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Comparison of Efficacy and Safety Of 2% Nigella Sativa Ointment with 2% Diltiazem Ointment in the Management of Chronic Anal Fissure

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Author`s Contribution

[1,2]Substantial contributions to the conception or design of the work; or the acquisition, [4]Active participation in active methodology, [2,3]analysis, or interpretation of data for the work, [5,6]Drafting the work or revising it critically for important intellectual content

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ABSTRACT

Objective: To compare the efficacy and safety of 2% diltiazem ointment with 2% nigella sativa ointment in the healing of chronic anal fissure (AF).

Methodology: This comparative experimental study was done at the Department of Pharmacology and Department of Surgery LUMHS, Jamshoro from October 2023 to March 2024. Diagnosed cases of chronic anal fissure of both genders and aged > 12 years were included and divided into two groups. Patients of group A underwent topical application of 2% Diltiazem (DTZ) ointment over the anal verge twice daily for a period of 6 weeks along with sitz bath. Patients of group B underwent topical application of 2% Nigella sativa ointment (NSO) ointment over the anal verge twice daily for a period of 6 weeks with sitz bath. Patients were evaluated on the basis of severity of pain and overall effect on the quality of life QOL at 1st visit and after 6th week of treatment. After completion of 6 weeks of treatment plan both groups were assessed for healing of fissure and possible side effects during treatment. All the information was collected via study proforma.

Results: Median duration of complaints in groups A and B was 8 and 10 months respectively. Males were in majority in both groups. Patients' VAS score decreased from 5.8±8.2 to 3.5±6.3 in DTZ group whereas in NSO group it decreased from 7.8±0.96 to 1.47±0.8 after 6th week. WHOQOL-BREF score in DTZ group did not show notable improvement in all four domains whereas patients in NSO group showed significantly elevated WHOQOL-BREF scores after 6th week of treatment. Overall fissure healing rate was significantly higher in NSO group (80.3%) compared to the DTZ group ($p<0.05$).

Conclusion: As per study conclusion, treatment with NSO was observed to be safer and more effective in comparison to DTZ.

Keywords: Chronic Anal Fissure, DTZ, NSO, Pain, Healing.

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Introduction

Anal fissure is common in both genders and commonly affect young and otherwise healthy individuals.[1] The global annual incidence worldwide is 0.11% (1.1 cases/1000-person years.[2] Incidence rates also differ by age, being notably higher among females 12–24 years, and males aged 55–64 years. In Pakistan, the estimated incidence of anal fissure is 11%.[3] Anal fissures are commonly caused by damage to the lining of the anus or anal canal in individuals with constipation, long-term diarrhea, low fiber consumption, trauma and previous anal surgery.[4] However, the exact cause of it remains uncertain, because few recent evidences, however, suggests that anal

fissures are most closely related to heightened resting pressure and the internal anal sphincter spasm. Anal fissure can be either acute or chronic depending on the duration. The treatment of anal fissure has evolved over last few years with the development of medical therapies aimed at reducing sphincter hypertonia.[5] In other cases, surgical intervention maybe necessary. Some medical treatments advised by surgeons include laxatives, stool softeners, topical analgesics, nitroglycerin, calcium channel blockers, and botox. Surgical options include lateral anal sphincterotomy but it can result in permanent fecal incontinence and other complications.[6]

Amongst the accessible conservative treatment options, the 2% diltiazem cream has recognized to be an effective and well-tolerated therapy for the anal fissure. It is a non-dihydropyridine calcium blocker, an effective and well-tolerated treatment for anal fissure, acting by blocking L-type calcium channels in smooth muscle to relax the internal anal sphincter, enhance anodermal flow of blood, afford early pain relief approximately during one week, and promote substantial healing of chronic fissure.[7] The healing process may take 6 weeks with good success rate but comes with common side effects like headache, dizziness, itching and rash at application site, and in some cases contact dermatitis. Nigella sativa is an herbaceous plant.[8] Its most prominent beneficial properties include anti- inflammatory, anti-bacterial and anti-oxidant, which contribute to wound healing attributed mainly to its active constituent Thymoquinone.[9]

However due to the developing concerns regarding adverse effects, potential drug interactions and the expenditure of synthetic medications have led to a progressively increasing interest in herbal remedies, and the medicinal plants widely used by the population for the management. Subsequently the *Nigella sativa* has been shown to promote wound healing of the skin through its anti-inflammatory properties, antioxidant activities, and capability to stimulate tissue regenerations.[10] Numerous studies have reported improvements in the symptoms of hemorrhoid like bleeding, pain, rectal prolapse, itching, number of hemorrhoidal cushions, enhanced wound healing and recurrence,[11-13] whereas comparable evidence for anal fissure remains inaccessible. Hence this study was carried out to assess the role played by nigella sativa in healing of chronic anal fissure with a potential chance of avoiding problematic side effects and compared by 2% diltiazem ointment as a medical treatment modality add to the list of other agents used in healing of anal fissure.

Methodology

This comparative experimental study was done at the Department of Pharmacology and Department of Surgery LUMHS, Jamshoro. Study was done during a period of 6 months from October 2023 to March 2024 after taking ethical approval from Ethical review committee of LUMHS Ref no lumhs/rec/61. Diagnosed cases of chronic anal fissure of both genders and all ages were included in the study. All diagnosed cases of acute anal fissure, hemorrhoids, inflammatory bowel disease and patients with history of bowel disease were excluded from the study. A total of 60 patients' sample size was calculated by using Raosoft sample size calculator by using anal fissure incidence of 11%, with 95% confidence level and 5% margin of error.14 Non-surgical treatment options for chronic anal fissure like diltiazem have a good healing rate but often cause side effects like headache, itching and contact dermatitis. This study was carried out to assess the role played by nigella sativa based on its wound healing, anti-inflammatory and anti-oxidant properties attributed mainly to its active constituent Thymoquinone; in healing of chronic anal fissure with a potential chance of avoiding troublesome side effects caused by other agents.12 All patients who fulfilled the inclusion criteria were enrolled in the study. Written informed consent was taken from each patient. Every patient went thorough pre-treatment evaluation that included the patient's medical history, a general physical examination, and a clinical fissure inspection. Patients of group A underwent topical application of 2% DTZ ointment over the anal verge twice daily for a period of 6 weeks along with sitz bath. Patients of group B underwent topical application of 2% NSO ointment over the anal verge twice daily for a period of 6 weeks with sitz bath. Patients were evaluated on the basis of severity of pain according to Visual analogue scale(VAS) overall affect on the quality of life according to WHOQOL-BREF scale at 1st visit and after 6th week of treatment.15,16 After completion of 6 weeks of treatment plan both groups were assessed for healing of fissure and possible side effects during treatment. All the information was collected via study proforma. Data was analysed on SPSS version 26. The quantitative variables were calculated in the form of mean and standard deviation. Significance of mean was tested by paired Student's t test. Significance of data was mentioned according to p value ≤ 0.05.

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Results

A total of 60 individuals divided into two groups were studied to compare the efficacy and safety of DTZ & NSO in healing of chronic anal fissure. Mean age of patients of group A was 39.20±12.35 years and mean age of group B patients was 38.19±13.65 years (p=0.767). Mean duration of complaints in patients of group A was 7.93+2.16 months and in patients of group B was 10.33+1.70 months (p=0.003) Males were in majority in both groups as compared to females. Most common reported complaint was pain which was present in 30 (100%) patients of group A and 30 (100%) patients of group B. Bleeding was 25 (84%) in group A and 21 (71%) in group B while constipation was 26 (86%) in group A and 25 (86%) in group B. In group A, patients had a baseline of VAS of 5.8±8.2, which slightly decreased to 3.5±6.3 after 6th week of treatment not showing much improvement (p=0.052). On the contrary, VAS in group B decreased significantly from 7.8±0.96 to 1.47±0.8 after 6th week denoting minimal pain (p=0.002). (Table I)

WHOQOL-BREF score in group A did not show notable improvement in all four domains, owing mainly to higher incidence of side effects in majority of patients (p >0.05). Whereas patients in group B showed significantly elevated WHOQOL-BREF scores after 6th week of treatment (p<0.05). (Table II)

Table III: Reported drug related side effects in DTZ & NSO groups.

Study group	DTZ (n=30)		NSO (n=30)	
Side effects	No. of patients	%	No. of patients	%
Headache	16	53%	0	0
Contact dermatitis	4	13%	0	0
Burning sensation per rectum	8	26%	1	3.%
Perianal itching	12	40%	3	10%
Rash	6	20%	0	0

Table IV: Comparison of overall fissure healing in both study groups. (n=60)

Variables		Study groups		Total
		DTZ	NSO	
Fissure healing	Yes	18	25	43
		60.0%	83.3%	71.7%
	No	12	5	17
		40.0%	16.7%	28.3%
Total		30	30	60
		100.0%	100.0%	100.0%
p-value			***0.045****	

Headache (53%), contact dermatitis (13%), burning sensation (26%), perianal itching (40%) and rash (20%) were reported in patients of group A. While group B reported side effects such as perianal itching and burning per rectum in only 10% and 3% patients respectively; denoting a much safer profile than group A. (Table III)

Fissure healing was seen in 60% (18) patients in DTZ group, while 83% (25) patients in NSO group showed fissure healing. These healing rates were noted through

Table I: Changes in VAS scores before & after treatment.

Variable	Study Group		Mean± SD	p-value
Mean Visual Analogue Score	DTZ (n=30)	Before treatment	5.8±8.2	0.052*
		After treatment	3.5±6.3	
	NSO (n=30)	Before treatment	7.8±0.96	0.002*
		After treatment	1.47±0.8	

Table II: Changes in WHOQOL-BREF scores of DTZ before & after treatment.

Variable	Study group	Domains		Mean± S.D	p-value
Mean WHOQOL-BREF score	DTZ (n=30)	Physical	Before treatment	58.4±8.9	0.063*
			After treatment	70.6±9.1	
		Mental	Before treatment	39.8±10.1	0.054*
			After treatment	50.6±11.8	
		Social	Before treatment	55.9±14.2	0.071*
			After treatment	64.6±11.4	
		Environmental	Before treatment	44.2±10.2	0.052*
			After treatment	53.7±12.8	
Mean WHOQOL-BREF score	NSO(n=30)	Physical	Before treatment	49.4±1.5	0.001*
			After treatment	70.2±0.6	
		Mental	Before treatment	34.8±2.2	0.004*
			After treatment	61.9±1.5	
		Social	Before treatment	51.6±2.6	0.002*
			After treatment	64.2±1.3	
		Environmental	Before treatment	46.9±2.1	0.001*
			After treatment	60.3±1.3	

general physical examination of anal area for signs of healing and through follow up of VAS and WHOQOL-BREF scores after 6th week of treatment. (Table IV)

Discussion

Surgical treatment of chronic anal fissures may lead to permanent fecal incontinence.[17] In contrast, topical treatments are less costly and pose a lower risk of serious complications. Healing rates and patient compliance with topical treatments differ across studies. This study was conducted to compare healing rates and side effects in patients with chronic anal fissures treated with topical DTZ versus NSO, aiming to determine the preferred first-line non-surgical therapy. Each group, DTZ and NSO, consisted of 30 patients. The mean age in group A was 39.20±12.35 years, while group B had a mean age of 38.19±13.65 years. Additionally, group A comprised 24 males (40.0%) and 6 females (10.0%), whereas group B included 20 males (33.3%) and 10 females (16.7%). The p-value of >0.05 indicates no statistically significant difference in gender distribution and mean age between the two groups. These findings align with the study by García MI et al, which included 70 patients, 37 of whom were men.[18] The average age of participants in our study was 49.04 years, ranging from 45.53 to 52.55 years. In the study by Aasole AG et al reported that the average age of the patients was 43.1±7.4 years.[19] The male predominance observed in these studies might be attributed to several factors. Men may have a higher prevalence of risk factors such as heavy lifting or straining, which can contribute to the development of anal fissures as seen in a study by Banerjee et al.[20]

In this study, the most commonly reported symptom was a combination of pain and constipation. Consistently, Salem AE et al et al reported that pain during bowel movements was the most common complaint among their patients, noted by nearly 90% of them.[21]

In this study, majority of group A patients reported troublesome side effects like headache, perianal itching, contact dermatitis and burning per rectum whereas few group B patients reported side effects which were negligible. Overall, the findings indicate that specific side effects may be more pronounced with one technique over the other. Future studies should aim to further elucidate these differences and explore strategies to minimize adverse effects, enhancing the safety was seen in 60% patients in group A and 83% patients in group and efficacy of treatment for chronic anal fissures. Fissure healing B. This shows superior efficacy of NSO in healing of anal fissure. Consistently Tavakoli-Dastjerdi S et al reported that the herbal medicine resulted in a notable decrease in pain compared to diltiazem ($P < 0.001$).[22] It also demonstrated a significant impact on wound healing by the end of the study period ($P < 0.001$).[22] However, these findings cannot be conclusively recommended due to several limitations. Overall this study, showed the significant treatment outcomes by *Nigella sativa*, offering emerging evidence for its potential role in the management of chronic AF. Conversely, due to the limited availability of comparable similar studies and confident methodological limitations, the findings cannot be considered finally conclusive. Hence, further large-scale, well-designed research studies incorporating pathophysiological evidence are suggested to validate and strengthen these findings and the support their interpretation into proper use clinically.

Conclusion

As per study conclusion, NSO has a higher healing rate of chronic anal fissure as well as a safer side effect profile in comparison to DTZ. Moreover, well-designed and large-scale studies are recommended to thoroughly investigate the potential effectiveness and safety of this herbal medicine i.e. nigella sativa in broader clinical settings.

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