bizaki for assistance in data analysis.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Holzheimer RG (2004) Hemorrhoidectomy: indications and risks. Eur J Med Res 9:18–36
2. Nisar PJ, Scholefield JH (2003) Managing haemorrhoids. Br Med J 327:847–851
3. You SY, Kim SH, Chung CS et al (2005) Open vs. closed hemorrhoidectomy. Dis Colon Rectum 48:108–113
4. Arbman G, Krook H, Haapaniemi S (2000) Closed vs. open hemorrhoidectomy—is there any difference? Dis Colon Rectum 43:31–34
5. Shalaby R, Desoky A (2001) Randomized clinical trial of stapled versus Milligan–Morgan haemorrhoidectomy. Br J Surg 88:1049–1053
6. Uzzaman MM, Siddiqui (2011) A brief literature review on the management of post-haemorrhoidectomy pain. Surg Tech Dev 1(e32):82–87
7. Wexner SD (2001) The quest for painless surgical treatment of hemorrhoids continues. J Am Coll Surg 193:174–178
8. Siddiqui MRS, Abraham-Igwe C, Shangumanandan A et al (2011) A literature review on the role of chemical sphincterotomy after Milligan–Morgan hemorrhoidectomy. Int J Colorectal Dis 26:685–692
9. Kisli E, Baser M, Güler O et al (2005) Comparison of the analgesic effect of betamethasone and diclofenac potassium in the management of postoperative haemorrhoidectomy pain. Acta Chir Belg 105:388–391
10. Goldstein ET, Williamson PR, Larach SW (1993) Subcutaneous morphine pump for postoperative hemorrhoidectomy pain management. Dis Colon Rectum 36:439–446
11. Jaffe JH, Martin WR (1985) Opioid analgesics and antagonists. In: Goodman LS, Gilman A (eds) The pharmacologic basis of therapeutics, 7th edn. Macmillan, New York, pp 491–531
12. Karanlik H, Akturk R, Camlica H et al (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
13. Ratnasingham K, Uzzaman MM, Andreani SM et al (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
14. Silverman R, Bendick PJ, Wasvary H (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
15. Chauhan A, Tiwari S, Mishra VK et al (2009) Comparison of internal sphincterotomy with topical diltiazem for post-hemorrhoidectomy pain relief: a prospective randomized trial. J Postgrad Med 55:22–26
16. Perrotti P, Dominici P, Grossi E et al (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
17. Ala S, Saeedi M, Eshghi F et al (2008) Topical metronidazole can reduce pain after surgery and pain on defecation in postoperative hemorrhoidectomy. Dis Colon Rectum 51:235–238
18. Nicholson T, Armstrong D (2004) Topical metronidazole (10 percent) decreases posthemorrhoidectomy pain and improves healing. Dis Colon Rectum 47:711–716
19. Davies J, Duffy D, Boyt N et al (2003) Botulinum toxin (Botox) reduces pain after hemorrhoidectomy, results of a double-blind, randomized study. Dis Colon Rectum 46:1097–1102
20. Patti R, Almasio PL, Arcara M et al (2006) Botulinum toxin vs. topical glyceryl trinitrate ointment for pain control in patients undergoing hemorrhoidectomy: a randomized trial. Dis Colon Rectum 49:1741–1748
21. Duedahl TH, Rømsing J, Møiniche S et al (2006) A qualitative systematic review of peri-operative dextromethorphan in post-operative pain. Acta Anaesthesiol Scand 50:1–13
22. Gupta PJ, Heda PS, Kalaskar S et al (2008) Topical sucralfate decreases pain after hemorrhoidectomy and improves healing: a randomized, blinded, controlled study. Dis Colon Rectum 51:231–234
23. Rodriguez JT, Huang TL, Ferry GD et al (1976) Treatment of skin around enterostomies with cholestyramine ointment. J Pediatr 88:659–661
24. Møller P, Lohmann M, Brynitz S (1987) Cholestyramine ointment in the treatment of perianal skin irritation following ileoanal anastomosis. Dis Colon Rectum 30:106–107
25. Bell SN, Varigos GA (1980) Treatment of skin irritations around biliary fistulas with cholestyramine. Br J Surg 67:785
26. White CM, Gailey RA, Lippe S (1996) Cholestyramine ointment to treat buttocks rash and anal excoriation in an infant. Ann Pharmacother 30:954–956
27. White CM, Kalus JS, Caron MF et al (2003) Cholestyramine ointment used on an infant for severe buttocks rash resistant to standard therapeutic modalities. J Pharm 19:11–13
28. Senon G, Hergott C, Micard S (2005) Treatment of severe perianal cutaneous lesions in hospitalized neonates: orabase ointment interest. J Gynecol Obstet Biol Reprod 34(1 Suppl):S84–S88 [in French]
29. Palmer RH, Glickman PB, Kappas A (1962) Pyrogenic and inflammatory properties of certain bile acids in man. J Clin Invest 41:1573
30. Gracey M, Papadimitriou J, Burke V et al (1973) Effects on small intestinal function and structure induced by feeding a deconjugated bile salt. Gut 14:519
31. Teem MV, Phillips SF (1972) Perfusion of the hamster jejunum with conjugated and unconjugated bile acids: inhibition of water absorption and effects on morphology. Gastroenterology 62:261
32. Milligan ET, Morgan CN, Jones LE et al (1937) Surgical anatomy of the anal canal and the operative treatment of haemorrhoids. Lancet 2:1119–1124
33. Acheson AG, Scholefield JH (2008) Management of haemorrhoids. BMJ 336:380–383
34. Shanmugam V, Thaha MA, Rabindranath KS et al (2005) Systematic review of randomised trials comparing rubber band ligation with excisional haemorrhoidectomy. Br J Surg 92:1481–1487