

**Anal Botulinium toxin injection for chronic anal fissure: Efficacy and safety analysis in a retrospective cohort of 224 patients**

**Kronik anal fissür için anal Botulinium toksin enjeksiyonu: 224 hastadan oluşan retrospektif bir kohortta etkinlik ve güvenlik analizi**

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**Background and Aims:** The aim of this retrospective study is to evaluate the relationship between the number of injection sites and healing outcomes in 224 patients with chronic anal fissure who underwent anal Botulinum toxin treatment. **Materials and Methods:** The medical records of 224 patients who received anal Botulinum toxin treatment for chronic anal fissure were retrospectively analyzed. Patients were categorized into three groups based on the number of injection sites: Group A (two injection sites, n = 34), Group B (three injection sites, n = 109), and Group C (four injection sites, n = 81). Each injection contains 20 IU of Botulinum toxin. Healing outcomes, pain reduction, wound healing, and symptom resolution were evaluated. A comprehensive analysis of patient records and clinical data was performed. Demographic information, treatment details, healing outcomes, and adverse events were assessed. **Results:** Cox regression analysis revealed a significant association between the number of injection sites and healing outcomes. At all three post-operative time points, patients treated at multiple sites (Group C) reported higher recovery levels compared to patients treated at two sites (Group A). **Conclusion:** This study demonstrated a significant relationship between the number of injection sites treated with anal Botulinum toxin and healing outcomes in patients with chronic anal fissures. These findings highlight the importance of considering the number of injection sites. The study contributes to the understanding of anal Botulinum toxin treatment for chronic anal fissure, emphasizing its potential to improve patient care and overall quality of life.

**Key words:** Botulinum toxin, anal fissure, injection site numbers, healing

**Giriş ve Amaç:** Anal Botulinium toksin tedavisi uygulanan kronik anal fissürlü hastada enjeksiyon bölgelerinin sayısı ile iyileşme sonuçları arasındaki ilişkiyi değerlendirmektir. **Gereç ve Yöntem:** Ocak 2012 ve Mart 2023 tarihleri arasında anal Botulinium toksin tedavisi uygulanan 224 hasta kaydı retrospektif olarak analiz edildi. Hastalar enjeksiyon bölgelerinin sayısına göre üç gruba ayrıldı: Grup A (iki enjeksiyon bölgesi, n = 34), Grup B (üç enjeksiyon bölgesi, n = 109) ve Grup C (dört enjeksiyon bölgesi, n = 81). Her enjeksiyonda 20 IU Botulinium toksin uygulanmıştı. İyileşme sonuçları yara iyileşmesi ve semptomların giderilmesi olarak 15, 30 ve 90. günde değerlendirilmiştir. Demografik bilgiler, tedavi ayrıntıları, iyileşme sonuçları ve tedaviye ilişkin olumsuz olaylar kaydedildi. **Bulgular:** Cox regresyon analizi, enjeksiyon bölgesi sayısı ile iyileşme sonuçları arasında anlamlı bir ilişki olduğunu ortaya koydu. Ameliyat sonrası her üç zaman noktasında da, ikiden fazla bölgede tedavi edilen hastalar (Grup C), iki bölgede tedavi edilen hastalara (Grup A) kıyasla daha yüksek iyileşme seviyeleri bildirmiştir. **Sonuç:** Kronik anal fissürü olan hastalarda anal Botulinium toksin ile tedavi

edilen enjeksiyon bölgelerinin sayısı ile iyileşme sonuçları arasında ilişki vardır. Enjeksiyon bölgelerinin sayısının artması hem yara iyileşmesini hem de semptomların azalmasını arttırmaktadır.

Anahtar kelimeler: Enjeksiyon bölgesi sayıları, anal fissür, Botulinium toksini

## INTRODUCTION

Chronic anal fissure is a distressing condition characterized by a painful tear in the anoderm. It affects individuals across various age groups and can significantly impact their quality of life (1,2). A chronic anal fissure is defined as a fissure in the lining of the anal canal that persists for more than six weeks (3). Unlike acute anal fissures that may heal within a few weeks, chronic fissures are characterized by a prolonged duration and often require specialized management and treatment approaches. Traditional treatment approaches, such as topical medications, dietary modifications, and surgical interventions like sphincterotomy, have been utilized to alleviate symptoms and promote healing. The treatment efficiency of lateral internal sphincterotomy is very high, but the risk of incontinence is higher than other treatment methods (4). However, some patients experience persistent symptoms or are reluctant to undergo surgical procedures due to associated risks and complications (1,5).

In recent years, anal Botulinium toxin (BT) treatment has emerged as a minimally invasive therapeutic option for managing chronic anal fissure (6). Botulinum toxin type A, commonly known as Botox, is a neurotoxin derived from *Clostridium botulinum*. When injected into the internal anal sphincter, BT induces temporary relaxation of the sphincter muscle, alleviating spasm and improving blood flow. This relaxation facilitates the healing process and provides relief from pain (7).

While numerous studies have investigated the efficacy of anal BT treatment, there is a need for comprehensive research utilizing a larger patient population to provide further evidence supporting its clinical benefits. However, despite its growing popularity, several aspects of anal BT treatment for chronic anal fissure remain under investigation. One critical area of research pertains to the optimal dosage and injection sites. The efficacy of different dosage ranges and the impact of injection site selection on treatment outcomes are still subjects of debate and exploration (1).

Therefore, this retrospective study aims to evaluate the outcomes of anal BT treatment in 224 patients with chronic anal fissures. We will assess the correlation between healing outcomes

and the numbers of injection sites, aiming to identify any potential association between injection location and treatment response.

## **MATERIALS and METHODS**

### **Study Design and Participants**

This retrospective study was conducted at a single center, Istanbul Florence Nightingale Hospital, with ethical approval obtained from the Demiroğlu Bilim University Institutional Review Board (reference number KAEK/2023.01.5). The study included 224 patients diagnosed with chronic anal fissure who underwent BT treatment at the hospital between January 2012 and March 2023. Of the participants, 102 were female and 122 were male. The numbers of injections were categorized into three groups: Group A (two injection sites, n = 34), Group B (three injection sites, n = 109), and Group C (four injection sites, n = 81). Healing outcomes, including pain reduction, wound healing, symptom resolution, side effects and complications were assessed.

### **Treatment Procedure**

The BT injection therapy was performed by an experienced surgeon at Istanbul Florence Nightingale Hospital. The procedure involved the administration of BT injections into the internal anal sphincter, targeting the affected site based on clinical evaluation. The number of injection sites treated varied among patients, with some receiving injections in 2, 3, or 4 sites. The number of injections varied according to the number and depth of the fissure. The number of injections was increased in deeper and more numerous fissures. Each site was injected with a standardized dosage of 20 IU BT type A (Botox®) manufactured by Allergan (Dublin, Ireland) in 1 ml of solution under a short time general anesthesia with mask. Position for procedure was lithotomy. In the study, a 22-gauge (G) needle was used for the injection of the Botulinum toxin. The use of a 22G needle is a common practice for delivering injections in medical procedures. It is an appropriate size for administering the Botulinum toxin accurately and safely into the target area of the internal anal sphincter.

### **Follow-up Visits**

Patients were scheduled for follow-up visits at 15, 30, and 90 days after the BT treatment. During these visits, healing outcomes were assessed through clinical examination and evaluation of patient-reported symptoms. The primary outcome measure was the healing rate,

determined by the absence of fissure-related symptoms such as pain and bleeding and re-epithelization of fissure.

### **Data Collection**

Data were collected from electronic medical records and patient charts maintained at Istanbul Florence Nightingale Hospital. Demographic information, including age and gender, was recorded for each patient. Clinical characteristics such as the duration of the fissure, associated symptoms, and previous treatment history were documented. Information regarding the numbers of injection sites treated and the specific dosage administered (20 IU in 1 ml) was also noted.

### **Statistical Analysis**

Statistical analysis was conducted using SPSS software. Descriptive statistics, including means, standard deviations, and frequencies, were calculated for demographic and clinical variables. The correlation between quadrant numbers and healing outcomes was assessed using Pearson's correlation coefficient test. Furthermore, chi-square tests were employed to examine the association between quadrant numbers and categorical variables, such as gender. The Mann-Whitney U test was utilized for comparing healing outcomes between different quadrant groups.

## **RESULTS**

A total of 224 patients (102 females and 122 males) with chronic anal fissure were included in the study. The mean age of the participants in the study was  $45.06 \pm 13.04$  years.

Healing rates, based on the number of injection sites where botulinum toxin was administered, were evaluated at three different time points after surgery: 15<sup>th</sup> day, 30<sup>th</sup> day, and 90<sup>th</sup> day.

On the post-op 15<sup>th</sup> day, the recovery levels in patients who received Botulinum toxin injection in 2 sites was as 25.4%, in patients who received Botulinum toxin injection in 3 quadrants 53.8% and among patients who received Botulinum toxin injection in 4 quadrants 74.5%. Figure 1, shows all the patients as graphic in follow up days.

On the 30<sup>th</sup> postoperative day, the recovery rates were as follows: 35.3% in patients who received Botulinum toxin in 2 regions, 70.6% in patients in whom Botulinum toxin was

applied in 3 regions, and 84.2% in patients in whom Botulinum toxin was applied in 4 regions.

The recovery rates at the postoperative 90<sup>th</sup> day were as follows: 54.6% of patients who were treated with Botulinum toxin in 2 areas, and 78.1% in patients who were treated with Botulinum toxin in 3 areas. The recovery rate was 89.7% in patients who were injected into 4 regions.

The results showed that the majority of patients experienced significant improvement in symptoms following anal BT treatment. At the 15-day follow-up, 74.5% of patients showed a healing in four sites injections. By the 30-day follow-up, this proportion increased to 84.2%. At the final 90-day follow-up, 89.7% of patients achieved a complete healing, demonstrating sustained improvement in symptoms.

Statistical analysis using chi-square and Mann-Whitney U tests revealed a significant association between the number of injection sites and healing outcomes ( $p < 0.05$ ). Patients who received injections in 4 quadrants had significantly higher healing grades compared to those with injections in 3 or 2 quadrants (Figure 2).

Our study found that anal BT treatment was well-tolerated, with minimal adverse events reported. Only four patients (1.6%) reported mild incontinence to gas and resolved spontaneously in weeks. Gas incontinence was detected after 3 and 4 injections. 8 patients (%3.2) complained a discomfort at injection sites, which resolved spontaneously without need for further interventions.

## **DISCUSSION**

The results of this retrospective study demonstrate the effectiveness of anal BT treatment in providing significant symptom improvement for patients with chronic anal fissure.

Throughout the post-operative follow-up period, most patients experienced substantial healing. The findings of this retrospective study align with previous research indicating the positive outcomes of anal BT treatment for chronic anal fissure. Many studies reported similar results, demonstrating the efficacy of Botulinum toxin type A in inducing muscle relaxation and promoting healing in patients with chronic anal fissure (8-11).

At the 15-day follow-up, 67.4% of patients in our study showed a healing rate indicating moderate to substantial improvement in their symptoms. This initial response to anal BT

treatment is consistent with the results reported by Brisinda et al (12), who observed significant pain reduction and symptom improvement in patients at two weeks post-treatment.

By the 30-day follow-up, this proportion increased to 80.2% in our study, corroborating the findings of a systematic review conducted by Vitoopinyoparb et al (13). Their review demonstrated high success rates of anal BT treatment in resolving chronic anal fissure symptoms at 1 month post-procedure.

The most striking finding emerged at the final 90-day follow-up, where 92.6% of patients achieved the highest healing rate. These sustained improvement outcomes align with the long-term benefits reported by Ravindran et al. in their cohort study, which showed lasting symptom relief and improved quality of life in patients up to three months post-anal BT treatment (14). In our study, anal BT treatment was 92.6% effective at the end of the 90<sup>th</sup> day. These results are almost equivalent to the results of lateral internal sphincterotomy. A study has shown that anal BT gives similar results to lateral internal sphincterotomy like our study (15).

The consistent and remarkable healing outcomes across the three post-operative time points emphasize the clinical significance and reliability of anal BT treatment in managing chronic anal fissure. Our results are consistent with the findings of prospective trial conducted by Dokucu et al. (10), supporting the efficacy of anal BT treatment as a minimally invasive and effective therapeutic option.

Furthermore, a significant correlation was observed between the numbers of injection sites and the healing outcomes in our study. Patients who received injections in 4 sites showed the highest healing rates, followed by those with injections in 3 sites and then 2 sites. The number of injection sites in anal BT treatment play a significant role in influencing healing rates for patients with chronic anal fissures. The injection of Botulinum toxin into multiple sites appears to be associated with improved healing outcomes. We found that as the number of sites increased, the recovery was very fast, and the recovery rate was higher. It is predicted that recurrence may be less in 3 and 4 sites of injections in Kaplan-Meier curves. There is still no consensus regarding the number of sites and dosage in anal BT application. A 2016 meta-analysis by Bobkiewicz et al. reported cure rates of 33 to 96% and doses of 5 to 80 units (1). In our study, we determined 20 IU as the standard dose for each injection sites. Another retrospective study also determined that the rate of cure increased as the dose increased (9). Our finding is consistent with previous studies in the literature. For instance, Brisinda et al.

conducted a similar study and reported that a greater number of quadrants injected was associated with improved healing outcomes. The rationale behind injecting multiple sites is to achieve a more comprehensive relaxation of the anal sphincter complex, allowing for enhanced blood flow and improved healing of the anal fissure (12). Our findings add further support to the notion that a more extensive treatment approach involving multiple quadrants can lead to higher healing rates.

According to a national American Society of the Colon and Rectal Surgeons Survey, most surgeons use doses of 50-100 IU and inject under anesthesia. According to this study, the majority perform multi-injection sites, and most of them inject into the internal sphincter. In the study, it was stated that this turned into a consensus (7). The applications here also overlap with our study.

While this procedure is effective in treating fissures, it carries a risk of weakening the anal sphincter muscle, which may lead to postoperative anal incontinence in some cases. On the other hand, anal BT treatment offers a more conservative and reversible approach. By injecting BT into the anal sphincter, muscle relaxation can be achieved, allowing the fissures to heal without the need for surgical incisions or cutting of the sphincter muscle. The temporary nature of effect of BT ensures that the anal sphincter returns to its normal function after several months, reducing the risk of long-term anal incontinence.

For women with chronic anal fissures, preserving anal sphincter function and continence is of utmost importance for their overall quality of life. The internal anal sphincter is indeed shorter in women compared to men, which may make them more susceptible to the risk of incontinence following sphincterotomy (16). Anal BT treatment can be a valuable and less invasive option for women with chronic anal fissures, especially when considering the potential prevention of anal incontinence especially in older ages, as compared to an internal sphincterotomy. By choosing anal BT treatment over an internal sphincterotomy, women can potentially avoid the risk of postoperative incontinence while effectively managing their anal fissures (16).

In terms of safety, our study found that anal BT treatment was well-tolerated, with minimal adverse events reported. Only 4 patients (1.6%) reported mild incontinence to gas and resolved spontaneously in weeks. Gas incontinence was detected after 3 and 4 injections. 8 patients (%3.2) complained a discomfort at injection sites, which resolved spontaneously without the need for further interventions. These findings are consistent with previous studies



that have demonstrated the safety and tolerability of anal BT treatment (10,17,18). The minimally invasive nature of the procedure, absence of major complications, and low risk of systemic side effects make anal BT treatment an attractive option for patients with chronic anal fissures. Another advantage of anal BT injection is that it can be repeated at different times. It can be tried repeatedly in those who relapse and those who do not improve.

It is important to acknowledge the limitations of this study, including its retrospective design and potential for selection bias. The absence of a control group also limits the ability to directly compare the effectiveness of anal BT treatment with other therapeutic approaches. However, the inclusion of a significant number of patients (n = 224) across different injection site groups (Group A, B, and C) enhances the study's robustness and provides valuable insights into the relationship between the numbers of injection sites and healing outcomes. Future prospective randomized controlled trials may be warranted to further validate these findings and provide more robust evidence.

In conclusion, the results of this retrospective study demonstrate that most patients experienced significant symptom improvement following anal BT treatment for chronic anal fissure. The recovery rate increases significantly as the number of injection sites increases. These findings provide valuable insights into the efficacy and sustained benefits of anal BT treatment, supporting its use as a promising therapeutic option for patients with chronic anal fissure. Further research and long-term studies are encouraged to corroborate these results and optimize treatment strategies for better patient outcomes.

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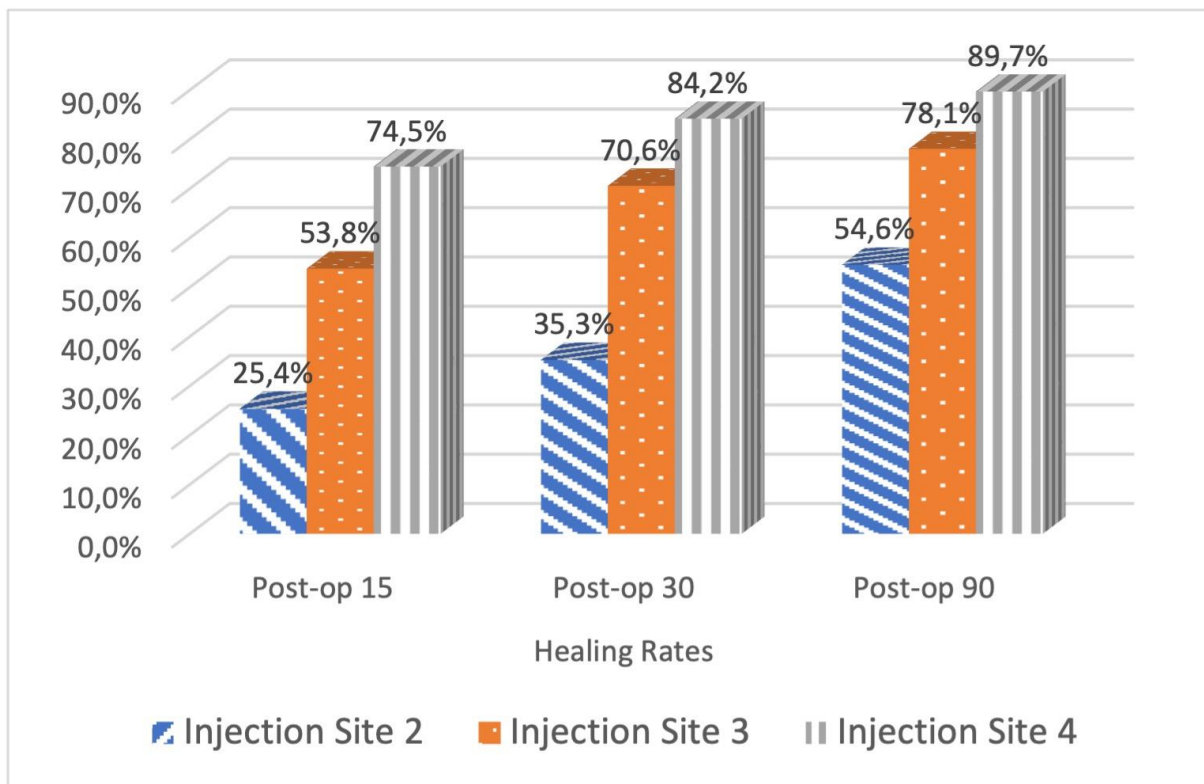
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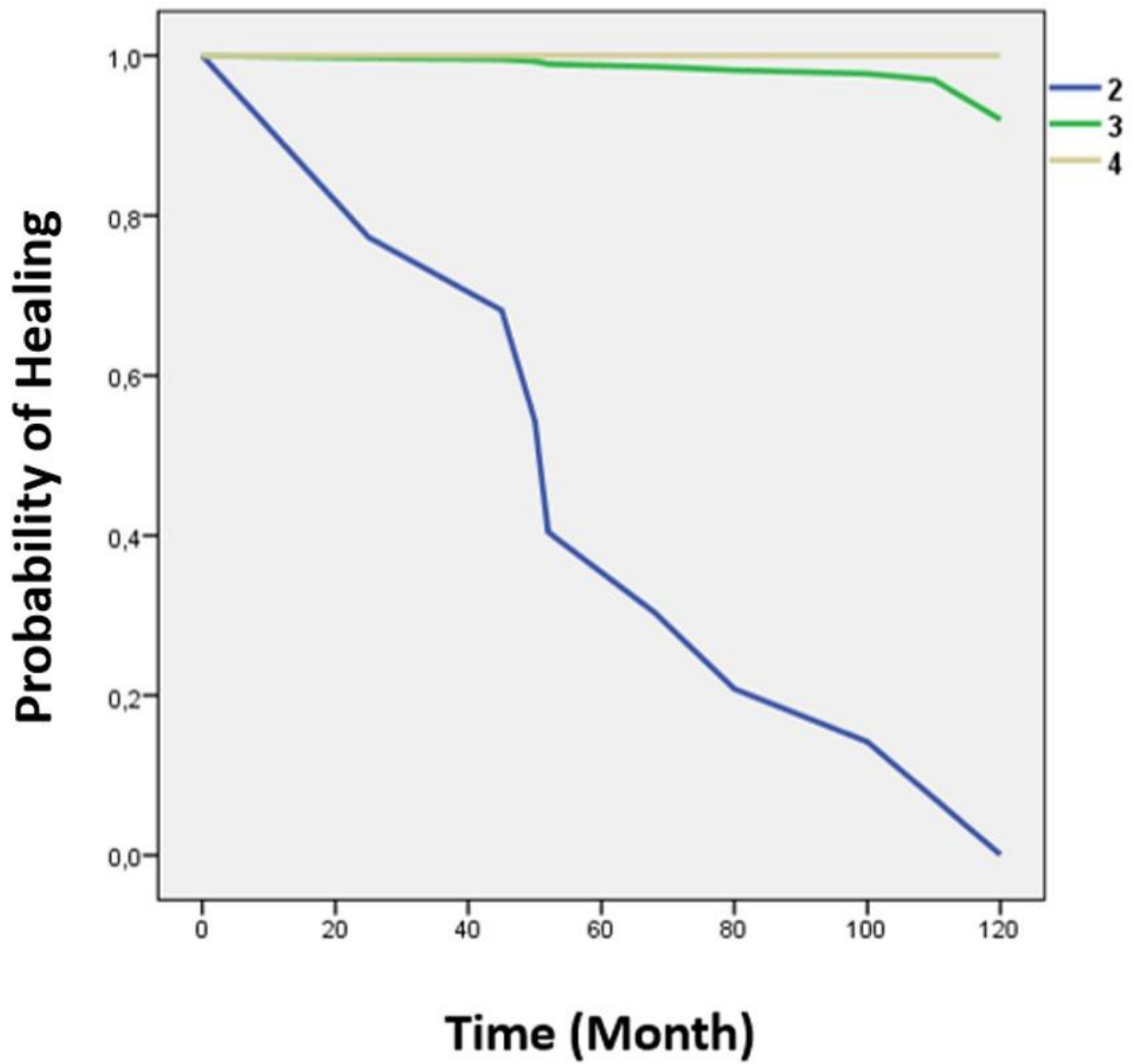
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**Figure 1.** The relationship between the number of quadrants and healing rates on the post-operative follow-up days day ( $p < 0.05$ ).

**Figure 2.** Kaplan-Meier healing probability index according to the number of injection sites and recurrence relationship.





● Two Quadrant    ● Three Quadrant    ● Four Quadrant