

## Comparison of outcome of botulinum toxin injection with and without glyceryl trinitrate in chronic anal fissure in terms of post operative pain and healing

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### Abstract

**Objective:** To compare the outcome of botulinum toxin injection with and without glyceryl trinitrate with respect to postoperative pain and healing in the treatment of anal fissures.

**Method:** The prospective, comparative study was conducted at the Department of General Surgery, Mayo Hospital, Lahore, Pakistan, from September 1, 2021, to August 31, 2022, and comprised adult chronic anal fissure patients of either gender. They were randomised using the lottery method into group A which received botulinum toxin injection, and group B which received botulinum toxin injection plus 1g of 0.2% topical glyceryl trinitrate cream. Post-operative pain was measured 24 hours after the procedure using the visual analogue scale. Healing was assessed by examining the wound for the appearance of granulation tissue 4 weeks post-procedure. Data was analysed using SPSS 26.

**Results:** Of the 88 patients, 44(50%) were in group A; 32(72.7%) males and 12(27.3%) females with mean age  $33.91 \pm 14.8$  years. There were 44(50%) patients in group B; 35(79.5%) males and 9(20.5%) females with mean age range  $36.33 \pm 14.9$  years. The mean postoperative pain at 24 hours in group A was  $4.67 \pm 1.16$  and it was  $3.06 \pm 0.65$  in group B ( $p=0.009$ ). In group A, 23(69.7%) patients showed complete healing at 4 weeks compared to 30(90.9%) in group B ( $p=0.030$ ).

**Conclusion:** Botulinum toxin injection with glyceryl trinitrate could be considered as first line of treatment for chronic anal fissure in patients who refuse surgery and with previous sphincter surgery.

**Keywords:** Anal fissure, Lateral internal anal sphincterotomy, Botulinum toxin injection, Glyceryl trinitrate, Granulation tissue. (JPMA 74: 1245; 2024) DOI: <https://doi.org/10.47391/JPMA.9726>

### Introduction

A condition of the anal canal, known as anal fissure (AF), is characterised by the development of cracks or tears on the stratified squamous epithelium of the anoderm.<sup>1</sup> Due to the tear's location in the squamous region of the epithelium, defecation is painful and results in fresh bleeding. AF significantly lowers quality of life (QOL), results in lost workdays, and is quite uncomfortable.<sup>2</sup> In the United States, there are 1,100 (700-1,700) AF cases per 100,000 people, or a 7.8% lifetime risk. Most AFs are small and are believed to go away on their own, but those that persist for >4-6 weeks are frequently referred to as chronic AF.<sup>3</sup> Although the exact cause of AF is unknown, it is believed that the majority of fissures are caused directly by the passage of firm stools or diarrhoea.<sup>4</sup>

Compared to other forms of medical therapy, surgical operations have consistently greater success rates (about

89%), but they are also more expensive and carry a significant risk of long-term anal incontinence.<sup>5</sup> Many topical or intravenous (IV) drugs have been suggested as pharmacological, or chemical sphincterotomy, alternatives to surgery over the past three decades. Chemical sphincterotomy has made considerable use of injections of botulinum toxin.<sup>6</sup> A botulinum toxin injection lowers resting anal pressure by preventing presynaptic nerve terminals from releasing acetylcholine. Glyceryl trinitrate, a topical vasodilator, causes the muscle fibres of the anal sphincter to relax, reducing sphincter hypertonia and pressure in the anal canal, enhancing local vascularisation, allowing the AF to contract and eventually heal.<sup>7</sup>

According to a study, botulinum toxin injections were effective in 61.5% of cases, and in 94% of cases when combined with glyceryl trinitrate ( $p=0.05$ ).<sup>8</sup> According to another study, second-line botulinum toxin/glyceryl trinitrate prevented lateral internal sphincterotomy in 85-90% cases.<sup>9</sup>

The current study was planned to compare the outcome of botulinum toxin injection with and without glyceryl trinitrate in the treatment of chronic AF.

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## Patients and Methods

The prospective, comparative study was conducted at the Department of General Surgery, Mayo Hospital, Lahore, Pakistan, from September 1, 2021, to August 31, 2022. The sample size was estimated using the formula:  $n = Z^2 \frac{P_1(1 - P_1) + P_2(1 - P_2)}{d^2}$  with 5% level of significance, 90% power of test, expected percentage of botulinum toxin injection 61.5% and botulinum toxin injection with glyceryl trinitrate 94%.<sup>10</sup>

After approval from the institutional ethics review board of the King Edward Medical University, Lahore, the sample was raised using non-convenience probability sampling from among those admitted through the Surgical outpatient department (OPD) of Mayo Hospital. Those included were all adult patients of either gender who had been diagnosed as cases of chronic AF, which was defined as fissure persisting for >4 weeks, or recurrent fissure with sign and symptoms of pain during defecation, and mucosal tear on digital rectal examination. Those with signs and symptoms of AF within the preceding 7 days, and no significant finding on digital rectal examination, having any other perianal inflammatory disease, like tuberculosis (TB), Crohn disease of any colorectal or perianal mass/malignancy were excluded. Informed consent was obtained from all the patients.

After collecting demographic data, the patients were randomised using the lottery method into groups A and B. Patients in group A underwent 0.2 ml botulinum toxin injection at each site into the inter-sphincteric plane away from AF at 3 O'clock and 9 O'clock at lithotomy position under strict aseptic measures. Group B patients underwent 0.2ml botulinum toxin injection at each site into the inter-sphincteric plane away from AF at 3 O'clock and 9 O'clock at lithotomy position under strict aseptic measures plus 1g 0.2% topical glyceryl trinitrate cream 8 hourly with dose of 1g on the middle finger's tip and applied around the anal canal circumferentially. All examination and procedures were done by consultants who had experience of >5 years dealing with colorectal and perianal diseases.

Outcome was recorded in terms of postoperative pain measured at 24 hours after the procedure using the visual analogue scale (VAS). Healing of anal fissure was assessed by examining the wound for the appearance of granulation tissue 4 weeks post-procedure.

Data was analysed using SPSS 26. Quantitative variables were presented as mean  $\pm$  standard deviation, while qualitative variables were presented as frequencies and percentages. Comparison of fissure healing between the groups was done using chi-square test, while comparison of pain score was done using t-test.  $P \leq 0.05$  was taken as

statistically significant.

## Results

Of the 88 patients, 44(50%) were in group A; 32(72.7%) males and 12(27.3%) females with mean age  $33.91 \pm 14.8$  years. There were 44(50%) patients in group B; 35(79.5%) males and 9(20.5%) females with mean age range  $36.33 \pm 14.9$  years. In group A, 22(50%) patients were aged 18-30 years, 13(29.5%) aged 31-45 years and 9(20.5%) aged 46-60 years. The corresponding values in group B were 24(54.5%), 13(29.5%) and 7(16%).

The mean postoperative pain at 24 hours in group A was  $4.67 \pm 1.16$  and it was  $3.06 \pm 0.65$  in group B ( $p=0.009$ ). In group A, 23(69.7%) patients showed complete healing at 4 weeks compared to 30(90.9%) in group B ( $p=0.030$ ) (Table 1). Wound healing status was further stratified according to gender (Table 2).

**Table-1:** Visual analogue score (VAS) and wound healing by granulation tissue in the study groups.

	Group A (Botulinum toxin only) (n=44)	Group B (Botulinum toxin with Glyceryl trinitrate) (n=44)	p-value
VAS for postoperative pain	$4.67 \pm 1.16$	$3.06 \pm 0.65$	0.009
Wound healing with granulation tissue after 4 weeks of surgery	30 (68.1 %)	39 (88.6 %)	0.030

**Table-2:** Stratification of wound healing with respect to gender.

Gender	Wound Healing	Group A n (%)	Group B n (%)	p-value
Male	Yes	9 (20.4)	17 (38.6)	0.045
	No	5 (11.3)	3 (6.81)	
	<b>Total</b>	14 (31.8)	<b>18 (40.9) ??</b>	
Female	Yes	8 (18.1)	18 (40.9)	0.023
	No	8 (18.1)	3 (6.81)	
	<b>Total</b>	16 (36.3)	21 (47.7)	

## Discussion

Although the exact cause of AF is unknown, it is believed that most AFs are caused directly by the passage of firm stools or diarrhoea.<sup>2</sup> However, only 25% of AF patients in a study on the origin of the condition reported chronic constipation. Just two women with AF had it prior to delivery in a prospective trial of 165 women throughout the final three months of pregnancy and the first 10 weeks after giving birth, while 25(15%) women developed it later, with 50% developing it more than two weeks post-delivery.<sup>11</sup> Crohn's disease, ulcerative colitis, human immunodeficiency virus (HIV) infection, neoplasia, syphilis, and TB can all be implicated in the discovery of many fissures or AFs in an uncommon lateral position.<sup>12</sup>

Two pharmacological approaches regarding the injection of botulinum toxin and application of nitroglycerin ointment have been used to treat chronic AF while averting the risk of permanent injury to the internal anal sphincter. The use of various topical organic nitrate preparations has been associated with healing rates ranging from 47% to 86% as well as a substantial reduction in pain within 5 minutes after the application of the ointment.<sup>13</sup> A study of 57 patients treated with 15-20 units of botulinum toxin showed that the higher dose was more effective than the lower dose with respect to long-term healing, and was not associated with a higher rate of complications.<sup>14</sup> The current study found that treatment with nitrates plus botulinum toxin was effective as an alternative to surgery for patients with chronic AF. Furthermore, combination of nitrates plus botulinum toxin was more effective than the botulinum toxin alone.

The current study found that toxin injected into the internal sphincter did not spread to the external sphincter, and it was easier to inject the toxin directly into the internal anal sphincter. The role of the weakening of the external anal sphincter in the treatment of chronic AF remains uncertain. Adverse effects of treatment were reported only by the patients who were treated with topical nitrates.<sup>3</sup> When topical nitrate preparations are used, there is a substantial incidence of transient headache (19-44%). Headache is particularly evident at higher concentrations of the drug. Anal burning as a result of treatment with nitroglycerin has also been reported.<sup>15</sup>

A study to determine the outcome of botulinum toxin injection and glyceryl trinitrate for the management of chronic AF reported AF healing in up to 94% compared to glyceryl trinitrate cream 60-71%.<sup>16</sup> Pain (68%), bleeding from wound site (25%) and wound sepsis (16%) were the common complications, followed by transient urinary retention (9%), incontinence (8%) and recurrence (7%).<sup>16</sup>

Another study showed that in uncomplicated chronic AF cases, the recovery rate was between 60% and 80%. The injection had a good safety profile, could be given as an outpatient procedure, and did not result in any long-term damage to the organ of continence.<sup>17</sup>

The stated efficacy for fissure healing, however, appears to be quite variable, and the research available is heterogeneous. In a study, after two months of follow-up after the internal anal sphincter received an injection of botulinum toxin 25 units, healing rate was 80%, and it was 90% following a second injection.<sup>18</sup> In another trial, 192 patients got an average dose of 40 units of botulinum toxin. The median follow-up was 9 months (range: 2-50 months), and 86.5% of the patients had a good outcome.<sup>19</sup>

A total of 1,577 patients received either dysport or botox treatments in a meta-analysis that included 34 prospective investigations. The reported effectiveness ranged 33-96%.<sup>20</sup>

How patient characteristics affect a patient's reaction to a botulinum toxin injection is a matter poorly understood. In a study, patient variables, such as gender, the presence of a sentinel pile, the length of the symptoms, the location of the fissure, and the preceding symptoms, did not have a statistically significant impact on the healing of fissures following botulinum toxin injections.<sup>21</sup> Besides, patient characteristics, such as disease duration, fissure type and location, and past topical therapy had no appreciable impact on how the patient responded to the toxin, and there was a non-significant trend towards faster recovery and shorter symptom duration in women.<sup>21</sup>

The current study has the limitation of being conducted at a single centre with a relatively small sample size. More multicentre studies with larger sample sizes are recommended.

## Conclusion

Botulinum toxin injection with glyceryl trinitrate could be considered as the first line of treatment for chronic AF for patients who refuse surgery, who have had previous sphincter surgery, or who are at a particular risk of incontinence with sphincterotomy.

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**Conflict of Interest:** None.

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#### Author Contribution:

SH: Concept, drafting, final approval and agreement to be accountable for all aspects of the work.

ASA, ARH, AA: Data acquisition, analysis, interpretation, revision, final approval and agreement to be accountable for all aspects of the work.

IA: Final approval and agreement to be accountable for all aspects of the work.