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Efficacy of nitroglycerine ointment in the treatment of pediatric anal fissure☆

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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.

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

☆ Conflict of interest: nil.

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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 the 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 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.

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

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.