JOURNAL OF THE
ANUS, RECTUM AND COLON
dx.doi.org/10.23922/jarc.2020-027
http://journal-arc.jp

Original Research Article

Botulinum Toxin Injection for Analgesic Effect after Hemorrhoidectomy: A Randomized Control Trial

Siripong Sirikurnpiboon and Paiboon Jivapaisarnpong

Division of Colorectal Surgery, Department of Surgery, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand

Abstract

Objectives: Hemorrhoid is a common disease in surgical practice, but only a few numbers of patients need surgical treatment. The most common concern of patients is postoperative pain. This study aimed to evaluate the efficacy and safety of an intersphincteric injection of botulinum toxin for post-hemorrhoidectomy pain relief.

Methods: Overall, 90 patients were enrolled, and 44 were randomized into a botulinum toxin injection group. Preoperative gradings were grade III 37 patients and grade II 2 patients. Patients received an intersphincteric injection of 0.5 ml of a solution containing 30 units of botulinum toxin (BTX). The postoperative data were collected pain score in a visual analog score (VAS), an analgesic used, hospital stay, and complication.

Results: The VAS was lower in the BTX group at 12 hours and 24 hours postoperative phase. VAS at 12 hours 4.435 ± 2.149 vs 6.232 ± 2.307 ($p < 0.001$), VAS at 24 hours 2.205 ± 2.079 vs 3.744 ± 2.361($p = 0.003$). The BTX group has a shorter time in defection without pain than the control group (3 vs. two days, $p = 0.007$). There was no difference in immediate and delay complications between the two groups.

Conclusions: Postoperative hemorrhoidectomy needs multimodalities for pain reduction. Botulinum toxin has some benefit in postoperative pain reduction.

Keywords

hemorrhoidectomy, pain, botulinum toxin, analgesic effect

J Anus Rectum Colon 2020; 4(4): 186-192

Introduction

Hemorrhoid is a common disease in surgical practice. Conservative management, such as toilet habit adaptation, diet modification, and office treatment, is usually effective, but a few patients require operative management. Indications for surgery include failed conservative management, grade III, and grade IV disease[1]. One of the patient's concerns is postoperative pain[2], causing patients to refuse to undergo the procedure. The etiology of postoperative pain is multifactorial, such as the method of anesthesia[3], hemorrhoidectomy technique[4], postoperative inflammation[5], secondary infection[6,7] and anal sphincter spasm[8,9]. Anal sphincter spasm is a key in post-hemorrhoidectomy pain. The botulinum toxin acts on the acetylcholine receptor, leading to temporary muscle paralysis and reducing the sphincter spasm. The result was reduced pain and wound healing.

Corresponding author: Siripong Sirikurnpiboon, Laizan99@hotmail.com
Received: April 6, 2020, Accepted: August 6, 2020

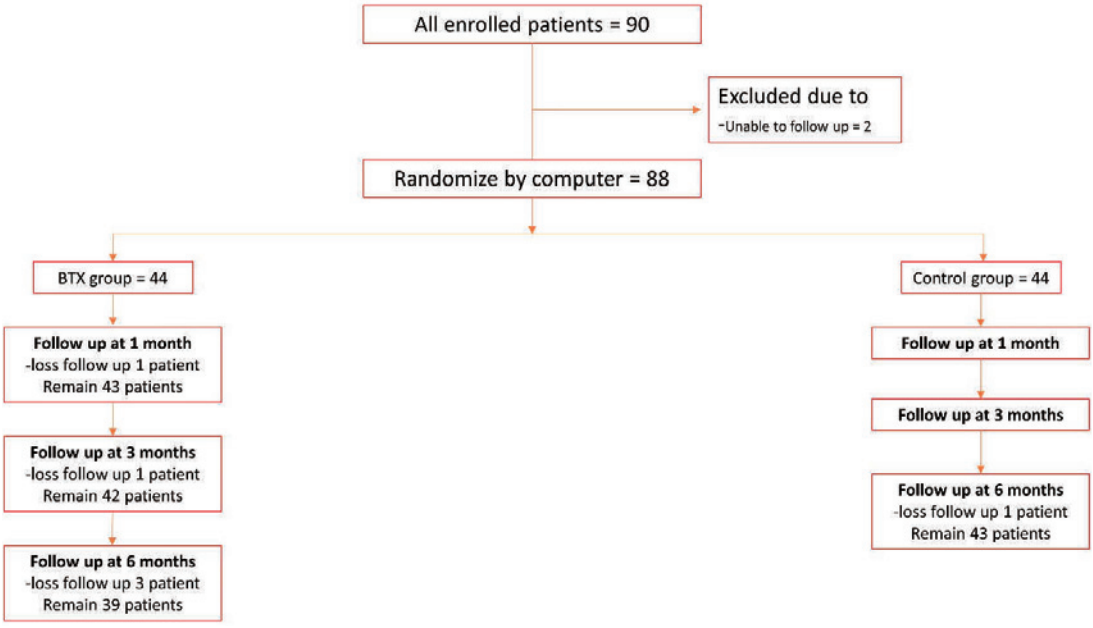

Figure 1. Methodology Flowchart.

Methods

Setting and study design

A randomized controlled trial was conducted. The aim of this study is post-hemorrhoidectomy pain reduction after a botulinum toxin injection correlation with a bowel movement activity. Inclusion criteria were age > 18 years, grade II-III disease, and fail conservative management. Exclusion criteria were emergency operation, denied or not fit for surgery, unable to follow up. The study has no plan to change after trial commencement. The ethics committee of Rajavithi Hospital approved this study (EC number 134/2558). The study is conducted between December 2015 and December 2018. A nurse explained the study protocol at the outpatient clinic, and patients were free to decide whether to participate in the study. All patients provided informed consent and agreed to our publishing information, including photographs. Figure 1 shows the methodology flowchart. The sample size was calculated by the average pain score from the previous study[10]. There were 40 subjects in each group. Ninety patients were randomized into two groups using the box of 4 method. Both groups received preemptive anesthesia with oral diclofenac 25 milligrams (mg) 4-6 hours before surgery unless preexisting comorbidities or allergy precluded its use.

Operative technique

Most patients were placed in the prone position (Prone-Jackknife); patients with general anesthesia (GA) were placed in a lithotomy position (Lloyd-Davies). The anesthetic method depended on the patient's condition. All patients underwent a close technique (Ferguson's technique) hemorrhoidectomy; the device depended on the surgeon's preference. Botulinum toxin injection (BTX) group were received an injection 30 unit of BTX solution at intersphincteric immediately after excision before closing the wound. The author decided to use 30 units of BTX since a previous study indicated[3] the presence of pain. Adding an analgesic requirement in 20 units used the decision to inject at the surgical site into the intesphincteric plane is controversial in many studies, possibly because of anal spasm. In cases where the patient required more than one hemorrhoidectomy, the surgeon decided to inject BTX in the widest excision site. The botulinum toxin in the study is on botulinum toxin A (Allergan, Inc., Ireland). During the postoperative period, all patients received two antibiotics oral (Metronidazole 400 mg, three times a day and Norfloxacin 400 mg, twice a day) with diclofenac 25 mg oral three times a day for one week.

Measured outcome

A nurse recorded immediate postoperative data on the patient's pain, using the visual analog score (VAS) 12 and 24 hours postoperatively, including whether the patient required additional pethidine within 24 hours or complications occurred. Upon discharge, patients received two types of antibiotics, diclofenac and acetaminophen for one week. Follow up period data were collected incontinence status in Wexner's incontinence score at 2, 4, and 16 weeks, wound dehiscence, time return to daily activity, and sick leave.

Statistical analyses

All statistical analyses were performed using the SPSS

Table 1. Group Demographic Data.

Factors	BTX group (n = 39)	Control group (n = 43)	p-value
Age (mean ± S.D.)	41.21 ± 13.94	42.23 ± 12.78	0.729
BMI (mean ± S.D.)	25.52 ± 4.27	24.12 ± 4.29	0.144
Male sex	21 (53.8)	23 (53.5)	0.974
History smoking (%)	13 (33.3)	13 (30.2)	0.763
History alcohol drinking (%)	21 (53.8)	20 (46.5)	0.507
History of laxative use	15 (38.5)	20 (46.5)	0.462
History toilet time (minute) (mean ± S.D.)	38.46 ± 17.49	34.07 ± 15.21	0.229
History bowel movement per week (mean ± S.D.)	6.46 ± 2.42	5.83 ± 2.33	0.239
Race			0.507
Thai	33 (84.6)	39 (90.7)	
ASEAN*	6 (15.4)	4 (9.3)	
ASA classification			0.238
I	31 (79.5)	33 (76.7)	
II	6 (15.3)	10 (23.3)	
III	2 (5.2)	0 (0)	
Previous treatment			0.811
Rubber band ligation	5 (12.8)	4 (9.3)	
Sclerosing injection	1 (2.6)	2 (4.7)	
Hemorrhoidectomy	2 (5.1)	1 (2.3)	
Non	31 (79.5)	36 (83.7)	
Preoperative grading			0.678
II	2 (5.1)	4 (9.3)	
III	37 (94.9)	39 (90.7)	
Preoperative Wexner's score median (min-max)	0.0 (0.0-2.0)	0.0 (0.0-4.0)	0.986
Bristol stool form scale (BSFS) (%)			0.026
I	1 (2.6)	3 (7.0)	
II	3 (7.7)	8 (18.6)	
III	17 (43.6)	22 (51.2)	
IV	10 (25.6)	6 (14.0)	
V	5 (12.8)	2 (4.7)	
VI	3 (7.7)	2 (4.7)	
Correlation BSFS with constipation [10] (%)	4 (10.3)	10 (23.3)	0.148
Correlation BSFS with constipation [11] (%)	20 (51.3)	33 (76.7)	0.016
Preemptive anesthesia	39 (100)	43 (100)	1.000

*ASEAN- south-east Asian race, excluding Thai.

Abbreviations: BMI-Body mass index. ASEAN-Association of Southeast Asian Nations, ASA classification- American Society of Anesthesiologists Classification

Statistics software (SPSS version 18.0 for Windows, Illinois, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile; IQR) and were compared using the Student t-test or Mann-Whitney U test. Categorical data were expressed as number (percentage) and were compared using the Pearson Chi-square test or Fisher exact probability test. A p-value of <0.05 was considered statistically significant.

Results

The demographic data was shown in Table 1. The 82 patients diagnosed hemorrhoid grade II-III was enrolled with a mean age 41.74 ± 13.26 years. Patient characteristics were comparable in both groups except the Bristol stool form scale and correlation with constipation in the ASIAN model[11,12]. The operative data were no difference in anesthetic method, excision device, and the number of excised hemorrhoidal heads, as shown in Table 2.

Postoperatively, the BTX group had lower VAS at 12 hours (4.435 ± 2.149 vs. 6.232 ± 2.307, p < 0.001) and 24 hours than the control group (2.205 ± 2.079 vs. 3.744 ± 2.361, p = 0.003) with statistical significance. Additional pethidine use and early postoperative complications were not different, as shown in Table 3. In the follow-up period, the BTX group had a significantly shorter time until defecation

Table 2. Operative Data.

Factors	BTX group	Control group	p-value
Anesthetic procedure (%)			0.489
Spinal anesthesia	33 (84.6)	32 (74.4)	
Perianal block	6 (15.4)	10 (23.3)	
General anesthesia	0 (0)	1 (2.3)	
Excision device (%)			0.092
Scissor	24 (61.5)	34 (79.1)	
Vascular sealing	15 (33.4)	9 (18.9)	
Number hemorrhoidal head excision median (min-max)	1 (1-3)	1 (1-3)	0.573

Table 3. Early Postoperative Results.

Factors	BTX group	Control group	p-value
VAS at 12 hours median (min-max)	5.0 (0.0-8.0)	6.0 (0.0-10.0)	< 0.001
VAS at 12 hours mean ± S.D.	4.435 ± 2.149	6.232 ± 2.307	< 0.001
VAS at 24 hours median (min-max)	2.0 (0.0-8.0)	4.0 (0.0-8.0)	0.003
VAS at 24 hours mean ± S.D.	2.205 ± 2.079	3.744 ± 2.361	0.003
Pethidine use (mg) median (min-max)	25.0 (0.0-100.0)	50.0 (0.0-100.0)	0.155
Early postoperative complication (%)			0.915
Delay bleeding	2 (5.1)	0 (0)	
Urinary retention	1 (2.6)	2 (4.7)	

Table 4. Follow up Data between the BTX and Control Groups.

Factors	BTX group	Control group	p-value
Wound dehiscence (%)	12 (30.8)	22 (51.2)	0.610
Acetaminophen use in one week (mg) median (min-max)	4000.0 (0.0-10000.0)	4000.0 (0.0-10000.0)	0.881
Postoperative Wexner's incontinence score at two weeks median (min-max)	1.0 (0.0-4.0)	0.0 (0.0-7.0)	0.251
Postoperative Wexner's incontinence score at four weeks median (min-max)	0.0 (0.0-4.0)	0.0 (0.0-4.0)	0.389
Postoperative Wexner's incontinence score at 16 weeks median (min-max)	0.0 (0.0-4.0)	0.0 (0.0-4.0)	0.637
Defecation without pain (days) median (min-max)	2 (1-4)	3 (1-7)	0.007
Sick leave (days) median (min-max)	5 (1-10)	7 (0-14)	0.098

Data are presented as n (%), median (min-max)

without pain than the control group (2 vs. 3 days, p = 0.007). However, wound dehiscence, acetaminophen used during the first week after the operation, and incontinence status (evaluated with Wexner's incontinence score between groups were no different, as shown in Table 4.

Discussion

Hemorrhoidectomy is one of the most painful operations. Methods of reducing postoperative pain can be divided into preoperative, intraoperative, and postoperative. In preoperative had a report to use dextromethorphan for pain reduction with predict in the mechanism at N-methyl-D-aspartate receptor antagonists[13,14]. Recently a randomized study combination of acetaminophen and gabapentin showed a promising result in mean pain score and required for hydromorphone[15]. In intraoperative, anesthetic methods have many comparative studies, such as local or perianal block and general anesthesia (GA), or local and spinal anesthesia, or regional anesthesia such as pudendal nerve block and spinal anesthesia. Most of the recent evidence prefer to regional anesthesia in pain reduction[16-18]. In the surgical technique have a more discussion point to study such as dilemma in open or close technique[19], staple hemorrhoi-

dopexy had an in good pain reduction but came with reports of complication in pelvic sepsis, free perforation, and tenesmus or pain on defecation[20-26].

Another intraoperative issue is reducing the internal sphincter spasm[27]. In the past, a report of combined internal sphincterotomy (IS) with hemorrhoidectomy showed a good result; 28.8% had an additional opioid in conventional hemorrhoidectomy compare with 10.4% in combine IS group. However, in combination with the IS group had an 8.8% incontinence rate[28,29]. Botulinum toxin was studied due to temporary action in muscle relaxation. The toxin binds rapidly and prevents the release of acetylcholine from the presynaptic nerve endings. In this study, the BTX group had lower VAS in 12 and 24 hours than the control group, but there was no difference in pethidine and acetaminophen used in the first week. The possible explanation is reducing spasms improves vascular supply, leading to improved tissue ischemia[30-32] and reducing spasm, breaking the vicious cycle of "spasm-pain-spasm." The previous study showed reduced maximal resting pressure in the BTX group from baseline 85 ± 15 mmHg to 68 ± 11 mmHg[33], but this is a limitation in this study because it did not measure an anal manometry data. The previous study showed significant postoperative pain reduction, but there was no difference in the number of analgesics used in the first week[3]. The author chose a 30 unit BTX dose. The explanation was first; the previous studies used 20 units, but patients needed adding analgesic doses postoperatively[3,31,33], which is common in BTX for anal fissure. The variation of BTX doses range from 20-40 unit; the higher doses gained more healing on observation[34-38].

Regarding the injection area, most previous studies were observed in anterior or posterior midline, which is similar to anal fissure. However, the author believes the pathogenesis of pain and the initiation point of tension was different[3,31,33,35,37,39]. Also, the injected area at intersphincteric space is due to the nearest area; the BTX would effect on the internal anal sphincter similar to previous studies[33,40]. In this study, the overall complications were not different between both groups. However, the BTX group had higher postoperative bleeding than the control group, but it was not statistically significant ($p = 0.915$). The usual postoperative bleeding rate is 0.9 %, depending on the surgical technique, and is more common in male patients[41]. In this study, the wound dehiscence was not different in both group differences from a previous study showed better wound healing in BTX group 23.8 ± 4.1 days and 31.3 ± 5.5 days in the control group ($p < 0.05$)[39] but the difference is technique use between study. However, this study showed a faster return to defecation without pain the same as previous[3]. The BTX in this study did not differ in Wexner's score at 2, 4, and 16 weeks postoperative about the incontinence.

In other studies on the chemical reduction of internal sphincter spasm, Trimebutine reduced anal resting pressure but did not affect pain scores or analgesic requirements[42]. Nitroglycerin showed reduced pain scores, additional analgesic requirements, and normalized physiology in patients with elevated anal resting pressure. Still, it did not show benefit in patients with normal resting anal pressures before surgery[43,44]. About constipation, the one etiology of the hemorrhoidal disease was found. There was no significant difference between groups by the correlation between Bristol stool form score and constipation with international interpretation[11]. There was a significant difference in interpretation in the Asian model[12] in the control group. The possible explanation of why the control group required more time to return to defecation without pain than the BTX group could be more strain. This study's limitation did not rule out constipation-dominant IBS, and there was no manometric study in anal pressure before or after hemorrhoidectomy.

Conclusions

Botulinum toxin can improve pain in postoperative hemorrhoidectomy by reducing anal tone without sacrificing the sphincter in anatomy and improve pain on defecation for some patients. Moreover, it has no side effects, does not require repeated applications further in the postoperative wound. However, further study will be needed.

Acknowledgement

This study was supported by the Rajavithi Hospital research fund. We are grateful to all participants to contribute to this study. We would also like to thank all staff members at the Division of Medical Research, Rajavithi Hospital, for assistance in conducting this study.

Conflicts of Interest

There are no conflicts of interest.

Source of Funding

This study was supported by the Rajavithi Hospital research fund.

Author Contributions

Sirikurnpiboon S and Jivapaisarnpong P conceived the original idea. Sirikurnpiboon S. mainly carried out the experiment and wrote the manuscript with support from Jivapaisarnpong P. All authors discussed the results and contributed to the final manuscript.

Approval by Institutional Review Board (IRB)

The ethics committee, Rajavithi hospital reviewed and approved this study. IRB number EC 134/2558

Consent to Participate

All participants included in this study provided informed consent.

Availability of Data and Material

Data were stored securely.

References

1. Hosch SB, Knoefel WT, Pichlmeier U, et al. Surgical treatment of piles: prospective, randomized study of Parks vs. Milligan-Morgan hemorrhoidectomy. Dis Colon Rectum. 1998 Feb; 41(2): 159-64.
2. Asfar SK, Juma TH, Ala-Edeen T. Hemorrhoidectomy and sphincterotomy. A prospective study comparing the effectiveness of anal stretch and sphincterotomy in reducing pain after hemorrhoidectomy. Dis Colon Rectum. 1988 Mar; 31(3): 181-5.
3. Davies J, Duffy D, Boyt N, et al. Botulinum toxin (Botox) reduces pain after hemorrhoidectomy: results of a double-blind, randomized study. Dis Colon Rectum. 2003 Aug; 46(8): 1097-102.
4. Khubchandani IT. Internal sphincterotomy with hemorrhoidectomy does not relieve pain: a prospective, randomized study. Dis Colon Rectum. 2002 Nov; 45(11): 1452-7.
5. Mlakar B, Kosorok P. Flavonoids to reduce bleeding and pain after stapled hemorrhoidopexy: a randomized controlled trial. Wien Klin Wochenschr. 2005 Aug; 117(15-16): 558-60.
6. Ala S, Saeedi M, Eshghi F, et al. Topical metronidazole can reduce pain after surgery and pain on defecation in postoperative hemorrhoidectomy. Dis Colon Rectum. 2008 Feb; 51(2): 235-8.
7. Carapeti EA, Kamm MA, McDonald PJ, et al. Double-blind randomised controlled trial of effect of metronidazole on pain after day-case haemorrhoidectomy. Lancet. 1998 Jan; 351(9097): 169-72.
8. Ho YH, Tan M. Ambulatory anorectal manometric findings in patients before and after haemorrhoidectomy. Int J Colorectal Dis. 1997 Oct; 12(5): 296-7.
9. Wasvary HJ, Hain J, Mosed-Vogel M, et al. Randomized, prospective, double-blind, placebo-controlled trial of effect of nitroglycerin ointment on pain after hemorrhoidectomy. Dis Colon Rectum. 2001 Aug; 44(8): 1069-73.
10. Sirikurnpiboon S, Siripattanakul A. Comparison of postoperative results after hemorrhoidectomy using local and spinal anesthesia. J Med Assoc Thai. 2017 Feb; 100(1): S33-9.
11. Heaton KW, O'Donnell LJ. An office guide to whole-gut transit time. Patients' recollection of their stool form. J Clin Gastroenterol. 1994 Jul; 19(1): 28-30.
12. Jaruvongvanich V, Patcharatrakul T, Gonlachanvit S. Prediction of delayed colonic transit using Bristol stool form and stool frequency in Eastern constipated patients: a difference from the West. J Neurogastroenterol Motil. 2017 Oct; 23(4): 561-8.
13. Weinbroum AA, Rudick V, Paret G, et al. The role of dextromethorphan in pain control. Can J Anaesth. 2000 Jun; 47(6): 585-96.
14. Liu ST, Wu CT, Yeh CC, et al. Premedication with dextromethorphan provides post hemorrhoidectomy pain relief. Dis Colon Rectum. 2000 Apr; 43(4): 507-10.
15. Van Backer JT, Jordan MR, Leahy DT, et al. Preemptive analgesia decreases pain following anorectal surgery: a prospective, randomized, double-blinded, placebo-controlled trial. Dis Colon Rectum. 2018 Jul; 61(7): 824-9.
16. Kushwaha R, Hutchings W, Davies C, et al. Randomized clinical trial comparing day-care open haemorrhoidectomy under local versus general anaesthesia. Br J Surg. 2008 May; 95(5): 555-63.
17. Castellví J, Sueiras A, Espinosa J, et al. LigaSure versus diathermy hemorrhoidectomy under spinal anesthesia or pudendal block with ropivacaine: a randomized prospective clinical study with 1-year follow-up. Int J Colorectal Dis. 2009 Sep; 24(9): 1011-8.
18. Joshi GP, Neugebauer EA, PROSPECT Collaboration. Evidence-based management of pain after haemorrhoidectomy surgery. Br J Surg. 2010 Aug; 97(8): 1155-68.
19. Gençosmanoglu R, Sad O, Koç D, et al. Hemorrhoidectomy: open or closed technique? A prospective, randomized clinical trial. Dis Colon Rectum. 2002 Jan; 45(1): 70-5.
20. Gravié JF, Lehur PA, Huten N, et al. Stapled hemorrhoidopexy versus Milligan-Morgan hemorrhoidectomy: a prospective, randomized, multicenter trial with 2-year postoperative follow up. Ann Surg. 2005 Jul; 242(1): 29-35.
21. Maw A, Eu KW, Seow-Choen F. Retroperitoneal sepsis complicating stapled hemorrhoidectomy: report of a case and review of the literature. Dis Colon Rectum. 2002 Jun; 45(6): 826-8.
22. Ryu S, Bae BN. Rectal free perforation after stapled hemorrhoidopexy: a case report of laparoscopic peritoneal lavage and repair without stoma. Int J Surg Case Rep. 2017 Jan; 30: 40-2.
23. Cipriani S, Pescatori M. Acute rectal obstruction after PPH stapled haemorrhoidectomy. Colorectal Dis. 2002 Sep; 4(5): 367-70.
24. Pessaux P, Lermite E, Tuech JJ, et al. Pelvic sepsis after stapled hemorrhoidectomy. J Am Coll Surg. 2004 Nov; 199(5): 824-5.
25. Ortiz H, Marzo J, Armendáriz P, et al. Stapled hemorrhoidopexy vs. diathermy excision for fourth-degree hemorrhoids: a randomized, clinical trial and review of the literature. Dis Colon Rectum. 2005 Apr; 48(4): 809-15.
26. Thaha MA, Irvine LA, Steele RJ, et al. Post defaecation pain syndrome after circular stapled anopexy is abolished by oral nifedipine. Br J Surg. 2005 Feb; 92(2): 208-10.
27. Pescatori M, Favetta U, Navarra L. Anal pressures after hemorrhoidectomy. Int J Colorectal Dis. 1998 Jun; 13(3): 149.
28. Diana G, Guercio G, Cudia B, et al. Internal sphincterotomy reduces postoperative pain after Milligan Morgan haemorrhoidectomy. BMC Surg. 2009 Dec; 9(1): 16.
29. Kanellos I, Zacharakis E, Christoforidis E, et al. Usefulness of lateral internal sphincterotomy in reducing postoperative pain after open hemorrhoidectomy. World J Surg. 2005 Apr; 29(4): 464-8.
30. Klosterhalfen B, Vogel P, Rixen H, et al. Topography of the inferior rectal artery: a possible cause of chronic, primary anal fissure. Dis Colon Rectum. 1989 Jan; 32(1): 43-52.
31. Jones OM, Moore JA, Brading AF, et al. Botulinum toxin injection inhibits myogenic tone and sympathetic nerve function in the porcine internal anal sphincter. Colorectal Dis. 2003 Nov; 5(6): 552-7.
32. Cook TA, Brading AF, Mortensen NJ. The pharmacology of the internal anal sphincter and new treatments of ano-rectal disorders. Aliment Pharmacol Ther. 2001 Jul; 15(7): 887-98.
33. Patti R, Almasio PL, Arcara M, et al. Botulinum toxin vs. topical glyceryl trinitrate ointment for pain control in patients undergoing hemorrhoidectomy: a randomized trial. Dis Colon Rectum. 2006 Nov; 49(11): 1741-8.
34. Yiannakopoulou E. Botulinum toxin and anal fissure: efficacy and safety systematic review. Int J Colorectal Dis. 2012 Jan; 27(1): 1-9.

35. Maria G, Brisinda G, Bentivoglio AR, et al. Influence of botulinum toxin site of injections on healing rate in patients with chronic anal fissure. Am J Surg. 2000 Jan; 179(1): 46-50.

36. Maria G, Brisinda G, Bentivoglio AR, et al. Botulinum toxin injections in the internal anal sphincter for the treatment of chronic anal fissure: long-term results after two different dosage regimens. Ann Surg. 1998 Nov; 228(5): 664-9.

37. Brisinda G, Maria G, Sganga G, et al. Effectiveness of higher doses of botulinum toxin to induce healing in patients with chronic anal fissures. Surgery. 2002 Feb; 131(2): 179-84.

38. Ravindran P, Chan DL, Ciampa C, et al. High-dose versus low-dose botulinum toxin in anal fissure disease. Tech Coloproctol. 2017 Oct; 21(10): 803-8.

39. Patti R, Almasio PL, Muggeo VM, et al. Improvement of wound healing after hemorrhoidectomy: a double-blind, randomized study of botulinum toxin injection. Dis Colon Rectum. 2005 Dec; 48 (12): 2173-9.

40. Chen HH, Wang JY, Changchien CR, et al. Risk factors associated with posthemorrhoidectomy secondary hemorrhage: a single-institution prospective study of 4,880 consecutive closed hemorrhoidectomies. Dis Colon Rectum. 2002 Aug; 45(8): 1096-9.

41. Singh B, Box B, Lindsey I, et al. Botulinum toxin reduces anal spasm but has no effect on pain after haemorrhoidectomy. Colorectal Dis. 2009 Feb; 11(2): 203-7.

42. Ho YH, Seow-Choen F, Low JY, et al. Randomized controlled trial of trimebutine (anal sphincter relaxant) for pain after haemorrhoidectomy. Br J Surg. 1997 Mar; 84(3): 377-9.

43. Coskun A, Duzgun SA, Uzunkoy A, et al. Nitroderm TTS band application for pain after hemorrhoidectomy. Dis Colon Rectum. 2001 May; 44(5): 680-5.

44. Brisinda G, Maria G, Bentivoglio AR, et al. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. N Engl J Med. 1999 Jul; 341 (2): 65-9.