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RESEARCH ARTICLE

Effect of 30% Silver Nitrate Treatment in Anal Fistulas: A Pilot Study

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ABSTRACT

Aim: Anal fistulas constitute a challenging entity for general surgeons. To date, there is no optimal treatment for anal fistulas. This study aims to determine the rate of complete clinical healing after applying a 30% silver nitrate solution to treat anal fistula.

Method: Consecutive adult patients with symptomatic, either primary or recurrent, crypto glandular anal fistulas presenting between February 2019 and January 2020 in one center were prospectively included in the study. Fistula tracts were irrigated with a 30% silver nitrate solution in an outpatient clinic, and irrigation was repeated when necessary. The primary outcome was the rate of complete clinical healing after the treatment. Factors that may have affected healing were also analyzed.

Results: Among 83 consecutive patients with anal fistulas admitted to one center between February 2019 and January 2020, 72 were included in the study. After 30% silver nitrate irrigation, 34 (47%) patients had complete clinical healing. Patients were followed up for a median of 9 (4-16) months after treatment. The patients (n=15) followed up at 12 months and beyond exhibited 73% (n=11) complete clinical healing, while those (n=57) followed-up before 12 months only had 40% (n=23) complete clinical healing (p=0.002). Kaplan-Meier analysis showed that the estimated rate of complete clinical healing was 88% throughout the 15-month follow-up period.

Conclusion: This study showed that 30% silver nitrate treatment is effective and safe for anal fistulas

Keywords: Anal fistula, proctology, silver nitrate

Introduction

Although anal fistulas were defined centuries ago, their optimal treatment has not yet been identified, and they still present a big dilemma for surgeons. The prevalence of anal fistulas is given as 0.01%.[1] Anal fistulas rarely heal spontaneously because they are lined with epithelial tissue, and there is a chronic gland infection.[2] The goal of anal fistula treatment is to reduce the recurrence rate, prevent anal abscess formation, and preserve sphincter function. To overcome the risk of fecal incontinence, many sphincter preserving techniques have been used, such as anorectal flaps, bioprosthetic plugs, and laser ablation of fistula tract (LAFT) and ligation of intersphincteric fistula tract (LIFT) treatments.[3,4] It has been reported that the causes of treatment failure are unnoticed concomitant tracts, insufficient drainage of the intersphincteric area, and the remnant epithelial or granulation tissue residues of the fistula tract.[5] In a previous study, this team showed that a chemical agent, 1% silver nitrate solution, is effective in fistula treatment with complete healing in approximately 50% of patients.[6] Silver nitrate causes ablation of fistula epithelial tissue and leads to healing with fibrosis and eventual tract closure without surgical intervention.

This study aims to determine the complete clinical healing rate after applying 30% silver nitrate solution for treating anal fistulas.

Materials and Methods

Study Design and Patients

This study was conducted prospectively. Adult patients with cryptoglandular anal fistulas admitted to the general surgery outpatient clinic in Marmara University Hospital between February 2019 and January 2020 were evaluated for inclusion in the study. Patients older than 18 years diagnosed with

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primary or recurrent cryptoglandular anal fistula admitted consecutively to the general surgery outpatient clinic were included in the study. Patients with Crohn's disease, patients who were not followed up after treatment, and patients who did not provide written informed consent were excluded from the study. This study was approved by the Marmara University Faculty of Medicine Ethics Committee (approval number: 09.2020.681, date: 24.07.2020), and all patients provided written informed consent.

Data Collected

Data regarding patients' demographics, complaints (discharge, itching, and perianal pain), comorbidities, alcohol consumption, smoking, history of anal surgery, and physical examination findings were recorded prospectively. Perianal magnetic resonance imaging (MRI) was performed for all patients before administering 30% silver nitrate, and fistulas were categorized according to Parks' classification. Patients with complaints such as bloody mucus stool, diarrhea, weight loss, and suspected inflammatory bowel disease (IBD) underwent colonoscopy and were referred to the gastroenterology department for IBD evaluation.

Silver Nitrate Application Procedure

After the patients were placed in the left lateral decubitus position, an 18 G cannula was inserted through the fistula's external orifice. Irrigation was applied to the fistula tract with a 30% silver nitrate solution (Figure 1). Depending on the length and width of the fistula, approximately 1-2 mL of silver nitrate was administered. During irrigation, whether the silver nitrate solution reached the internal orifice was confirmed by asking the patient to state when they felt a cold or burning sensation (due to the silver nitrate solution) in the anal canal. Subsequently, the cannula was retracted slowly while irrigation was performed up to the external orifice.

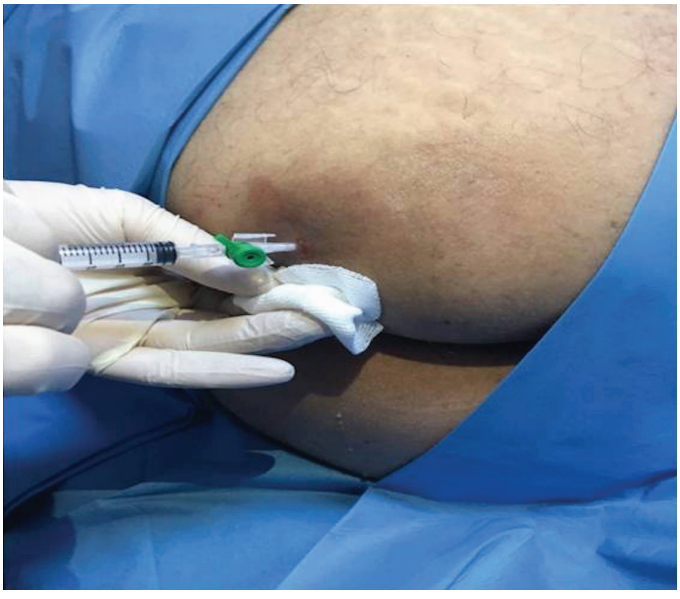

Figure 1. Irrigation of the fistula tract by silver nitrate solution

Follow-up

The patients were called to the outpatient clinic 2 months after the irrigation and evaluated in terms of perianal pain and discharge complaints. The second irrigation was applied to the patients whose discharge did not stop. Irrigation with a 30% silver nitrate solution was applied every 2 months (up to five times) for these patients. Complete clinical healing was defined as no discharge and closure of the external orifice for at least 30 days after the treatment, while treatment failure was defined as no discharge reduction. Patients with complete clinical healing were radiologically evaluated by perianal MRI 2 months after healing.

Statistical Analysis

SPSS 23.0 (SPSS, Inc., Chicago, IL, USA) was used to analyze the data. The t-test or Mann-Whitney U test was used to analyze continuous data. Fisher's exact test or the chi-squared test was used to analyze categorical data. All tests were two-sided. P-values less than 0.050 were considered statistically significant. The cumulative probability of fistula healing after treatment was estimated using Kaplan-Meier analysis. A logistic regression model was used for multivariate analysis.

Outcomes

The primary outcome of this study was to determine the complete clinical healing rate after 30% silver nitrate treatment. The secondary outcome was to identify the factors affecting healing.

Results

Between February 2019 and January 2020, 83 consecutive patients with complaints of anal fistulas applied to the general surgery outpatient clinic in the Marmara University Hospital. Seventy-five of these patients were diagnosed with crypto glandular anal fistulas. The remaining eight patients were diagnosed with anal fistulas secondary to IBD. Silver nitrate treatment was recommended for all patients diagnosed with crypto glandular anal fistulas, and 74 of them received this treatment. One of the patients refused the treatment with silver nitrate. Two patients were excluded from the study because they were not followed up after treatment. A total of 72 patients were included in the study. The median age was 43 (18-64), and 56 (78%) patients were male. All patients had complaints of discharge. Thirty-four (47%) of the patients complained of daily discharge, and the rest defined

their discharge as intermittent. Fifty-eight (81%) patients described pain due to fistulas, and the median visual analog scale pain score (out of 10) was above 5 for 35 (60%) of them. Irrigations were applied twice to 29 (40%) patients and thrice to 27 (38%). One irrigation was applied to the remaining 16 (22%) patients.

The patients were followed up for a median of 9 (4-16) months after treatment (Table 1). Complete clinical healing was achieved in 34 (47%) patients after 30% silver nitrate treatment (Figure 2, 3). Using Kaplan-Meier analysis, the estimated complete healing rate was 88% after the 15-month follow-up period (Figure 4).

The number of patients with intersphincteric fistulas was significantly higher among patients with complete clinical healing than among those with failure to heal [27 (79%) vs 21 (55%), respectively, p=0.030] (Table 2).

Compared with patients with continuous discharge (n=31), patients with intermittent discharge (n=36) had a significantly higher rate of complete clinical healing (31% vs 64%, p=0.005) (Table 2). The patients with a follow-up period of ≥12 months (n=15) after the first irrigation with silver nitrate had a higher complete clinical healing rate than those with a follow-up period <12 months (n=57) [73% (n=11) vs 40% (n=23)], respectively, p=0.020).

Fifteen (21%) patients were determined to have no change in discharge symptoms. However, 23 (32%) patients were determined to have between 40% and 80% reduction in discharge after treatment compared with that before treatment. While 58 (81%) patients had pain due to fistulas before treatment, only seven (10%) had this pain after treatment. This decrease was statistically significant (p<0.001). Only one (3%) of the patients who did not describe complete healing accepted fistula surgery. However, the patients without complete healing described a significant increase in their quality of life due to decreased discharge and pain. Furthermore, they did not feel the need for the surgical treatment that had been recommended after their silver nitrate treatment failed. Mild perianal pain was described during silver nitrate irrigation in 16 (22%) patients. Two patients developed temporary induration along the fistula tract after irrigation during the early follow-up period. A small perianal abscess developed in two (3%) patients during the follow-up period after irrigation, and drainage occurred spontaneously without any intervention.

Discussion

In this single-center study, 30% silver nitrate treatment was applied to 72 patients with a crypto glandular fistula. The study showed that after applying 30% silver nitrate treatment, nearly half of the patients had complete clinical healing. Significant reductions in pain and discharge

Figure 2. View of the external orifice after healing

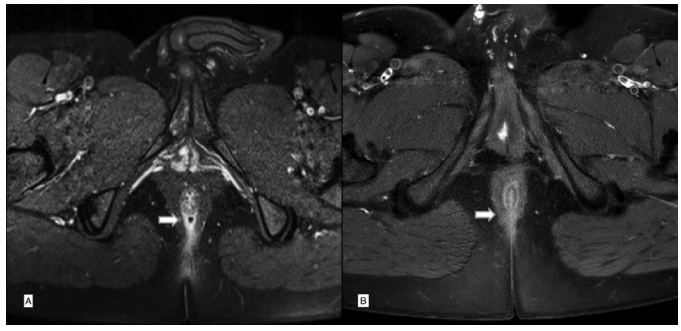

Figure 3. Pre-treatment (A) and post-treatment (B) contrast-enhanced magnetic resonance images

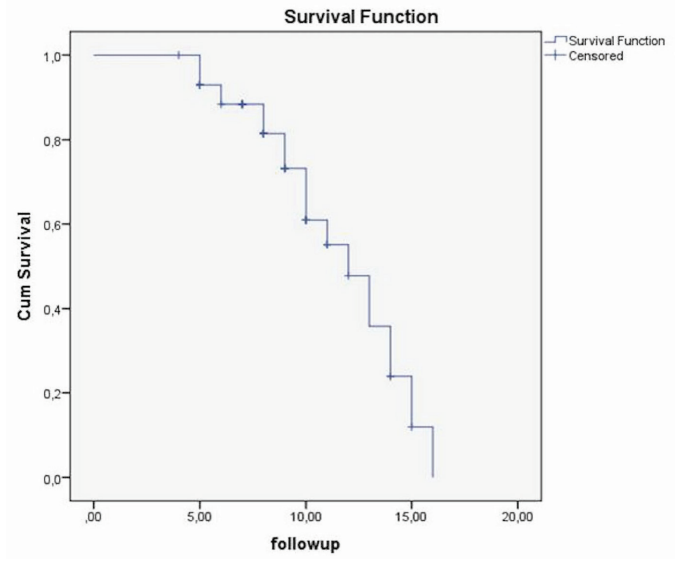

Figure 4. Estimated healing rate based on Kaplan-Meier analysis for all patients

Table 1. Demographic and clinical characteristics of the patients

Age, years, median (range)		43 (18-64)
Gender, n (%)		
Male	56 (78%)	
Female	16 (22%)	
Body mass index, median (range)	28 (16-42)	
Primary fistula	61 (85%)	
Recurrent fistula	11 (15%)	
Duration of discharge before treatment (months), median (range)		12 (1-360)
Discharge frequency, n (%)		
Continuous	34 (47%)	
Intermittent	38 (53%)	
Pain complaints, n (%)	58 (81%)	
Pain VAS score, median (range)		4 (0-10)
Itching, n (%)	47 (65%)	
Comorbidity, n (%)		
Hypertension	10 (14%)	
Diabetes mellitus	3 (4%)	
Coronary artery disease	5 (7%)	
Smoking, n (%)	22 (31%)	
Alcohol consumption, n (%)	3 (4%)	
History of hemorrhoidectomy, n (%)	4 (6%)	
History of anal fissure surgery, n (%)	4 (6%)	
External orifice		
Single	64 (89%)	
Multiple	8 (11%)	
Type of fistula, n (%)		
Intersphincteric	49 (68%)	
Transsphincteric	17 (24%)	
Exstrasphincteric	1 (1%)	
Horseshoe	5 (7%)	
Number of irrigations, n (%)		2 (1-5)
Single	10 (14%)	
Multiple	62 (86%)	
Complications, n (%)		
Induration	2 (3%)	
Abscess	2 (3%)	
Duration of follow-up (months), median (range)		9 (4-16)

VAS: Visual analog scale

symptoms were observed in most patients who were not described as completely healing. The clinical complete healing rate was higher in patients with longer follow-up periods after treatment. To the best of this study's knowledge, this is the first study to use 30% silver nitrate in adult patients for treating anal fistulas. The strengths of this study are the prospective design, inclusion of consecutive patients, and radiological confirmation of clinical healing. The advantages of this treatment modality are that it can be easily applied in outpatient clinics without anesthesia, is reproducible and cheap, and does not cause any major side effects. The limitations of this study are the lack of a control group and the short follow-up period. The success rate of fistulotomy, which has been used for a long time in treating anal fistulas, is still high. However, this surgery's serious complications, such as fecal incontinence, made it necessary to develop alternative modalities.

Although many treatments have been described for anal fistulas, there is no optimal treatment with consensus. New surgical techniques such as LIFT, LAFT, and video-assisted anal fistula treatment have been described in the last two decades.[2] The success rates of different anal fistula treatments vary widely according to the technique applied. The success rate of the LIFT technique was reported as between 40% and 95%.[7] However, no sufficient data regarding fecal incontinence after treatment with the LIFT technique has been reported. In this study, the success rate of silver nitrate irrigation without any surgical intervention is close to that of the LIFT treatment. Furthermore, incontinence is not expected in silver nitrate irrigation since no surgical procedure was performed, and no patient complained of fecal incontinence after treatment in this study. Wilhelm[9] performed LAFT on 33 patients with anal fistulas and achieved complete healing in 26 (78%) patients

Table 2. Characteristics of patients segregated based on treatment outcome

	Patients with complete clinical healing (n=34)	Patients with failure to heal (n=38)	p
Age, years, median (range)	46 (21-64)	38 (18-63)	0.060
Gender, n (%)			0.800
Female	8 (23%)	8 (21%)	
Male	26 (77%)	30 (79%)	
Body mass index, median (range)	27 (21-42)	27 (16-37)	0.700
Duration of discharge before treatment (months), median (range)	15 (1-360)	12 (3-240)	0.500
Smoking, n (%)	13 (38%)	9 (23%)	0.200
Alcohol consumption, n (%)	0 (0%)	3 (7%)	0.200
Comorbidity, n (%)	7 (21%)	5 (13%)	0.300
History of anal fistula surgery, n (%)	5 (14%)	6 (15%)	0.900
External orifice			1,000
Single	30 (88%)	34 (89%)	
Multiple	4 (12%)	4 (11%)	
Type of fistula, n (%)			
Intersphincteric	27 (79%)	21 (55%)	0.03
Transsphincteric	5 (18%)	11 (29%)	0.3
Exstrasphincteric	0 (0%)	1 (0.3%)	
Suprasphincteric	0 (0%)	0 (0%)	
Horseshoe	2 (6%)	3 (8%)	0.4
Discharge frequency, n (%)			0.005
Continuous	11 (32%)	25 (66%)	
Intermittent	23 (68%)	13 (34%)	
Number of irrigations, median (range)	2 (1-5)	3 (1-5)	0.1
Duration of follow-up before treatment (months), median (range)	10 (5-16)	8 (4-15)	0.08

after a mean follow-up period of 7.4 months. However, Ozturk et al. reported a success rate of 60% in patients treated by LAFT in a series of 20 patients, and it was found that this success rate decreased in long-term follow-ups. In the previous LAFT studies, these success rates are caused by combined additional procedures, such as bridging with seton, internal orifice closure during primary surgery, and excision of the distal part of the fistula tract, rather than laser treatment alone. Furthermore, the authors stated that the LAFT technique could not close secondary tracts.[9]

However, the authors of this study believe that silver nitrate in solution form can ablate the primary and secondary tracts. Some disadvantages of using LAFT include anesthesia requirements, the high cost, and the possibility of widening the fistula diameter in some patients. This study achieved complete healing using only silver nitrate irrigation and without applying combined processes. Further studies with silver nitrate combined with other procedures, such as internal orifice closure, bridging with seton, internal orifice closure, or excision of the distal part of the fistula tract, may cause higher success rates in the future. In the LAFT technique, the fistula is healed by ablating the epithelial tissue of the fistula tract using laser energy.

This study used silver nitrate solution as a corrosive chemical agent instead of a laser probe for ablating the epithelial tissue of the fistula tract, and it showed similar healing rates. Silver nitrate is a cost-effective treatment and can be applied in outpatient conditions without anesthesia. This makes this treatment advantageous compared with the LAFT technique. The silver+ (Ag+) ion, the active biological form of the silver molecule, shows its effect in two phases. In the early phase, Ag+ ions denature proteins. In the late phase, the silver proteinate progressively ionizes and thus creates a slow but long-lasting effect. The Ag+ ions also have an antiseptic effect by denaturing bacterial cell wall proteins. This study found that the silver nitrate molecule causes fistulas to heal with its corrosive and antibacterial effects.[10-12] Silver nitrate treatment for anal fistulas was described for the first time by Attaallah et al.[6] in 2014. After irrigating anal fistulas with 1% silver nitrate, complete clinical healing was achieved in 52% of patients.[13] Although a higher concentration of silver nitrate (30%) was used in this study, a higher healing rate was not achieved compared with the previous study. The authors of this study believe that further studies need to use combined methods, such as internal orifice closure combined with silver nitrate irrigation, which could improve the outcomes. Doll and Vassiliu[14] reported a 27% success rate in a series of 15 patients who were treated with 1% silver nitrate irrigation. The authors stated the relatively low success rate in this study to have possibly been due to the short follow-up period after treatment.

In a study conducted by Tomasello et al.[15], after using Argentum-quartz solution as a corrosive agent, they stated that two out of three patients had complete healing. Placer-Galán et al.[16] reported a complete healing rate of 44.4% after treatment with silver nitrate 1% solution in recurrent or persistent anal fistulas. The authors stated that in a recurrent or persistent complex anal fistula, local conservative treatment with a 1% silver nitrate solution instillation is an alternative that should be considered to reduce the risk of incontinence.[16] In a series of 76 patients treated by Iqbal et al.[17], the complete healing rate was 76.3% after using a 1% silver nitrate solution. The high rate of complete healing in that study can be explained by the combination of silver nitrate irrigation with curettage of the fistula tract with a blunt-tipped cannula before irrigation. In a series of 113 infants treated by Utsunomiya et al.[18], 30% silver nitrate solution was used, and it was reported that 76% of the patients healed without serious complications. In a prospective study of 49 patients with intersphincteric and transsphincteric fistula by Kaya et al.[19], a 67% complete healing rate was achieved after using 20% silver nitrate solution.

Intermittent discharge frequency was a good prognostic factor for healing (Table 2). It can be explained by the minimal complications, and smaller fistulas may have closed easily with fibrosis after silver nitrate irrigation. Furthermore, the longer follow-up period after treatment was also a good prognostic factor for healing. This can be explained by fibrosis being a time-consuming process. Curettage of the fistula tract with an endoscopic brush before irrigation may have been a cause of higher rates of complete healing in that study. No serious complications were observed in this study. The study used a 30% silver nitrate solution as effectively as it was reported by the previous studies.[14-19] Due to the coronavirus disease pandemic, most elective surgeries became unavailable, patient waiting times were prolonged, patients became afraid of hospitalization, and operations for benign diseases, such as anal fistula, were postponed. In such situations, outpatient conservative treatments with silver nitrate may be a good alternative treatment for anal fistulas. However, based on these prospective results, more comprehensively planned, prospective, randomized controlled studies need to be conducted.

Conclusion

This study showed that 30% silver nitrate is an effective and safe treatment for anal fistulas. Due to its advantages of being non-invasive and cost effective; having acceptable healing rates, no major complications, and no need for anesthesia; and providing outpatient applicability, it can be used as the

first-line anal fistula treatment. Surgical treatment is still an option for patients whose silver nitrate treatment fails.

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Ethics

Ethics Committee Approval: This study was approved by the Marmara University Faculty of Medicine Ethics Committee (approval number: 09.2020.681, date: 24.07.2020).

Informed Consent: All patients provided written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: W.A., A.T., Concept: W.A., A.T., Design: W.A., A.T., Data Collection or Processing: W.A., A.T., Analysis or Interpretation: W.A., A.T., Literature Search: W.A., A.T., Writing: W.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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