Int Surg 2012;**97**:112–119

Glyceryl Trinitrate Ointment Did Not Reduce Pain After Stapled Hemorrhoidectomy: A Randomized Controlled Trial

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Medications, including topical 0.2% glyceryl trinitrate (GTN), can reduce anal spasm and pain after excisional hemorrhoidectomy. GTN after stapled hemorrhoidopexy was compared with routine postoperative management. Patients with symptomatic grade 3/4 hemorrhoids were recruited. After stapled hemorrhoidopexy, residual perianal skin tags were excised as appropriate. Those requiring double purse-string mucosectomy were excluded. Postoperative pain, pain duration, and complications were assessed. One hundred ten patients (74 men; mean age 50.6 years) were enrolled in the control group and 100 patients (57 men; mean age 49.8 years) in the GTN group. Maximum pain was higher in the GTN group ($P = 0.015$). There were no differences between the two groups in residual perianal skin tags requiring excision, postoperative complications, recurrence rates, follow-up period, average pain, duration of pain, or satisfaction scores. Sixteen GTN patients were noncompliant due to side effects. None had persistent perianal skin tags. GTN did not reduce postoperative pain after stapled hemorrhoidectomy.

Key words: Stapled hemorrhoidectomy – Glyceryl trinitrate – Pain – Postoperative complications – Surgery

Hemorrhoids are the anal cushions that become symptomatic due to bleeding or prolapse from the anal canal. They affect between 4% and 36% of the general population and can cause symptoms of prolapse, discomfort, and bleeding.[1] Formal hemorrhoidectomy is usually indicated for prolapsed

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irreducible hemorrhoids or hemorrhoids that recur and persist despite more conservative measures. Stapled hemorrhoidectomy or anopexy was first introduced in 1997.[2] It is now widely used and research has shown that it results in less postoperative pain, a shorter hospital stay, faster recovery, and greater patient satisfaction.[3–5] The transanal introduction of a circular intraluminal stapling device to excise redundant rectal mucosa has been described[6] and the technique is further refined to interrupt the feeding superior hemorrhoidal arteries.[7] The excessive prolapsed mucosa is stapled in the anal canal after being drawn back and then secured by a stapled anastomosis.[8–10] It is thought that the stapling device works to reposition the rectal mucosa higher, restoring the normal anatomy of the anal canal, and enabling the hemorrhoidal cushions to perform their role in continence.[11] This is opposed to the conventional operation that only excises abundant tissues.[12,13] Although stapled hemorrhoidectomy offers some benefits versus the conventional operation, total complication rates have been reported to be similar for both techniques[5,6,14] and the added cost of the single use stapler must be weighed against its advantages.[3,13,15]

Glyceryl trinitrate (GTN) is an intra-anal formulation indicated for the treatment of chronic anal fissure pain.[16–18] It is a nitric oxide donor that reduces the increased anal canal pressure caused by a hypertonic internal anal sphincter. Hypertonicity of the internal, but not the external, anal sphincter has been shown to predispose the formation of anal fissures.[16] Blood vessels to the anoderm course through the internal anal sphincter. Therefore, hypertonicity of the internal anal sphincter may decrease blood flow and cause ischemia to this region.[17] Research has also shown that GTN, as well as other anal spasmolytic agents, are helpful in reducing postoperative pain and healing time after open hemorrhoidectomy.[19–21] However, this benefit has not been explored in patients after stapled hemorrhoidectomy. The aim of this study was to conduct a randomized controlled trial comparing pain after stapled hemorrhoidectomy in patients with topical GTN and without (control patients) postoperatively. The primary end points were the maximum and average pain assessed using 1–10 visual analogue pain scores.

Patients and Methods

Participants

After obtaining ethical approval from the Mater Miscordiae private hospital and the Townsville Day Surgery facility in Townsville, consecutive patients with symptomatic prolapsing irreducible hemorrhoids were recruited. All patients signed informed consent forms. Where appropriate, colonoscopy was performed to exclude any colorectal pathology. Exclusion criteria were patients with previous hemorrhoid surgery (except for rubber band ligation), significant rectal mucosal prolapse that would have required a double purse-string stapled hemorrhoidectomy technique, acute thrombosed internal hemorrhoids, concomitant anorectal pathology that would have required another procedure, preexisting fecal incontinence, and bleeding disorders. Group allocation was by computerized randomization, with those allocated to the GTN group prescribed 0.2% GTN ointment, which they were instructed to apply into the anal canal three times a day, with a gloved finger for 2 weeks after surgery.

Procedure

Surgery was performed under general anesthesia, with the patient in the lithotomy position. A circular anal dilator was introduced after the reduction of the prolapsed anoderm and anal mucosa. An endoanal purse-string suture was placed circumferentially above the dentate line. The circular stapler (Ethicon Endosurgery, Cincinatti, Ohio) was introduced through the anus and the purse-string suture tied down onto the shaft. The stapler was fired incorporating the mucosal tissue, the circular knife excised the redundant tissue, and anastomosis was performed with a double row of titanium staples.[13] Any residual perianal skin tags after the procedure were addressed with diathermy excision. All patients were discharged when stable, on the day of the procedure. Fiber supplements and nonsteroidal inflammatory analgesia were prescribed, to be used as required. Those who had perianal skin tags excised were advised to use sitz baths on a regular basis.

Data collection and statistical analysis

The patients were interviewed within 48 hours after operation by a clinical nurse to assess recovery and compliance with postoperative care including medications prescribed. Patients with early postoperative problems were reviewed promptly in the clinic. Otherwise, routine review was conducted at 1 month. Patients completed visual analogue scores measuring maximum pain, average pain, and satisfaction, administered by an independent observer

Table 1 Characteristics and outcomes of participants receiving stapled hemorrhoidopexy for grade 3 or 4 hemorrhoids

Characteristics	Routine postoperative management (n = 110) (control)	Glyceryl trinitrate (n = 100) (intervention)	*P* value
Gender	74 men/36 women	57 men/43 women	0.125[a]
Age (y)[b]	50.64 (21.5–78.5)	49.84 (21.8–79.0)	0.801[c]
Skin tags (5 missing)	33/105 (31.4%)	38/100 (38%)	0.323[d]
Outcomes			
Maximum pain[e] (0 = none, 10 = maximum)	7.0 (5.0–8.75)	8.0 (6.25–9.0)	0.015[d]
Average pain[e] (0 = none, 10 = maximum)	5.0 (3.0–7.0)	5.0 (4.0–7.0)	0.079[d]
Duration of pain (d)[e]	7.0 (4.0–11.0)	8.0 (5.0–12.5)	0.285[d]
Daily bowel movement (#)[e]	2.0 (1.5–3.0)	2.0 (1.9–3.0)	0.425[d]
Follow-up (mo)[e,f]	11.9 (6.0–16.7) 11.6 (SEM 0.554)	11.0 (6.0–17.0) 11.3 (SEM 0.603)	0.801[d]
Satisfaction[e] (0 = none, 10 = maximum)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	0.506[d]
Characteristics after surgery			
Incontinence	14/103 (13.6%)	14/93 (15.1%)	0.770[d]
Drug side effect	7/102 (6.9%)	16/94 (17.0%)	0.027[d]
Complications	17/108 (15.7%)	19/99 (19.2%)	0.513[d]
Subsequent procedures	6/108 (5.6%)	4/99 (4.0%)	0.612[d]
Recurrence	6/110 (5.5%)	2/100 (2%)	0.173[g]

[a]Pearson χ^2.

[b]Mean (range).

[c]Student's *t*-test.

[d]Mann-Whitney *U* test.

[e]Median (interquartile range).

[f]Mean/SEM presented for comparison with other studies.

[g]Fisher's exact test.

blinded to the randomization. Bowel function, continence, persistent/recurrent hemorrhoidal symptoms, and medication side effects were also assessed by questionnaire at this time. The patients were assessed clinically for wound healing including the stapled hemorrhoidectomy anastomosis, residual skin tags, and persistent hemorrhoids. Those with persistent problems were reviewed at 2-month intervals until they were symptom free. All patients agreed to a telephone interview conducted at the end of the study and clinical review was invited as required.

Data were analyzed on an intention-to-treat basis. It was estimated that 100 patients in each arm would provide a 0.8 power to detect a 10% difference in pain scores. Patients who failed to complete the program were treated as missing. Numerical data are presented as mean and range, or median and interquartile range (IQR), depending on the distribution. Comparisons between characteristics were calculated using χ^2 tests and χ^2 tests for trend, nonparametric Wilcoxon tests, and *t* tests. Statistical analysis was conducted using SPSS for Windows, version 18 (SPSS Inc, Chicago, Illinois). A significance level of 0.05 was adopted *a priori*.

Results

Eight patients were excluded due to very significant rectal mucosal prolapsed requiring double purse-string mucosectomy. This is of the 218 patients with symptomatic prolapsed irreducible hemorrhoids who were assessed for eligibility to participate in the study. A total of 210 patients, (131 men) mean age 50 years (range 21–79 years), consented to participate (Table 1). The two groups (GTN: 100 patients; control: 110 patients) were well matched with regard to age, gender, and skin tags. Approximately 38% of the GTN and 31% of the control group had pre-existing skin tags as well as grade III or IV hemorrhoids. The median follow-up was 11.0 months (IQR: 6.0–17.0 months) in the GTN group and 11.9 months (IQR: 6.0–16.7 months) in the control group ($P = 0.779$; Table 1). Figure 1 shows the flow of patients through the study.

The postoperative pain and bowel function are shown in Table 1. Maximum pain score was higher in the GTN group. This was not related to residual perianal skin tag excised, as the maximum pain in GTN group was a median of 8 both with and without skin tags excised ($P = 0.168$). There were no

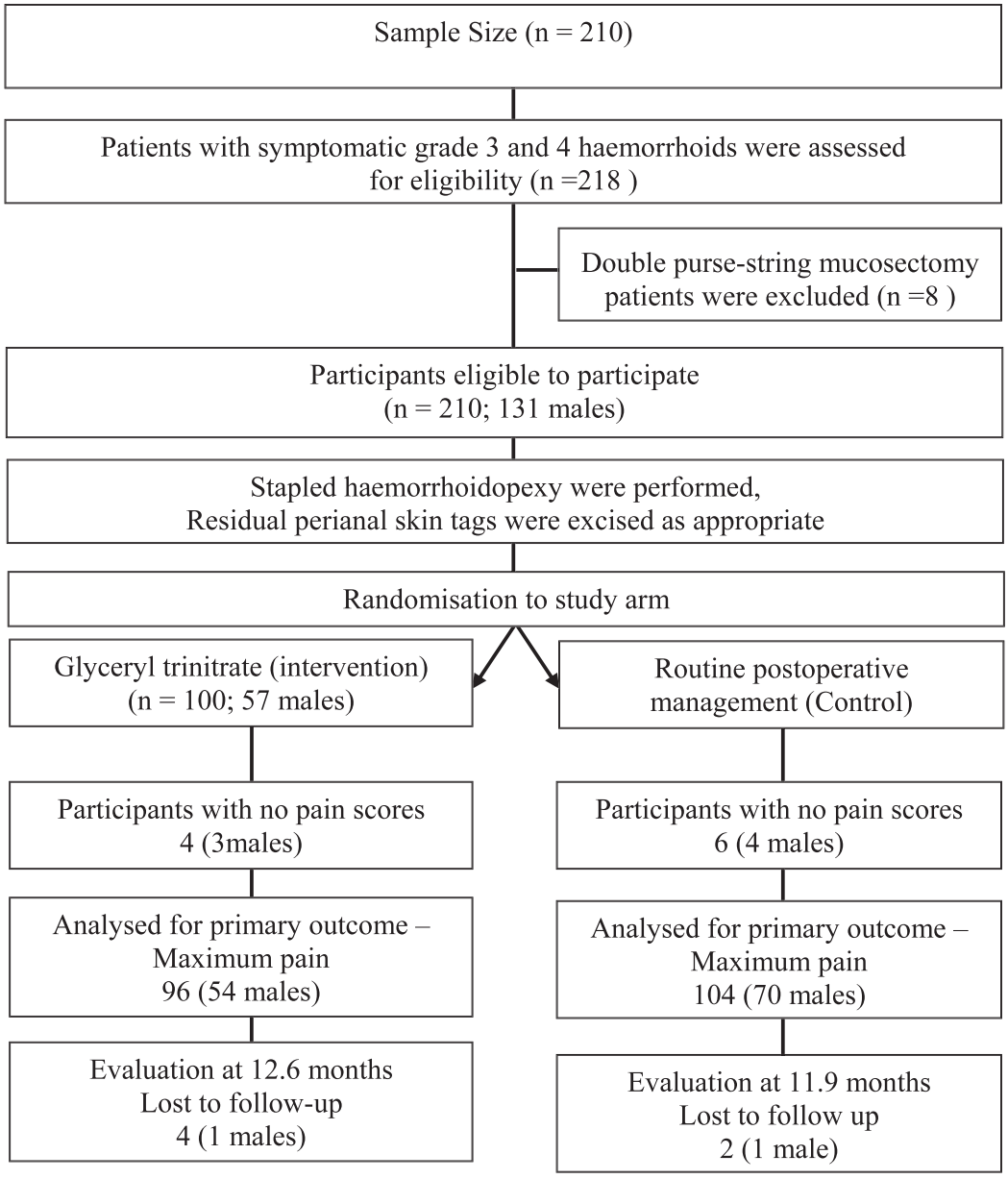

Fig. 1 Progress of participants through study.

significant differences between the two groups in patient-reported average pain score, duration of pain, bowel frequency, or satisfaction score. There was no difference in satisfaction scores at 8 weeks after surgery (Table 1). Patients in the GTN group, who required residual perianal skin tags excised, reported a higher average pain score (median = 6) than those who did not have skin tag excision (median = 5; $P = 0.028$). However, duration of pain (GTN group with skin tags excised, 8 months; without skin tags excised, 8 months; $P = 0.869$) and satisfaction (GTN group with skin tags excised, 9; without skin tags excised, 9; $P = 0.634$) were not different. In the control group, there were no differences in the maximum pain score (with skin tags excised, 8; without skin tags excised, 6; $P = 0.256$), average pain score (with skin tags excised, 5; without skin tags excised, 5; $P = 0.483$), duration of pain (with skin tags excised, 10 months; without skin tags excised, 7 months; $P = 0.355$), and satisfaction score (with skin tags excised, 9; without skin tags excised, 9; $P = 0.215$) between patients who did and did not require residual perianal skin tag excision.

Table 2 Complications after stapled hemorrhoidopexy for grade 3 or 4 hemorrhoids

Complication	Routine postoperative management (n = 110) (control)	Glyceryl trinitrate (n = 100) (intervention)	*P* value[a]
None	91 (84.3%)	80 (80.8%)	0.287
Constipation	4 (3.7%)	2 (2.0%)	
Fecal impaction	9 (8.3%)	8 (8.1%)	
Urine retention	1 (0.9%)	2 (2.0%)	
Bleeding	1 (0.9%)	2 (2.0%)	
Thrombosis	0 (0)	3 (3.0%)	
Nodule	0 (0)	1 (1.0%)	
Stricture	1 (0.9%)	1 (1.0%)	
Fissure	1 (0.9%)	0 (0)	

[a]χ^2 for trend.

There were no significant differences in the overall complication rates for the control and GTN patients (Table 2). Fecal impaction was the most common complication in both groups, but was readily treated with a Johnson & Johnson Microlax Microenema application (Solletuna, Sweden). Patients with constipation in both groups responded to lactulose prescribed in addition to routine fiber supplements. Patients with urinary retention responded to a single in-out urinary catheter placement to empty the bladder, with no recurrences. Four patients, all in the GTN group (4%), had thrombosed perianal varix nodules, which resolved with nonsteroidal inflammatory drug analgesia and stitz baths. Two patients (1 GTN, 1 control) had soft anorectal web strictures of the anorectal stapled hemorrhoidectomy anastomosis, which were readily dilated and tolerated well in the outpatient clinic. The patients were prescribed additional fiber supplements and had no further recurrences of the strictures. Episodes of minor fecal incontinence in the first few days after surgery occurred in 14 control patients (13.6%) and 14 GTN patients (15.1%; $P = 0.770$). These incontinent episodes were likely related to postoperative discomfort and all have settled without need for further management. Recurrences (bleeding from early internal hemorrhoids) occurred in 6 (5.5%) control patients and 2 GTN patients (2%; $P = 0.173$). All of these complications occurred within 2 to 23 months after the stapled hemorrhoidectomy, and responded well to rubber band ligation with no further recurrences. There were no recurrent prolapse of hemorrhoids and there were no recurrent perianal skin tags noted by either the assessing physician or patient.

Sixteen patients (17%) had side effects from GTN, causing them to stop complying with the medication (Table 3). The described side effects included headache (n = 5; 5.3%), dizziness (n = 1; 1.1%), constipation (n = 1; 1.1%), and rash (n = 1; 1.1%). Eight patients (8.5%) in the GTN group also reported undescribed side effects. When the noncompliant patients were excluded from analysis the results for GTN (control) participants were: maximum pain score = 8 (7), $P = 0.012$; average pain score = 5 (5), $P = 0.053$; pain duration = 8 (7) days, $P = 0.414$; number of daily bowel movements = 2 (2), $P = 0.532$; follow-up 12.6 (11.9) months, $P = 0.619$; and satisfaction score 9 (9), $P = 0.563$.

Discussion

GTN did not reduce pain in patients after stapled hemorrhoidopexy, whether or not residual perianal skin tags needed to be excised. The maximum pain

Table 3 Side effects of drugs after stapled hemorrhoidopexy for grade 3 or 4 hemorrhoids

Drug side effect	Routine postoperative management (n = 110) (control)	Glyceryl trinitrate (n = 100) (intervention)	*P* value
Any side effect	7/102 (6.9%)	16/94 (17.0%)	0.027[a]
Dizziness	0 (0)	1 (1.1%)	0.018[b]
Headache	2 (2.0%)	5 (5.3%)	
Constipation	0 (0)	1 (1.1%)	
Rash	0 (0)	1 (1.1%)	
Not described	5 (4.9%)	8 (8.5%)	

[a]Pearson χ^2.

[b]χ^2 for trend.

score was significantly higher in the GTN group. However, the average pain score and pain duration were similar for the GTN and control groups when the proportion of patients with excised residual perianal skin tags were similar. This is different from the situation after conventional excisional hemorrhoidectomy where topical GTN has been shown to reduce postoperative pain and improve wound healing.[19,20] Studies of the benefit of treatment with GTN after hemorrhoidectomy have shown mixed results[22,23] with some reporting that GTN decreased pain after open hemorrhoidectomy compared with placebo, whereas other investigators lacked power based on their low number of participants.[20] For example, GTN improved healing rates without improving pain in subjects in a small study of 40 patients.[20] These mixed results prompted a meta-analysis[19] in 2010 that reviewed 5 robust trials and found that GTN ointment used after hemorrhoidectomy has a significant analgesic effect in the intermediate time period. GTN ointment was also shown to significantly improve wound healing 3 weeks after surgery.

It is possible that GTN did not provided an analgesic effect after stapled hemorrhoidopexy because that pain is different from the one after excisional hemorrhoidectomy, which might be of rectal origin and hence not responsive to topical GTN. An extensive study of post-defecation pain syndrome showed that GTN acts in the anal canal and not in the rectum.[24] Stapled hemorrhoidopexy excises and constructs an anastomosis above the dentate line.[25] Nifedipine, a systemic therapy which relaxes the rectal muscles, has been reported to be effective in alleviating cases of prolonged pain related to rectal spasm after stapled hemorrhoidectomy.[24] GTN, a topical agent, acts on the area of application only (*i.e.*, the anal mucosa rather than the external anal sphincter muscle). The most significant pain after hemorrhoidectomy is related to the wound in the sensitive perianal skin distal to the dentate line. Thus patients in the GTN group may have been more sensitive to pain in the postoperative area as they had to apply the ointment digitally. This issue could have been overcome by providing the control group with a placebo ointment to apply in a similar manner, resulting in both groups experiencing the same degree or reduction in anal spasm, which could be relieved by medications such as diazepam.[26,27] GTN has a direct action on anal sphincter muscles and as a consequence acts by reducing the pressure of the anal canal and the hypertonicity of the internal anal sphincter.[27] The internal anal sphincter is relaxed and the anoderm blood flow is increased, thus resulting in decreased pain and increased healing.[25,27]

An unexpected finding was that our GTN patients, who had residual perianal skin tags excised, had more pain than those who did not, whereas there was no difference in the control patients, whether or not residual perianal skin tags were excised. Although the findings of statistical subset analysis need to be interpreted with caution, it is possible that the relatively smaller amount of tissue excised when removing residual skin tags compared with a formal excisional hemorrhoidectomy may make the differences between the 2 groups less clear. A possibility is the application of the GTN ointment to the perianal area after hemorrhoidectomy stimulated pain in this group. A placebo ointment application may have been helpful in examining this finding. Following these results we are currently planning a study of the effects of nifedipine or similar agents in reducing pain after stapled hemorrhoidectomy. However, as stapled hemorrhoidectomy results in less pain than excisional hemorrhoidectomy,[28] it is possible that the reduced level of discomfort can only be minimally further reduced by any other method and hence would not be perceptible by the patient.

This study was analyzed on an intention-to-treat basis and there was 16% noncompliance in the GTN group due to known side effects. Exclusion of noncompliant patients from the analysis did not aler the main findings. GTN did not contribute any additional complications. Interestingly despite reducing anal sphincter tone as demonstrated in previous studies,[26,27] transient minor incontinence did not differ between the two groups.

The limitations of this study include the lack of a placebo ointment in the control group, the lack of clinical supervision in the application of the GTN ointment, and the inclusion of a quality of life questionnaire 4 and 8 weeks after surgery. The lack of a placebo ointment in the control group resulted in the inability to appropriately compare pain caused by applying the ointment, which may be responsible for the disparity in the skin tag subset analysis. A medical or nursing-led instruction session with a step-by-step application protocol for the GTN with follow-up at 1 to 2 weeks would have strengthened the protocol. Finally, the inclusion of a quality of life questionnaire at 4 and 8 week after treatment would have provided more in-depth information about symptom control in the GTN and placebo groups.

In conclusion, our results show that the anal sphincter spasmolytic agent, topical GTN, did not reduce pain after stapled hemorrhoidectomy and therefore, cannot be recommended routinely after the procedure because of unnecessary side effects and added costs.

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