

The efficiency of various doses of topical isosorbide dinitrate in the treatment of chronic anal fissure and the long-term results: A prospective, randomized and controlled clinical trial

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Background/aims: In recent years, numerous studies have reported that the application of topical isosorbide dinitrate can cause fissure recovery with the relaxation of the internal anal sphincter. However, there is no consensus about the dose or duration of the drugs to be applied. In addition, long-term results of the patients with chronic anal fissure treated with nitrate-containing compounds are unknown. In this study, the goal was to investigate the effects of various doses of isosorbide dinitrate on chronic anal fissure and their long-term effects. **Methods:** Seventy-five sequential patients with chronic anal fissure were divided into three groups. Only symptomatic treatments were applied to patients in the first group (n=15). The patients in second and third groups (n=30 each) were treated with topical isosorbide dinitrate 5% and 10%, respectively. The patients were examined three times at 20-day intervals. Five years later, 44 patients who were responsive to treatment were contacted by telephone. **Results:** The rate of full response in the 10% isosorbide dinitrate group was statistically higher than of the 5% isosorbide dinitrate group on the 20th day (53.3% vs. 26.7%, p<0.05). However, the rate of full response did not differ between these groups on the 40th and 60th days (63.3% and 70% vs. 56.7% and 63.3%, p>0.05). Five years later, 52.3% of patients who were responsive to treatment had a symptomatic relapse. **Conclusions:** Topical isosorbide dinitrate is a good alternative therapy to protect internal anal sphincter in the treatment of chronic anal fissure. However, the recurrence rates are high in the long-term.

Key words: Chronic anal fissure, isosorbide dinitrate, internal anal sphincter

Kronik anal fissür tedavisinde topikal isosorbid dinitratın farklı dozlarının etkinliği ve uzun dönem sonuçları: Prospektif, randomize ve kontrollü bir klinik çalışma

Amaç: Son yıllarda, topikal isosorbid dinitrat uygulamasının internal anal sfinkterde gevşeme ile kronik anal fissürde iyileşmeye neden olabileceğini bildiren çok sayıda çalışma bildirilmiştir. Ancak uygulanacak ilaçların dozları ve süreleri hakkında fikir birliği yoktur. Ayrıca nitratlı bileşiklerle tedavi edilmiş kronik anal fissürlü hastaların uzun dönem sonuçları bilinmemektedir. Bu çalışmada isosorbid dinitratın farklı dozlarının kronik anal fissür üzerindeki etkilerini ve uzun dönem sonuçlarını incelemeyi amaçladık. **Yöntem:** Kronik anal fissür tanısı konulan ardışık 75 hasta 3 gruba bölündü. I. gruba (n=15) sadece semptomatik tedavi verildi. II. ve III. gruplara (n=30) ise sırasıyla %5 ve %10 topikal isosorbid dinitrat uygulandı. 20 gün aralıklarla 3 kontrol yapıldı. Tedaviye yanıt alınan 44 hasta ile 5 yıl sonra telefonda görüşüldü. **Bulgular:** Tedavinin 20. gününde %10 isosorbid dinitrat grubunda sağlanan tam iyileşme oranı, %5 isosorbid dinitrat grubundakinden belirgin olarak daha fazlaydı (%53.3 vs. %26.7, p<0.05). Ancak tedavinin 40. ve 60. günlerinde bu iki grupta sağlanan tam iyileşme oranları biri birinden anlamlı olarak farklı değildi (%63.3 ve %70 vs. %56.7 ve %63.3, p>0.05). Beş yıl sonra, tedaviden fayda gören hastaların %52.3'ünde semptomların nüks ettiği saptandı. **Sonuç:** Topikal isosorbid dinitrat uygulaması kronik anal fissürün tedavisinde internal anal sfinkteri korumaya yönelik iyi bir alternatiftir. Ancak uzun dönemde nüks oranları yüksektir.

Anahtar kelimeler: Kronik anal fissür, isosorbid dinitrat, internal anal sfinkter

INTRODUCTION

Chronic anal fissure is a common problem causing severe pain and rectal bleeding. One of the asserted reasons is the increased maximum resting anal pressure (MRP) and associated local ischemia that develops. This pressure is based on the activity of the internal and external sphincter muscles (1). The suggested treatment for chronic anal fissure is reduction of resting pressure surgically via a lateral internal sphincterotomy (LIS) (2).

In recent years, nitric oxide has been shown to be the most important inhibitory neurotransmitter for the internal anal sphincter (IAS), and numerous studies have reported that application of topical glyceryl trinitrate (GTN) and isosorbide dinitrate (ISDN) can cause the fissure to recover with IAS relaxation (3-5). However, there is no consensus about the dose or duration of the drugs to be applied. In addition, the long-term results of the patients with chronic anal fissure treated with nitrate-containing compounds are unknown. Our goal was to examine the effects and the long-term results of various doses of nitric oxide donor ISDN on chronic anal fissure in a controlled and randomized study.

MATERIALS AND METHODS

This study was performed in two phases between May 2004 and March 2010. The first prospective, randomized and controlled phase was between May 2004 and March 2005. Ethics Board approval and informed patient consents were obtained. Seventy-five patients, with no ischemic heart disease diagnosis, hypotension, palpitations, use of any nitrate compounds, or history of surgery for fissure, and who were diagnosed with chronic anal fissure upon observation of the existence of sentinel crease, fissure and hypertrophic papillae were recruited to the study. The first 15 patients that were admitted were given symptomatic treatment for 40 days with diet, laxatives, sitting in hot baths, and lidocaine pomades as they waited for botulinum toxin (BT) injection. These patients were considered the control group. In 30 patients, a 5% ISDN ointment was given along with symptomatic treatment. The remaining 30 patients were given a 10% ISDN ointment. The ISDN ointments were prescribed to be applied twice a day to the anal canal. Dosage was defined as approximately the size of a pea.

The patients were examined at 20-day intervals with performance of anal examination. Complete disappearance of the ulcer base of the fissure was recorded as a complete recovery, and its shrinkage was recorded as partial recovery. The treatment was stopped in patients whose ulcer was completely closed. In patients with no shrinkage in the ulcer area in the second follow-up examination, the treatment was stopped and BT injection or LIS was performed. In patients with shrinkage in the ulcer area, the treatment was extended to 60 days. At the end of 60 days, the treatment was stopped even if the ulcer was not completely closed. Additional interventions were not performed on patients whose symptoms disappeared. BT injection and LIS were performed on those in whom the symptoms persisted.

In March 2005, the final physical examinations of the patients were performed, and the patients were surveyed with a questionnaire regarding their satisfaction with the ISDN treatment, their compliance with the treatment, and the persistence of any side effects.

In March 2010, those patients who did not require additional interventions at the end of the ISDN treatment, such as BT injection or LIS, were contacted via telephone. These patients were queried as to whether they had experienced symptoms such as pain, bleeding or constipation that could be associated with the anal fissure, whether these symptoms recurred at any period after the treatment, if these symptoms existed, and whether they received any additional treatment.

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 12.0 software package. Data based on measurements were compared using the t test and data based on observations were compared using the chi-square test, at a confidence interval of 95%.

RESULTS

The demographic characteristics of all the groups were similar (Table 1). The responses of the patients to the treatment noted at the examinations on day 20, day 40, and day 60 of the treatment are presented in Tables 2, 3 and 4, respectively. The recovery rates of those in the nitrate treatment groups were significantly higher than of those in the control group on day 20 and day 40 ($p < 0.001$). The complete recovery rate on day 20 in the 10% ISDN group was significantly higher than that in

Table 1. The demographics and characteristics of the groups

	Control group (n=15)	ISDN 5% group (n=30)	ISDN 10% group (n=30)
Age	40.4±10.8	37.6±12.6	38.6±11.7
Sex (F/M)	7/8	16/14	17/13
Symptoms (%)			
Pain	73	77	73
Bleeding	93	70	73
Constipation	80	77	80
Duration of symptoms (months)	22.7±20.2	28.1±29.8	19.7±22.2

ISDN: Isosorbide dinitrate

Table 2. The response at the 20th day of treatment

	Control group (n=15)	ISDN 5% group (n=30)	ISDN 10% group (n=30)
No recovery	13	11	10
Partial recovery	2	11	4
Full recovery	0	8	16

ISDN: Isosorbide dinitrate

Table 3. The response at the 40th day of treatment

	Control group (n=15)	ISDN 5% group (n=30)	ISDN 10% group (n=30)
No recovery	11	9	8
Partial recovery	4	4	3
Full recovery	0	17	19

ISDN: Isosorbide dinitrate

Table 4. The response at the 40th day of treatment

	ISDN 5% group (n=30)	ISDN 10% group (n=30)
No recovery	7	6
Partial recovery	4	3
Full recovery	19	21

ISDN: Isosorbide dinitrate

the 5% ISDN group ($p<0.05$). However, the complete and partial recovery rates obtained in these two groups were similar on days 40 and 60 of the treatment ($p>0.05$).

There was a significant relationship between recovery in the ISDN groups and compliance of the patient to treatment ($p<0.001$). Out of the 49 patients who stated that they had fully complied with the treatment as prescribed, complete recovery was obtained in 40 patients and partial recovery was obtained in 5 patients. Partial recovery was observed in only 2 of the 11 patients who did not comply with the treatment, while no recovery was observed in the remaining. The success rates were significantly different between patients who complied with the treatment and those that did not ($p<0.001$).

Following an average of 10.3 ± 7.3 months of follow-up, in March 2005, it was found that fissures had recurred in their previous localization in 2 partially recovered and 1 completely recovered patients in the 5% ISDN group and in 1 partially recovered patient in the 10% ISDN group. All of these patients were given a treatment of 10% ISDN. The difference between the recurrence rates was not statistically significant ($p>0.05$).

Seventy-three percent of the patients in the control group and 20% of the patients in the nitrate treatment groups were not satisfied with the treatment. The rates of the patients who reported a reduction in symptoms were 27%, 20%, and 10%, respectively, whereas the rates of the patients who reported that their symptoms had completely disappeared were 0%, 60%, and 70%. The patients

in the treatment groups were more satisfied with the treatment than those in the control group ($p < 0.001$); however, there was no statistically significant difference between the treatment groups in terms of patient satisfaction ($p > 0.5$).

In the 10% ISDN group, only 2 patients reported spontaneously disappearing headaches as a side effect, and no side effects were observed in the other groups. The frequency of the side effects was not statistically significant in any of the groups ($p > 0.05$).

It was not possible to contact 1 patient from the 5% ISDN group and 2 patients from the 10% ISDN group in March 2010. It was understood that the complaints repeated in time in 12 of the 22 patients that could be contacted in the 5% ISDN group and in 11 of the 22 patients that could be contacted in the 10% ISDN group ($p > 0.5$). All of these patients suffered from constipation at the beginning and throughout the treatment period. Eleven of the patients underwent the LIS operation at other centers within this time. Other patients continued to use ISDN ointment when their complaints recurred.

DISCUSSION

This study has shown that chronic anal fissure can be treated in about two-thirds of the patients with the addition of ISDN ointments to symptomatic treatments. Furthermore, while the dose of ISDN does not affect the recovery rate, it does increase the rate of healing.

Although the tonic contraction of the IAS constitutes 70% of the resting anal canal pressure, its role in the achievement of continence is not as apparent as with the external anal sphincter (6). Therefore, in the treatment of chronic anal fissure, which is considered to develop due to MRP increase, the first objective is to reduce the IAS tonus. Even following LIS, which has lower recurrence and incontinence rates among surgical interventions targeting the IAS and is therefore the preferred choice of many surgeons today, gas incontinence is reported in 1.5-15% and fecal contamination is reported in 0-11% of the patients (7). This is exacerbated with post-surgery complications such as bleeding and wound infections. As a result, researchers have been looking for medical treatments to reduce resting anal pressure, such as topical GTN, ISDN, diltiazem, bethanechol, and BT injection into the IAS (8-11).

Nitric oxide has been shown to be a regulator of the enteric nervous system and to mediate noradrenergic and noncholinergic relaxation of the IAS (3,12). Based on this observation, it is considered that topical nitrates could be absorbed through the anoderm and reduced to nitric oxide, thereby relaxing the IAS (13). The most frequently used nitric oxide donors for this purpose are GTN and ISDN. Regional applications of ISDN have been shown to reduce anal pressure, increase the anodermal blood flow, and enable the healing of the fissure (5). However, drug doses and durations of treatment have varied in the previously reported series (5,8,9,14,15). Lysy et al. (15) reported that treatment with 2.5 mg ISDN spray three times a day provided a success rate of 83% at the end of one month, and recurring patients recovered with the application of one additional cure. Parellada (9), on the other hand, reported a success rate of 67% with a five-week 0.2% ISDN treatment and a success rate of 89% with a 10-week treatment. It was not clear in these studies whether "recovery" meant a complete closure of the ulcer or a reduction in the ulcer base along with symptomatic improvement. When we considered 40-day treatment results in our study to make the data comparable, the proportions of patients in whom the fissure closed completely for the 5% and 10% ISDN groups were 56.7% and 63.3%, respectively. The recovery rates increased to 76.7% for both groups when we included the patients in which the ulcer was reduced.

Although success in the treatment of chronic anal fissure is achievable with nitrate compounds, recurrence can develop months and even years after the treatment. Lund and Scholefield (16) reported that recurrence occurred in 27% of the patients who were successfully treated with GTN, throughout a 28-month follow-up. Carapeti et al. (17), on the other hand, reported a recurrence rate of 33% in a follow-up of nine months. We found in our study, in which the follow-up period was longer as compared with other studies (approximately 5 years), that of the patients successfully treated using ISDN who could be contacted via telephone, the symptoms had recurred in 52.3%. This result is supportive of the study by Arroyo et al. (18), who highlighted that surgical sphincterotomy is superior to chemical sphincterotomy. It should be kept in mind that chemical medical treatments are considered safer than surgical treatments.

The most frequently observed side effect following topical nitrate applications is headache. It is reported to develop in 12-80% of the patients, and the headaches disappeared spontaneously within 2 to 5 days when the drug application was continued (19,20). Topical nitrate applications can also cause syncope, dizziness or a burning sensation in the anal region (9). The side effects rate was very low in our study (3.3% headache). Although the patients in this series were selected very carefully,

when we consider that the reason for the headaches was triggered by nitrates causing cerebral vasodilation, we are unable to explain the very low rate.

In conclusion, this study shows that topical ISDN administration is a good alternative treatment to surgery to protect the sphincter. However, recurrence rates of chronic anal fissure after ISDN treatment are high in the long term. When the concentration of the topically applied ISDN is high, quicker responses are obtained.

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