Int J Colorectal Dis (2013) 28:365–369
DOI 10.1007/s00384-012-1544-1

ORIGINAL ARTICLE

Role of 0.4% glyceryl trinitrate ointment after haemorrhoidectomy: results of a prospective randomised study

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Accepted: 10 July 2012 / Published online: 5 August 2012

Abstract
Introduction Conventional haemorrhoidectomy (CH) is well known to cause significant post-operative pain and delayed return to daily activities. Both surgical wounds and sphincterial apparatus spasms are likely responsible for the pain. In this study, we evaluated the role of glyceryl trinitrate ointment (GTN) in reducing post-operative pain, ameliorating wound healing and recovery after CH.
Patients and methods Between 01/08 and 12/11, 203 patients with symptomatic haemorrhoids were enrolled in the study and received (103 patients) or not (100 patients) 0.4 % GTN ointment for 6 weeks after surgery. Pain was assessed using a 10-cm linear visual analogue scale (VAS). Data on post-operative pain, wound secretion and bleeding, return to normal activities and complications were recorded. Data were analysed using Fisher's exact and Mann–Whitney tests.
Results GTN-treated group experienced significantly less pain during the first week after surgery ($p<0.0001$). This difference was more evident starting from post-operative day 4 ($p<0.0001$). A significant higher percentage of untreated patients experienced severe pain (mean VAS score>7) (10 % vs 31 %). There were significant differences in terms of secretion time ($p=0.0052$) and bleeding time ($p=0.02$) in favor of GTN. In addition, the duration of itching was less in the GTN group ($p=0.0145$). Patients treated with GTN were able to an early return to daily activities compared to untreated ($p<0.0001$). Fifteen GTN-treated patients (14.6 %) discontinued the application because of local discomfort and headache.
Conclusions GTN ointment enhances significantly post-operative recovery, reducing pain in terms of duration and intensity. This effect might be secondary to a faster wound healing expressed by reduced secretion, bleeding and itching time.

Keywords Glyceryl trinitrate ointment · Haemorrhoids · Pain · Haemorrhoidectomy

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Introduction

Pain control after haemorrhoidectomy is constantly under debate, fearfully for the patient and challenging for the surgeon. Moreover, this matter is important because of the financial burden on clinical practice and because of the ongoing search for efficiency in the health system [1].

The aetiopathology is multifactorial, depending on individual pain tolerance, type of anesthesia, post-operative analgesia, use of stool softeners, and surgical technique [2].

Several attempts have been made to reduce or alleviate the pain after haemorrhoidectomy. Non-steroidal anti-inflammatory drugs (NSAIDs) and opiates have often been used to control pain, but their use is confined to a short period time and is associated with frequent side effects [3]. Post-operative pain after haemorrhoidectomy has two major

causes: discomfort in sensitive wounded anoderm and internal anal sphincter spasm with subsequent hypertonia.

Although the spasm of the voluntary external sphincter may also play a role in generating pain, internal sphincter spasm is thought to be the major contributor [4, 5]. During the past years, conservative and surgical solutions have been proposed to reduce this effect.

Even if surgical approaches, conceptually, are more effective in reducing anal spasm, several studies failed in demonstrating pain control at 12 h after surgery (53.8 % vs 48.7 %; $p=0.8$), and at 1 week after surgery ($p=0.05$) [6]; moreover, an added risk of incontinence should be considered (as high as 5 %)[7].

Conversely, as for the treatment of anal fissures, chemical sphincterotomy has been proposed using mainly botulinum toxin injection (BTX) or glyceryl trinitrate ointment with discordant results. BTX seems to be effective in some studies, but it is expensive [8]. On the other hand, topical application of GTN might be the valid alternative for a temporary internal sphincter paralysis as shown for the treatment of anal fissure, reducing anal resting pressure and increasing anodermal blood flow [9]. This effect, translated to post-haemorrrhoidectomy, could control pain thus facilitate wound healing and recovery time.

As a matter of fact a recent meta-analysis indicates that this treatment appears a valid post-operative pain defender, although the authors conclude that inadequate availability of studies, which means a low number of patients involved in the meta-analysis, is an objective limitation [10].

In this prospective randomised study, we evaluated the role of glyceryl trinitrate ointment in reducing post-operative pain, improving wound healing and recovery after conventional haemorrhoidectomy.

Patients and Methods

A total of 203 patients with symptomatic third- or fourth-degree haemorrhoids were enrolled and listed for excisional haemorrhoidectomy between 01/08 and 12/11 at the Department of Surgical Sciences, Tor Vergata University. They were randomly assigned to receive (103) or not (100) 0.4 % GTN ointment (Rectogesic, Prostrakan Group, Galashiels, UK) for 6 weeks following surgery.

Randomisation in one of the two groups was performed in the operating theatre, just prior to surgery, by using a shuffling method.

Before surgery, all patients underwent routine clinical investigations by digital examination, proctoscopy and laboratory tests. Colonoscopy, anorectal manometry and/or ultrasonography were performed if necessary.

Any patients with inflammatory bowel disease, with associated diseases of the anus such as fistulas or anal fissures or with previous anal surgery were excluded from this study.

Detailed written informed consent was obtained from all patients. All operations were performed as a day case, with the patient in lithotomy position under local anaesthesia using injection of 20 ml of naropine 0.75 % in the anal verge and submucosa of the anal canal. Antibiotic prophylaxis was administered using a second-generation cephalosporin (1 g) and metronidazole (500 mg) i.v., immediately before surgery.

Haemorrhoidectomy was conducted using an Eisenhammer or Ferguson–Hill retractor. Each haemorrhoid was grasped and gently elevated. Radiofrequency device Ligasure™ (Covidien Healthcare, Ireland) was then positioned and activated, sealing the tissue. Then, the coagulated tissue was transected along the coagulation line and the haemorrhoid excised.

Post-operatively, at home, in both groups, patients were prescribed oral analgesia (Paracetamol 1 g, three times a day plus, if required, oral Ketorolac 15 drops maximum three times a day) and stool softeners for 7 days. A high-fibre diet was recommended together with adequate oral fluid intake; *warm sitz baths* were also suggested.

In addition to this therapy, patients assigned to GTN group received written instructions explaining the topical application of the cream, twice a day for 6 weeks as well as the risk of side effects.

Patients were seen 1 week after surgery, and pain was assessed using a 10-cm linear visual analogue scale (VAS) each day for the first 7 days. Further controls were at 1, 3, and 6 months after surgery or if required. Clinical outcome was assessed by a validated questionnaire on post-operative symptoms and satisfaction supplemented by the Wexner Continence Score.

Data on post-operative pain (including intensity and duration), wound healing (expressed as secretion time, bleeding and itching) as well as early (<30 days) and late (>30 days) complications were recorded and prospectively entered in a database. Data were analysed according to the intention-to-treat principles, using Fisher's exact and Mann–Whitney tests.

Results

Demographics

Two hundred and three patients (125 male and 78 female), affected by III/IV degree haemorrhoids, underwent RF haemorrhoidectomy in this study. All patients were identified on a prospectively maintained database. Mean age of the population examined was 48.7±12 years (range, 27–76 years). Mean follow-up period after surgery was 14.1±7 months (range, 3–36 months), similar between the two groups ($p>0.05$).

One hundred and three patients (41.7 % female and 58.3 % male; mean age, 45.6±10) received 0.4 % GTN ointment after surgery and 100 (35 % female and 65 % male; mean age, 51.5±12) were the control group.

Among the 103 patients assigned to the GTN group, 15 (14.6 %) discontinued the application because of headache (12.6 %) or local discomfort (2 %), whereas seven (6.8 %) did not apply the cream in the correct way as prescribed.

One patient was admitted to the hospital for overnight staying after surgery, due to uncontrolled post-operative pain; another one was admitted to the emergency room (ER) department 1 week post-operatively for anorectal bleeding and required surgical haemostasis. No intraoperative complications were observed.

Patient groups were similar in terms of mean age, gender distribution, degree of disease and follow-up (Table 1). There were no differences in the amount of analgesic drugs taken by the patients ($p>0.05$).

With the aim to perform an intention-to-treat analysis, all the patients randomly assigned to one of the two groups were considered in the statistical calculation to avoid selection bias.

Pain (intensity and duration)

In the evaluation of the pain intensity, recording the VAS score each day for 7 days, we observed that the GTN group experienced significantly less pain during the first week after surgery (4.1±1.8 vs 7.5±1.4; $p<0.0001$, expressed as mean VAS score). This difference was more evident starting from post-operative day 4 (2.0±1 vs 4.3±1, $p<0.0001$).

Moreover, GTN group patients experienced less severe post-operative pain (expressed as VAS>7) after defecation and at rest compared to the control group (10 % vs 31 %, $p<0.0001$).

In addition, the pain duration in days was significantly shorter in treated group (11.5±10 vs 23.7±2; $p=0.001$).

Wound healing (secretion, bleeding, and itching times)

There were significant differences between the two groups in terms of secretion time in favor of GTN (9.6±10 vs 19.2± 25 days, $p=0.0052$). During the post-operative period, we observed significant bleeding decrease, defined as discharge of blood material not requiring ER admission, respectively 10.7±11.2 days in GTN and 17.2±25.0 days in control group ($p=0.02$). The duration of itching was shorter in the GTN group in comparison to untreated patients (8.4±10.3 vs 12.6± 11.4 days, $p=0.0145$).

Time elapsing before returning to work or full activity was longer in the untreated group (13.0±6.0 vs 27.2± 15.8 days, $p<0.0001$).

Complications and side effects

The two groups were similar in terms of ER admission, hospital readmissions and overall early and late complications.

Fifteen patients (14.6 %) complained one of the recognized GTN side effects, headache (12.6 %) and local discomfort (as itching or anal burning, 2 %) determining the interruption of the treatment.

Patients' satisfaction scores were also similar.

These results are summarised in Table 2, Figures 1 and 2.

Discussion

Surgical haemorrhoidectomy is currently the most popular treatment for patients with third- and fourth-degree haemorrhoids [11]. The commonest discomfort for patients after this procedure is the post-operative pain. The exact aetiopathology of post-operative pain after haemorrhoidectomy has not been defined yet, although hypertonia of internal anal sphincter (IAS) is widely believed to be the major contributor. Another contributing factor may be the manipulation of the sensitive anoderm, which may activate the somatic pain receptors [4, 6]. Eisenhammer was the first to propagate the idea that post-haemorrhoidectomy pain is due to the spasm of the internal sphincter and described that its division through one of the hemorrhoid wounds is certainly an effective way to lessen post-operative pain. In the literature, several attempts have been made to reduce or alleviate post-operative pain after haemorrhoids excision.

Table 1 Patients' demographics according to study group

Demographics	GTsN	Control	*p* value
Patients (*n*)	103	100	ns
Females (*n*/%)	43 (41.7 %)	35 (35 %)	ns
Males (*n*/%)	60 (58.3 %)	65 (65 %)	ns
Age (mean±SD)	45.6±10	51.5±12	ns
Haemorrhoids degree (%)	III: 37 % IV: 63 %	III: 43 % IV: 57 %	ns

Table 2 Postoperative outcomes according to study groups

Parameter	GTN	Control	*p* value
Post-operative pain 1st week (VAS: mean±SD)	4.1±1.8	7.5±1.4	<0.0001
Severe pain (VAS>7)	10 %	31 %	0.0001
Pain duration (days: mean±SD)	11.5±10	23.7±2	=0.001
Pain from post-operative day 4 (mean±SD)	2.0±1	4.3±1	<0.0001
Secretion (days: mean±SD)	9.6±10	19.2±25	=0.0052
Bleeding (days: mean±SD)	10.7±11.2	17.2±25	=0.02
Itching (days: mean±SD)	8.4±10	12.6±11.	=0.0145
Return to work (days: mean±SD)	13±6	27.2±15.8	<0.0001

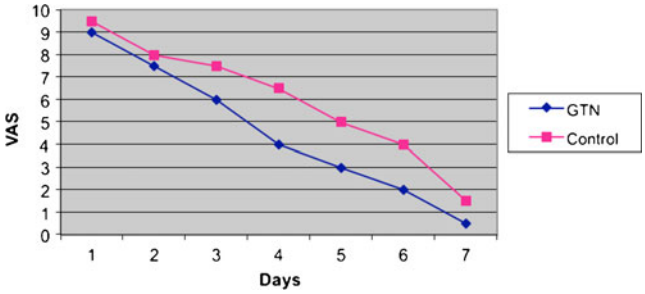

Fig. 1 Pain GTN vs Control during the first post-operative week (mean VAS score)

Different surgical approaches, including open, closed, stapled, semi-closed, diathermy or radiofrequency haemorrhoidectomy [12, 13] have been compared in effort to reduce post-operative pain.

Among excisional haemorrhoidectomy, radiofrequency approach may offer several benefits, including a limited post-operative pain, as shown in a recent meta-analysis [22]. In this study, we used radiofrequency since we have previously observed a significantly lower severe post-operative pain (express as percentage of VAS score>7) with radiofrequency approach versus conventional one [23].

Much of the information concerning pain control after anorectal procedures has been acquired in the treatment of anal fissures. The most consistently demonstrated physiological abnormality in patients with haemorrhoids is an increased maximum anal resting pressure. This fact, together with the assumption that spasm within internal sphincter is responsible for the post-operative pain, has led to attempts, either surgically or chemically, at the same time as haemorrhoidectomy is performed. Several clinical trials compared the post-operative course of haemorrhoidectomy alone and haemorrhoidectomy plus lateral internal sphincterotomy. Galiza et al. [14] showed significant differences in the pain scores and the analgesic requirements between the two groups. Conversely, Khubchandani reported no statistical difference in the post-operative pain in each of the two groups at 4 h and 4 days after surgery [6]. Mathai, who performed the same clinical trial among 33 patients, reported similar results and claimed that a sphincterotomy increases significantly the risk of post-operative incontinence [15]. To overcome the irreversibility

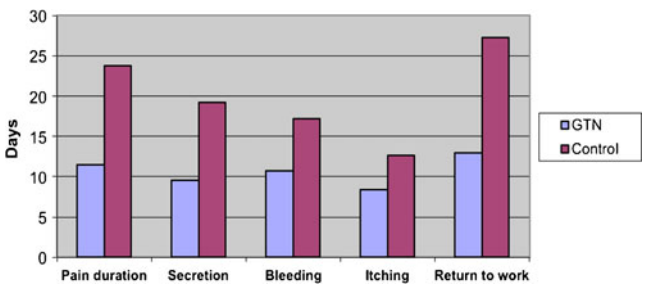

Fig. 2 GTN vs control, post-operative parameters

of lateral sphincterotomy and the effects on incontinence, botulinum toxin injection (Botox®, Allergan Ltd, Bucks, UK) has also been attempted after haemorrhoidectomy. Davies et al. [16] reported lower pain scores in patients who received botulinum toxin, which only became significant by day 6. Patti et al. [17] similarly found a reduction in post-operative pain scores, which were significant from post-operative day 1 in patients given Botox injection. Conversely, Singh et al. [8] failed to show a statistically significant effect of botulinum toxin on post-operative pain following open haemorrhoidectomy and claimed the not justifiable cost for that treatment.

More recently, some investigators have exposed the concept of chemical sphincterotomy with topical nitrates. Recent evidences suggest that IAS is innervated by neurons that release nitric oxide (NO); stimulation of these nerves results in the release of NO, which then causes relaxation of the IAS by relaxation of smooth muscle. Exogenous GTN ointment is an NO donor, which relaxes the IAS and thus reduce pain [18, 24]. There are several forms of nitrates such as Nitroderm bands used after haemorrhoidectomy to reduce the IAS spasm; however, the ointment is the most commonly available and used form. Ratnasingham et al. in their meta-analysis showed that the post-hemorrhoidectomy use of 0.2% GTN ointment was statistically significant in reducing post-operative pain on days 3 and 7, but not statistically significant in reducing pain on post-operative day 1, probably because the major contributor of pain in the early period post-operatively is due to the surgical trauma [10]. In our study, 0.4 % GTN ointment showed a significantly effect on post-operative pain reduction during the first week after surgery (4.1±1.8 vs 7.5±1.4, $p<0.0001$, expressed as mean VAS score). This difference was more evident starting from post-operative days 4 (2.0±1 vs 4.3±1, $p<0.0001$). In addition, the pain duration in days was significantly shorter in the treated group (11.5±10 vs 23.7±2; $p=0.001$). Moreover, the GTN group experienced significant less severe post-operative pain (VAS>7) after defecation and at rest compared to the control group ($p<0.0001$). These data are consistent with the results above mentioned even if the 0.2 % GTN ointment used in that meta-analysis is a very low dose, resulting approximately in a mean weight of 1 g/day used by each patient. Conversely, in our study, a roughly twice daily 375 mg application of 0.4 % nitroglycerin ointment, delivering a daily nitroglycerin dose of 3 mg, significantly increased the rate of reduction in mean visual analogue scale pain scores. We observed statistic differences in terms of secretion, bleeding and itching time, associated to an early return to daily activities in the GTN-treated group ($p<0.0001$). Similarly, the study by Tan et al. [19] showed a rate of wound healing consistently faster in patients who received GTN ointment, with completely epithelialized wounds compared to the placebo group. Furthermore, Karalink et al. [18] showed a significant facilitating effect of GTN ointment on post-

haemorrhoidectomy wound healing (76.7 % healing at 3 weeks for GTN vs 46.7 % for placebo, $p=0.02$).

In the meta-analysis of Ratnasingham et al. [10], on three studies, it has been shown that application of 0.2 % GTN ointment is associated with a significantly improved rate of wound healing at 3 weeks compared to matched placebo controls. A theory is that GTN may works in the same manner as in anal fissures, increasing the anodermal blood flow. Good wound healing is essential to prevent perianal irritation, discharge and pain, dehiscence, bacterial infection and reactionary bleeding [20]. Similar findings have been reported in several studies done using metronidazole. It is believed that the analgesic effect of metronidazole is due to improved wound healing. However, there are other studies such that of Balfour et al. [21], which have shown that metronidazole does not reduce post-operative pain.

The most common side effect of GTN treatment is the development of headaches. Others include hypotension, crescendo angina, rebound hypertension, tolerance and allergic skin reaction, anal burning or itching. In our study, 15 patients (14.6 %) discontinued the treatment because of headache (12.6 %) and local discomfort (2 %). This percentage is similar to other studies that used different GTN concentration [25–27].

In conclusion, GTN ointment enhances significantly post-operative recovery, reducing pain in terms of duration and intensity. This effect might be secondary to a faster wound healing expressed as reduced secretion, bleeding and itching. Further trials are needed to improve our knowledge on the potential benefits of glyceryl trinitrate ointment after conventional haemorrhoidectomy.

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