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

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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

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.
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
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.
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 hydro-morphone[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 compared 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.

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**Conflicts of Interest**

There are no conflicts of interest.

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**Author Contributions**

SiriKurnpiboon S and Jivapaaisalpong P conceived the original idea. SiriKurnpiboon S. mainly carried out the experiment and wrote the manuscript with support from Jivapaaisalpong 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.

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