

The Effect of 0.2% Glyceryl Trinitrate Ointment on Pain and Wound Healing after Hemorrhoidectomy

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Abstract: Symptomatic hemorrhoidal veins are one of the most common afflictions. Pain is the single most important reason why patients avoid hemorrhoidectomy. Spasm of internal sphincter plays an important role. Glyceryl Trinitrate (GTN) has been used widely as a chemical sphincterotomy agent. On the other hand, Nitric oxide has some effects on wound healing. We designed this study to investigate topical GTN effects on postoperative pain and wound healing after hemorrhoidectomy. The study done in Semnan, Iran in years between 2006 and 2007. Patients with grades 3 and 4 hemorrhoids that undergone open hemorrhoidectomy entered the study. For the patients of case group 0.2% GTN ointment used. The post-operative pain and four weeks wound healing incidence assessed. Forty-four patients (22 for case and 22 for control groups) entered the study. Need for Opiates and NSAIDs thereafter (as indicators of pain) were lower in the case group. The four weeks wound healing incidence was higher and mean of time needed for it was lower in GTN group. Our study concluded that topical application of 0.2% GTN ointment can reduce postoperative pain and improve wound healing after open hemorrhoidectomy, but headache, which is a common side effect, can affect its usual use.

Key words: Glyceryl trinitrate ointment, hemorrhoidectomy, wound healing, postoperative pain

INTRODUCTION

Hemorrhoidal veins are essentially normal parts of the human anatomy but symptomatic hemorrhoids are one of the most common afflictions of Western civilization. The problem can occur at any age and can affect both sexes. It has been estimated that at least 50% of individuals over the age of 50 years have experienced at some times hemorrhoidal complaints. Some factors like constipation, straining, nutrition, drugs, pregnancy have been suggested that contribute to the development of hemorrhoids (Corman, 1998).

Although, diet bowel regulation, or elastic ligation will alleviate most symptoms of internal hemorrhoids, occasionally, an excisional hemorrhoidectomy will be necessary. The excision of hemorrhoids should be limited to large third and fourth degree hemorrhoids that cannot treated on an outpatient basis, mixed hemorrhoids, acutely thrombosed, incarcerated hemorrhoids with severe pain and impending gangrene (Schwartz *et al.*, 1999). Numerous approaches have been used for the surgical removal of hemorrhoids. Closed hemorrhoidectomy involves resection of hemorrhoidal tissue and closure of the wound with absorbable suture.

Open hemorrhoidectomy follows the same principles of excision but the wound are left open and allowed to heal by secondary intention. Complications following hemorrhoidectomy are urinary retention, hemorrhage, infection, constipation, anal stricture and

Although, pain is not actually a complication of surgery, it is nonetheless the single most important reason why patients avoid hemorrhoidectomy (Corman, 1998; Svendsen and Matzen, 2002). A great deal of emphasis has been applied to the management of this pain, not only because of the pain itself, but because of the role it plays in urinary symptoms. Pain and fluid overload are the primary factors that cause urinary retention, which is the most complication after hemorrhoidectomy. If pain medication is inadequate, the patient cannot relax the sphincter mechanism sufficiently to urinate (Corman, 1998). Different options has been employed for analgesia after hemorrhoidectomy such as narcotics, injection of Tradol (Ketorolac tromethamine) into the anal sphincter at the time of operation, application of transdermal Fentanyl (Corman, 1998; Donovan *et al.*, 1994). Attempts to reduce this pain have been continued. Even postoperative oral or topical Metronidazole is used (Balfour *et al.*, 2002; Carapeti *et al.*, 1998; Nicholson and Armstrong, 2004).

Some surgeons believe that internal anal sphincterotomy concomitant with hemorrhoidectomy reduces pain after operation (Corman, 1998) because spasm of internal sphincter plays an important role in this postoperative pain (Davies *et al.*, 2003; Wasvary *et al.*, 2001). Therefore, if we can reduce the spasm of internal sphincter with a drug, we can reduce the pain and if we can promote healing of these patient's wound, we can reduce the recovery time. It peers that Glyceryl Trinitrate (GTN) ointment has both effects. This medication has been used widely in treatment of chronic anal fissure in recent years as a chemical sphincterotomy agent (Libertiny *et al.*, 2002; Schwartz *et al.*, 1999; Svendsen and Matzen, 2002). On the other hand, Nitric Oxide (NO) has some effects on wound healing. Indeed some believed that NO is a wound healing stimulant (Hegggers *et al.*, 1997). Therefore, we designed this study to investigate topical GTN effects on postoperative pain and wound healing after hemorrhoidectomy.

MATERIALS AND METHODS

The study designed as a Double blind randomized clinical trial in Semnan, Iran in years between 2006 and 2007. Patients with grades 3 and 4 hemorrhoids that undergone open hemorrhoidectomy for only one pile entered the study. For elimination of possible confounding effect of sex on pain tolerance, only female patients entered the study. Patients systemically randomized to case and control groups using Epi Info statistical software (Version 6.04 b, CDC and WHO). For the patients of case group 0.2% GTN ointment used after operation and control group used placebo. For producing 0.2% GTN ointment, the 2% ointment (CADILA Pharmaceuticals, Dholka, India) mixed with Vaseline in the ratio of 1-10. The placebo contained only Vaseline ointment. The containers and volume of the GTN and placebo ointments were exactly similar. These ointments prescribed to the surgical wound once after operation by the surgeon and thereafter bid by the patient for 3 weeks. The surgeon or the patient had no information about the type of ointment that were using. The post-operative pain was assessed by the need of patients for Opiates (Morphine, IM, 10 mg for every request) in the first day and NSAIDs (Ibuprofen tablets, 400 mg) after that. Wound status was assessed by examining patients at the end of second and third weeks; complete disappearance of the wound and closure of skin borders considered as wound healing. In this case, the examiner had no information about the case-control group of the patient too. All of the patients received general anesthesia and

operated with the same surgeon. All patients followed up for 4 weeks. Patients that operated by the closed method, or had other problems like Anal fissure or fistula excluded from the study. All the data entered to the SPSS software (Release 11.5.0, © SPSS Inc.), T-test (or Mann-Whitney test if needed) for quantitative variables and χ^2 test (and Fisher exact test if necessary) for qualitative variables used, $\alpha = 0.05$ considered significant in all tests. We used Epi Info statistical software for calculation of power too.

Ethical considerations: GTN is used for many years in cardiac diseases and for Anal fissure in recent years and no significant complication seen in the patients. All patients informed about the study and possible complications of the drug and signed consent received from them. This study supervised and approved by the Research council and Ethical committee of Semnan University of Medical Sciences.

RESULTS

Forty-nine patients enrolled into the study that all of them were female; 3 patients in case group due to severe headache and two patients from control group due to loss of follow up excluded. At the end, 44 patients, 22 for case and 22 for control groups entered the study.

As shown in Table 1, mean of the age and grades of hemorrhoid in 2 groups show no significant differences. The incidence of headache was greater in GTN group relative to placebo group (Table 2). According to exclusion of 3 patients from the case group due to severe headache, this complication is remarkable, although in most instances was mild and tolerable. Table 3 need for Opiates in the first day after operation and NSAIDs thereafter (as indicators of pain) were lower in the case group. The 4 weeks wound healing incidence was higher and mean of time needed for it was lower in GTN group (Table 4).

Table 1: Prevalence of possible confounding variables in case and control groups

Variable	GTN	Placebo	p-value
Age (Mean±SD, years)	33.7±10.8	36.05±15.3	>0.05
Grade of hemorrhoid			
III	17 (77.3%)	14 (63.6%)	>0.05
IV	5 (22.7%)	8 (36.4%)	

GTN: Glyceryl Trinitrate

Table 2: Incidence of headache in case and control groups

	GTN	Placebo	p-value
Headache			
+	7 (31.8%)	0	0.009
-	15 (68.2%)	22 (100%)	

GTN: Glyceryl Trinitrate

Table 3: Comparison of post-operative pain relative variables in case and control groups

Variable	GTN*	Placebo*	p-value
Opiates (requests)	1.32±0.7	1.91±0.6	0.008
NSAIDs use in 1st week (tablets)	6.95±3.5	9.32±2.8	0.019
NSAIDs use in 2nd week (tablets)	2.14±1.9	4.55±2.2	0.001
NSAIDs use in 3rd week (tablets)	0.14±0.6	0.77±1.2	0.039
NSAIDs use in 3 weeks (tablets)	9.23±5.3	14.64±5.2	0.002

*Mean±SD, GTN: Glyceryl Trinitrate

Table 4: Comparison of "Wound healing time" and "four weeks wound healing incidence" in case and control groups

	GTN	Placebo	p-value
Wound healing time (Mean±SD, weeks)	2.5±0.59	3.5±0.59	<0.001
Four weeks wound healing	21 (95.5%)	10 (45.5%)	<0.001*

GTN: Glyceryl Trinitrate, *RR = 2.1 (CI95%: 1.31-3.34) for Healing in case group, Power = 0.94 (for $\alpha = 0.05$ and RR = 2.1)

DISCUSSION

Postoperative pain and wound healing remains the most dreaded part of hemorrhoidectomy in the minds of both patients and doctors. It may delay patient discharge, recovery and return to work. Our study showed that topical GTN could reduce postoperative pain and improve wound healing after hemorrhoidectomy.

Although, pain after hemorrhoidectomy appears to be multi-factorial and depended on individual pain tolerance, mode of anesthesia, postoperative analgesia and surgical technique, but spasm of internal sphincter is believed to play an important role (Davies *et al.*, 2003; Wasvary *et al.*, 2001). In Davies *et al.* (2003) study, injection of Botulinum toxin reduced pain after hemorrhoidectomy by reduction of this spasm. In some studies topical GTN reduced anal resting pressure (Thornton *et al.*, 2005; Winter *et al.*, 2004; Zuberi *et al.*, 2000) and improved fissure as they concluded that internal sphincterotomy should be reserved for the patients who fail to respond to initial chemical sphincterotomy with GTN (Libertiny *et al.*, 2002; Schwartz *et al.*, 1999; Svendsen and Matzen, 2002). Therefore, relaxation of internal sphincter can be the principal way of pain control in our study. In addition, GTN reduces pain with other mechanisms. It is now believed to exert its action through NO. These molecules are referred to as NO donors (Parfitt, 1999). NO causes vascular and lymphatic dilation, decreases swelling and edema thereby reducing pressure on nerves, which reduces pain (Leduc *et al.*, 1981; Moncada and Higgs, 2002). In addition, it is the direct mediator of the analgesic effect of Morphine (Ferreira *et al.*, 1999). Therefore, GTN can be a more effective analgesic drug in pain control after hemorrhoidectomy.

In a similar study, Hwang showed that GTN can significantly lower pain score and demand for analgesic during hospital stay after hemorrhoidectomy

(Hwang *et al.*, 2003). In another study, topical application of 0.2% GTN ointment in patients underwent hemorrhoidectomy, reduced maximum resting pressure after 5 days and postoperative pain both at rest and during defecation (Papapetropoulos, 1997). Also, in Wasvary *et al.* (2001) study, patients who applied this ointment to the perianal region 3 times daily for 7 days, had less pain and greater benefit than the placebo group, though the differences were not significant. Of course, narcotic use was significantly higher in the placebo group on the 2nd postoperative day (Wasvary *et al.*, 2001). All of these studies support the findings of our study in correlation to analgesic effect of GTN ointment in patients underwent hemorrhoidectomy.

On the other hand, Elton entered twenty patients (10 in each group) into a trial and evaluated their pain score daily for 6 weeks after hemorrhoidectomy. There was no significant difference in median pain score between both groups (Elton *et al.*, 2001). It peers that the reason of this converse result may be the different way of pain evaluation. They scored pain only by using a visual analogue scale, which is a subjective scale, whereas we estimated pain with objective scale such as narcotic demands and the mean number of NSAIDs drugs used for relief anal pain. In addition, authors of this study did not express this negative result with certainty as they finally concluded meta-analysis would provide a more definitive answer.

On the other hand, NO has some effects on wound healing. It is essential for angiogenesis, increases circulation, stimulates collagen synthesis and mediates growth factors (Boykin, 1999; Brush, 1998; Kua *et al.*, 2001; Lee, 1999; Moncada and Higgs, 2002; Papapetropoulos, 1997; Schaffer, 1996; Sc Um, 1998). Indeed NO is a wound healing stimulant (Heggors *et al.*, 1997), but the studies on GTN effect on wound healing after hemorrhoidectomy are rare. In 2 of these studies, topical application of 0.2% GTN ointment induced more rapid healing of hemorrhoidectomy wounds and return to normal activity (Hwang *et al.*, 2003; Papapetropoulos, 1997) and in any case, they confirm our study's finding.

Although, Hwang *et al.* (2003) concluded that GTN ointment reduced pain and healing rate after hemorrhoidectomy without any specific complications, in our study headache was the main complication in GTN group (Table 2), as it caused elimination of three patients from the study, although this side effect did not incite the majority of our patients to abandon their treatment. In similar studies incidence of headache was significantly high and the authors concluded that side effects might limit its extensive use (Carapeti *et al.*, 1999; Elton *et al.*, 2001; Wasvary *et al.*, 2001).

CONCLUSION

Our study concluded that topical application of 0.2% GTN ointment can reduce postoperative pain and improve wound healing after open hemorrhoidectomy, but headache, which is a common side effect, can affect its usual use.

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