



# Efficacy of nitroglycerine ointment in the treatment of pediatric anal fissure<sup>☆</sup>



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## ABSTRACT

**Background:** Anal fissure is the most common anal disease in children. In the past few decades, the understanding of its pathophysiology has led to a progressive reduction in invasive procedures in favor of conservative treatment based on stool softeners and the relaxation of the anal sphincter. This randomized controlled study assessed the safety and efficacy of nitroglycerine (NTG) ointment in the treatment of pediatric anal fissure, which had not yet been proved.

**Patients and methods:** An unequal randomized controlled study included 105 pediatric patients with anal fissure who had presented to the private and outpatient clinics of the Central Teaching Hospital of Pediatrics during the period from February 2015 to May 2016. The control group consisted of 70 patients. Both groups were treated with classical conservative therapy of sitz bath, stool softener, and local anesthetic. In the second group, chemical sphincterotomy with 0.2% NTG ointment was used in 35 patients, and was applied at the anal canal twice daily for 8 weeks. The primary outcomes of symptomatic improvement and healed fissure, as well as side effects, were analyzed.

**Results:** The average age of patients was 2 years (range, 4 months to 5 years). Patients in the NTG group had 77% symptomatic relief and 60% healed fissure compared to the control group, which had 54% and 32.8% respectively. All were statistically significant. No serious adverse effects were noticed during the treatment period.

**Conclusion:** The use of 0.2% NTG ointment is an effective therapy for anal fissure in children in terms of good healing rate and rapid symptom relief, but it has the drawback of a long treatment period, making patient compliance more difficult, in addition to the problems of tolerance and recurrence.

**Type of study:** Prospective randomized controlled study (treatment study).

**Level of evidence:** Type 2.

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Anal fissure is the most common cause of hematochezia in childhood and should be considered in the differential diagnosis of a painful anal condition [1]. Despite its high frequency, the problem remains underestimated by most clinicians. Its possible pathophysiology is trauma to the anal canal caused by passage of a hard fecal mass [2]. Hypertonicity of the internal anal sphincter with its associated ischemia is thought to be an important initiating factor [1].

Nitroglycerine (NTG) is an organic nitrate degraded by cellular metabolism, releasing nitric oxide (an important inhibitory neurotransmitter) [3]. NTG applied to the anal mucosa causes relaxation of the internal anal sphincter and a decrease in maximum anal resting pressure. Thus, NTG relieves the pain associated with sphincter spasm and increases blood flow to the anal mucosa. This randomized controlled

study assessed the safety and effectiveness of NTG ointment in the treatment of pediatric anal fissure, which had not yet been proved.

## 1. Patients and method

An unequal randomized controlled study was prospectively performed on a total of 105 patients over a period of 18 months from February 2015 to May 2016.

Consecutive patients with anal fissure were unequally randomized with a ratio 2:1, in which patients with every third number were assigned to the NTG treatment group. The reason beyond this type of randomization is to gain great experience in the new treatment (NTG) and to be more economically efficient by a substantial cost saving with only a modest loss in statistical power (from 0.95 for equal allocation 1:1 to 0.85 in 2:1 unequal randomization). After randomization, the patients were divided into two groups (case and control groups) according to treatment regimen. A fully informed written consent was obtained from parents or guardians. The study was approved by the

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ethical committee in the university hospital. The inclusion criteria were cases of anal fissure having any of the following features:

- Anal pain during or after defecation for more than 8 weeks associated with bleeding, pruritus, discharge, and chronic constipation
- Presence of an anal skin tag
- Exposure of horizontal fibers at the base of the anal fissure

The following cases were excluded from the study:

- Fissure associated with other conditions (e.g., inflammatory bowel disease, tuberculosis, malignancy, perianal dermatitis)
- Previous surgery
- Noncompliance: patient reluctant to use, or discontinued the treatment
- Patient lost to follow-up

All the patients underwent a pretreatment evaluation, including a thorough history and clinical inspection of the anal verge and, if the patient's condition permitted, a simple proctoscopy.

1.1. Medication

Children in the control group were treated classically with stool softener in the form of glycerin suppositories and oral lactulose with local anesthetic; they were advised to use a sitz bath following each bowel movement. Children in the second group were supplied with 0.2% NTG ointment by formal prescription in addition to the classical treatment. The parents were instructed to apply the allocated ointment initially on a ruler to measure the amount (1 cm = 0.1 g), then apply the ointment by fingertip endoanally. The dose was adjusted according to age (Table 1) [4].

Parents were advised to apply the ointment after cleaning the anus and without any topical treatment used simultaneously. The ointment should be applied inside the anal canal on the mucosa and on the fissured area, not just on the anal verge or perianally. The reason for these instructions is that when the ointment is applied endoanally it will be absorbed by the portal circulation and undergoes first-pass metabolism in the liver & metabolized into dinitrate metabolites which have slight vasodilatory effect, and hence less headache [5]. The ointment was applied every 12 h for 8 weeks. Both groups were instructed to have a follow-up visit every 2 weeks, and the parents were given a phone number for questions and to report side effects between appointments. Dietary modification was advised for all patients in both groups, including increasing fluid and fiber intake. During the follow-up visit, we ensured that the ointment was being used properly, identified any adverse drug reactions, and adjusted the dose of stool softener and ointment according to response, in addition to performing clinical assessment for improved symptoms and healed fissure. Painful defecation can be assessed using behavioral observation by parents according to developmental stage of the child (e.g., crying, agitation, brow bulge, eye squeezing or blinking, nasolabial furrow, stretched mouth, thigh adduction, respiratory responses, and verbal expression of pain in older infants and children) [6]. Patients with reported adverse effects were called for examination and investigation to document whether the effects were related to the NTG therapy or were coincidental. The parents were notified to bring their children back for evaluation if they noticed any unusual behavior like low energy, poor appetite, irritability, unexplained crying, sleep disturbance or

Table 1 Dosage of 0.2% NTG ointment [4].

Age (y)	Dose 0.2% NTG
<1	0.2 g twice daily
1–5	0.3 g twice daily
5–10	0.4 g twice daily
10–15	0.5 g twice daily

Table 2 Demographic variables.

Variable	NTG (N = 35)	Control (n = 70)	P-value
Median age (month)	24.41	25.57	0.329
Sex ratio (M/F)	17/18	31/39	0.681
Median duration of symptom(week)	25.04	17.44	0.398
Previous medical treatment	29 (82.85%)	54 (77.14%)	0.409
Pain on defecation	32 (91.42%)	67 (95.70%)	0.377
Bleeding	7 (20.00%)	19 (27.14%)	0.348
Constipation	33 (94.28%)	68 (97.14%)	0.476
Hard stool	30 (85.71%)	63 (90.00%)	0.679
Anal skin tag	11 (31.42%)	27 (38.50%)	0.478

mood changes & sometimes pulling on his ear which could be a clue to headache as a side effect of treatment [7]. Patients who were non-compliant or discontinued treatment altogether were excluded from study. For patients who had a partial improvement in their condition after 8 weeks of treatment, a treatment extension for another 8 weeks was offered. Cases of no response to extended conservative therapy were recommended for surgical sphincterotomy. The patients were followed up for 4 to 10 months after completed therapy.

1.2. Statistical analysis

Descriptive analysis of the demographic variables and clinical presentation data was done using SPSS version 18 software (IMB Corporation). Symptoms before and after starting treatment were analyzed using paired sample t-test, and an independent t-test was used to compare the results between the two groups. A Kaplan–Meier survival curve was used to demonstrate time for painless defecation. We performed a Pearson correlation test for the development of side effects. A p value less than 0.05 was considered significant.

2. Results

A total of 105 successive patients with anal fissure completed the study; 35 patients were given treatment with 0.2% NTG ointment (the case group), and 70 patients were given classical treatment (the control group). The average age of patients was 2 years (range, 4 months to 5 years). The demographic variables of the patients in the two groups were compared with no significant difference by independent sample t-test (Table 2).

The variables of age, sex, duration of symptoms, previous medical therapy, and site of the fissure were not significant predictors of response, whereas treatment with NTG ointment was a significant predictor of healing, with P < 0.008 when using multiple logistic regressions with healing at 8 weeks as the dependent variable (Table 3).

On examination of the anal verge, the fissure was situated posteriorly in 36.19%, anteriorly in 27.61%, laterally in 18.09%, multiple sites in 10.47%, and on both anterior and posterior sides in 7.61% of cases, with no significant differences between the two groups as shown in Fig. 1.

On the sixth week of treatment, complete healing of the fissure was seen in 20 patients treated with NTG ointment and painless defecation was reported in 27 of 32 patients who had experienced pain and crying on defecation before starting treatment (3 patients were already having

Table 3 Multiple logistic regression of the variables as predictors of response.

Variables	P value
Sex	0.996
Age	0.495
Duration	0.075
Previous treatment	0.998
Site of fissure	1.000
NTG use	0.008*

\* Significant when p > 0.001.

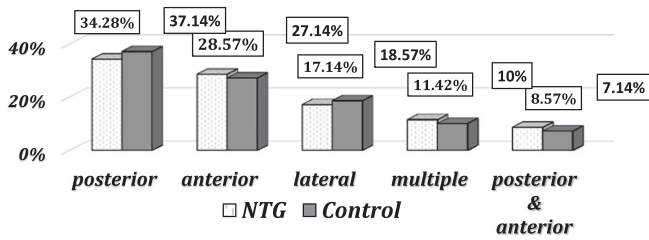


Fig. 1. Site of anal fissure.

no pain on presentation). The incidence of anal bleeding declined from 20% to 2.85%. Other symptoms related to anal fissure such as hard stooling and constipation were improved with a statistically significant P-value as shown in Table 4.

At the end of 8 weeks of treatment, the average time to symptomatic improvement was 4 weeks (i.e., complete resolution of all presenting symptoms; 27/35 patients). Twenty-one patients had healed fissure. Patients who failed to respond to treatment after 8 weeks were regarded as nonresponders; eight of these patients were treated with an extended course of NTG therapy, and three of them were improved after 16 weeks of NTG therapy, making the overall healing rate 68.57% (24/35) for the 16-week treatment period. Two patients did not get a response to treatment, and were offered surgical treatment. The remaining three patients were lost to follow-up.

Patients treated with NTG had statistically significant symptomatic improvement ( $P = 0.023$ ), rate of healed anal fissure ( $P = 0.008$ ), and time to achieve painless defecation ( $P = 0.014$ ) compared with the control group (Table 5). There was no statistically significant difference in the compliance rate between the two groups ( $P = 0.652$ ). Four of thirty-five patients in the NTG group had a recurrence of anal fissure compared with 6 of 70 control patients ( $P = 0.642$ ) over a period ranging from 4 to 10 months after stopping the treatment. Those four patients were successfully re-treated with NTG ointment, and no more relapses were recorded for another 4 months of follow-up. The six patients in the control group were treated with the same control group treatment protocol for another 8 weeks, and four of them showed complete symptomatic relief and fissure healing, whereas the other two were recommended for surgical sphincterotomy.

There was a significant difference in the percent and time to achieve painless defecation between the two groups ( $p = 0.014$ , Fig. 2).

During the treatment period, the following events were noticed or reported by parents, and were assumed to be side effects; these did not require discontinuation of treatment. The most significant adverse effects noticed were perianal erythema, colicky abdominal pain, and unexplained crying or nervousness, with a P value = 0.013 (Table 6). No serious adverse effects were noted during the period of treatment. The perianal erythema resolved on discontinuing the ointment.

### 3. Discussion

Nitroglycerine ointment is FDA approved for moderate-to-severe pain associated with anal fissures [8]. The ointment is already approved in the European Union and has been prescribed outside Europe in

Table 4  
Symptoms before & on the 6th week of NTG therapy.

Symptoms	Before NTG (n = 35)	6 weeks after NTG (n = 35)	P-value
Pain on defecation	32 (91.42%)	5 (15.62%)	0.001**
Bleeding	7 (20%)	1 (2.85%)	0.012*
Hard stool	30 (85.71%)	12 (34.28%)	0.003**
Constipation	33 (94.28%)	16 (45.71%)	0.001**
Healed fissure	0 (0%)	20 (57%)	0.000**

\* Significant paired t-test when  $p > 0.05$ .

\*\* Significant paired t-test when  $p > 0.01$ .

Table 5

Comparative results between case & control group after 8 weeks.

Result	NTG group (n = 35)	Control group (n = 70)	P-value
Symptomatic improvement	27 (77.14%)	38 (54.28%)	0.023*
Healed fissure	21 (60%)	23 (32.85%)	0.008**
No improvement	8 (22.85%)	32 (45.71%)	0.023*
Average time to achieve painless defecation	4.2 weeks	6.7 weeks	0.014*
Recurrence rate of anal fissure	4 (11.42%)	6 (8.57%)	0.642
Compliance rate	91.42%	88.57%	0.652

\* Significant independent t-test when  $p > 0.05$ .

\*\* Significant independent t-test when  $p > 0.01$ .

34 countries worldwide [9]. In this study, we aimed to call attention to the safety and efficacy of using 0.2% NTG ointment in children with anal fissure.

In the NTG group, there was a significant improvement in the symptoms and fissure healing (Table 4). Although this improvement could be partially attributed to NTG, the stool softeners also had a role in relieving constipation and fissure healing.

In the present study, significant differences were found in the rates of fissure healing, symptomatic relief, and time to achieve painless defecation between the group receiving NTG and those receiving only classical treatment (Table 5). Our finding of 68.57% healing rate is in keeping with a Cochrane review that reported cure rates of between 50% and 68% [10]. Sonmez et al. reported a 91% and 82% symptomatic relief and healing rate, respectively, with a faster response rate by NTG application compared with lidocaine and a eutectic mixture of local anesthetics (EMLA) [11]. Another review noted that the cure rate of topical nitrates was significantly superior to placebo [12]. Altomare et al. found a notable effect of this drug in reducing pain in a shorter time [12]. We also recorded a significantly faster time of relief of painful defecation in the NTG group compared with the control group ( $p = 0.014$ , Fig. 2).

The observed fissure healing rate (68.57%) is still less than adult results reported by Luai et al. [13] in Iraq in 2014 because the pathogenesis of anal fissure in children may vary from that in adults. Previous adult studies have showed that ischemia of the anal sphincter is an important mechanism in the pathogenesis [14]; thus, a chemical agent, such as NTG, which reduces spasm of the anal sphincter and improves anodermal blood supply would have better therapeutic results. Whereas children are more likely than adults to assume maladaptive patterns of behavior in response to painful defecation, such as fecal retention, anal fissure in this group is less amenable to medical treatment [15].

The variations in healing rates between several studies might be explained by different definitions of the cure period, concentration of NTG used, site of application, and patient selection.

The simple conservative measures such as diet modification, improving habits of defecation, sitz bath, and use of a laxative were advised to all patients, as these are essential to providing a cure in patients with anal fissure [16].

Approximately 23% (8/35) of the eligible patients did not respond to NTG therapy during the 8-week period. Five of those patients had deep fissures that resisted chemical sphincterotomy, and the remaining three patients had poor compliance. This finding is supported by the criteria of the scoring system of Thornton et al. [17], who concluded that higher fissure score responds poorly to medical therapy and should be considered directly for surgical treatment. Recently, Gil et al. [18] showed that there is a low chance of fissure healing in response to chemical sphincterotomy when the PI index (change between resting and squeezing pressure) is low. Unfortunately, we have no anorectal manometry to support this fact.

The perianal erythema and itching were seen in three patients; because these resolved spontaneously on discontinuing the ointment, they were related to NTG therapy. These side effects may be attributed

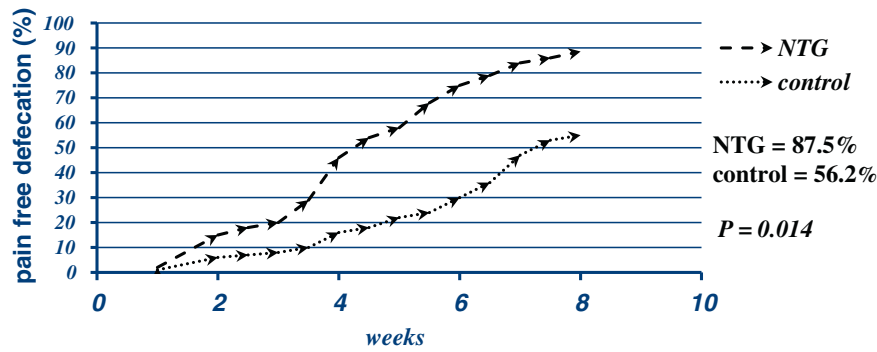


Fig. 2. Percent of painless defecation over time by Kaplan–Meier curve.

to sphincter relaxation that results in frequent perineal soiling, or perhaps owing to an ointment ingredient. This is supported by the manufacturer information leaflet, which states that the ointment formulation contains propylene glycol and lanolin, which may cause skin irritations and skin reactions [19]. This finding was also reported in a Turkish study [20].

Colicky abdominal pain seen in our patients resulted from overuse of laxatives, and these symptoms improved on adjusting the dose. Another three patients had unexplained crying and nervousness for unknown reasons; these could be owing to headache or light headedness. Other reported events, such as flulike illness, diarrhea, and vomiting, were investigated and attributed to intercurrent illnesses.

There were no reported cases of incontinence or documented headache in our study, as Demirbag et al. [20] mentioned in their study, whereas headache was reported in 36% of adult patients in the study of Bansal et al. [21]. The difference in headache experience in our patients was because of several factors: endoanal application of the ointment in our patients, which significantly reduced the frequency of headache rather than perianal application, which may result in considerable headache (reaching 54% in one study [22]), inability of this age group to describe frank headache, and interaction with many other medicines used in adults that may potentiate the blood pressure lowering effects of NTG and cause headache [19] (e.g., vasodilators, calcium channel blockers, ACE inhibitors, beta blockers, diuretics, anti-hypertensives, tricyclic antidepressants, major tranquilizers, phosphodiesterase inhibitors, and alcohol).

During the 4- to 10-month follow-up period in the present study, 4 of 35 patients (11.4%) had recurrent fissure on cessation of treatment, but all were successfully treated by a second course of NTG therapy without complications. Long-term follow-up showed a 32.3% recurrence rate in one study [20]. Late recurrence may be common, occurring in approximately 50% of people whose fissures were initially cured [10]. Indeed, early recurrence will remain a problem with all types of chemical sphincterotomy because the resting anal pressure may return to the pretreatment level on cessation of treatment, and any further trauma to the anoderm is likely to produce recurrence [23].

**Table 6**  
Reported adverse effects.

Adverse effect	No.	P-value
Perianal erythema, itching	3	0.013*
Localized or generalized rash	1	0.139
Flulike illness	2	0.044*
Colicky abdominal pain	3	0.013*
Vomiting	1	0.139
Nervousness & unexplained crying	3	0.013*
Diarrhea	1	0.139

\* Significant Pearson correlation when  $p > 0.05$ .

Tachyphylaxis was the major drawback to this treatment; nitrate has a tolerance effect in some patients, requiring increasing the dose or the frequency with time. It has been suggested that tachyphylaxis may occur when NTG is used to treat anal fissure [24], just as it occurs in cardiovascular disease. Cundall et al. showed that there is some evidence that the internal anal sphincter demonstrates a dose-related response to the application of NTG [24]. Bansal et al. identified those patients who required increasing the concentration of NTG to overcome the problem of tolerance [21]. In our study, we increased the dose of NTG ointment in eight patients who experienced partial or no response to the initial 8-week treatment. This modified course resulted in fissure healing in three patients.

#### 4. Conclusion

Our findings suggest that nitroglycerine is an effective treatment for anal fissure in children in terms of good healing rate, rapid symptomatic relief, and fewer side effects. However, this treatment requires a long treatment period, which effects patient compliance in addition to the problems of tolerance and recurrence. Long-term follow-up with a larger number of patients should be implemented in future studies.

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