



Botulinum toxin injection versus lateral internal sphincterotomy for chronic anal fissure: a meta-analysis of randomized control trials

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Abstract

Background Anal fissures, tears in the epithelium of the anal canal that cause pain and bleeding, have a lifetime prevalence of 11%. While surgical treatments, such as lateral internal sphincterotomy are traditional, they pose postoperative complications. Recent studies investigated less invasive options involving botulinum toxin injection, showing promise with fewer adverse effects. The aim of this study is to compare the outcomes of botulinum toxin injection to lateral internal sphincterotomy for chronic anal fissures.

Method Up to October 2023, an extensive literature search was conducted in PubMed, Scopus, and Google Scholar to identify relevant papers. This systematic review and meta-analysis examined the comparative effectiveness of lateral internal sphincterotomy and botulinum toxin injection in the treatment of chronic anal fissures. The methodology adheres to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria, and the study protocol has been registered with the Open Science Framework (OSF).

Results A total of 1,839 patients from 18 trials were included in the meta-analysis. Patients undergoing lateral internal sphincterotomy had higher healing compared to botulinum toxin injection (pooled effect=0.77; 95% CI= [0.69– 0.83]; $I^2=90.95\%$; $P=0.00$).

Conclusion Our study revealed the efficacy of lateral internal sphincterotomy over botulinum toxin injection in promoting healing for chronic anal fissures. These findings emphasize the clinical advantage of traditional surgical interventions in the management of this condition. However, further studies with long-term follow-up are required to confirm our observations.

Keywords Anal fissure · Botulism · Botulinum toxin · Lateral internal sphincterotomy · Meta-analysis

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Introduction

Anal Fissure (AF) is a disorder that affects the anal canal and is characterized by the presence of cracks or tears on the stratified squamous epithelium of the anoderm. These tears occur in the squamous part of the epithelium and lead to notable pain and fresh bleeding during defecation [1]. Anal fissures are estimated to have a prevalence of 11% among individuals over their lifetime [2]. An acute injury that induces pain and spasm of the internal anal sphincter is the most probable cause of anal fissures. This spasm results in reduced blood flow, ischemia, and impaired healing by increasing the pressure of the resting sphincter [3, 4].

Numerous conservative and surgical interventions have been suggested, although the clinical approach to managing chronic anal fissures remains contentious, notwithstanding multiple reviews [5, 6]. Among the surgical methods, including anal dilatation, posterior midline sphincterotomy, and lateral internal sphincterotomy (LIS), the latter has traditionally been considered the optimal treatment for anal fissures [7]. However, all surgical techniques are prone to significant postoperative complications, encompassing pain, bleeding, incontinence, and recurrence [8]. LIS is the most effective therapy for persistent anal fissures that do not improve with conservative treatment methods [9]. Notably, studies indicate that patients who undergo LIS experience more effective symptom relief and a shorter hospitalization duration [10].

In recent years, there has been a surge in exploring less invasive treatment alternatives, including procedures like botulinum toxin injection (Botox), topical nitrates, and calcium antagonists [11]. The utilization of botulinum toxin for chemical sphincterotomy (CS) has shown promise, exhibiting a reduced recurrence rate and fewer adverse effects in comparison to the application of nitrates in CS [12]. Previous studies have shown inconsistent results, although Alyanak et al., showed redo-LIS and Botox injection for recurrent anal fissures found that redo-LIS provided significantly greater pain relief over a 3-month period, with no deterioration in incontinence scores after six months [13]. In contrast, another study, which compared LIS and high-dose Botox for treatment-resistant anal fissures, reported

that Botox led to shorter hospitalization times and lower first-week pain scores, but there were no significant differences in long-term outcomes such as Five-Point Horizontal Scale score, follow-up periods, and recurrence rates [14]. To ascertain the more effective approach, a meta-analysis was conducted, comparing the effects of botulinum toxin injection with those of LIS for chronic anal fissures, specifically focusing on the outcomes after the surgical procedure.

Method

In this systematic review and meta-analysis, we compare the effectiveness of LIS and botulinum toxin injection for treating chronic anal fissure. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria are followed by our methodology. The Open Science Framework (OSF) was notified of the study protocol for this review.

Literature search

Up until October 2023, an advanced literature search was carried out to find pertinent papers in the databases PubMed, Scopus, and Google Scholar. The major three keyword subgroups and Medical Subject Headings (MeSH) make up the search strategy. The terms connected to botulinum toxin injection made up one subgroup, and the terms for LIS and chronic anal fissure, respectively, made up the other two. No constraints were placed on the date or kind of publication when combining the subgroups using the 'AND' operator, however only English-language references were included in the meta-analysis. According to the query structure for each database, the search technique was modified (Table 1). In order to reduce the possibility of excluding pertinent papers, we carefully examined the reference lists of pertinent systematic reviews and only included studies that could be evaluated in our investigation. Two reviewers did each stage separately, and any disagreements were settled through conversation between the reviewers. Using Endnote (Version X20, Thomson Reuters), the search results were controlled.

Table 1 Search strategy

Search engine	Search strategy	Additional filter
PubMed	((("botulinum"[title/abstract]) OR ("toxin"[title/abstract])) AND ((("lateral internal sphincterotomy"[Title/Abstract]) OR ("sphincterotomy"[Title/Abstract])) AND ((("anal fissure"[Title/Abstract]))	16th August 2023
Scopus	TI=((botulinum OR toxin) AND (lateral internal sphincterotomy OR sphincterotomy) AND (anal fissure))	16th August 2023

Criteria for selecting studies

For studies to be considered in this meta-analysis, the following criteria should be met:

- Observational methods (to eliminate the confounding impact of any intervention).
- The main interest was to assess the link between botulinum toxin injection and chronic fissures.
- The study population consisted of people who had chronic fissures.
- Chronic fissure definitions were reported according to the study design.

Studies that used different methodologies with animal models are not included.

Data extraction and study quality assessment

Each study's title and abstract were examined by two independent reviewers (Re.HZ and F.E) to determine whether it qualified for inclusion in this meta-analysis. A third reviewer (A.B) then independently reviewed the full-text

papers to ensure quality and resolve any disagreements. Studies that did not fit our requirements were disqualified. The remaining papers' whole texts were scrutinized, and those that met the criteria for data extraction started the procedure. Next, four sets of the following items were retrieved for extraction: (1) study characteristics (authors, location, year, and study type); (2) patient-specific factors (eligibility criteria for simple botulinum toxin injection without any other interventions, such as simultaneous ointment application, LIS, and others); and (3) no history of botulinum toxin treatment); 3. research design (including participant count, sampling strategy, and definition of a chronic fissure); (4) the results (i.e., the incidence of chronic fissures and botulinum toxin injection). The Cochrane checklists for randomized controlled trial studies (Fig. 1), were used by the two reviewers. In cases of disagreement, a third author took part in the process.

Statistical analysis

We analyzed our data using STATA 13.1 software, which was created by StataCorp LP in College Station, Texas, the United States. Results were displayed in a forest plot

Fig. 1 Quality assessment checklist of included studies based on the Cochrane tool

Author / bias type	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other
Zngana 2021	Green	Yellow	Green	Green	Green	Green	Green
Tawfeeq 2019	Green	Yellow	Green	Green	Green	Green	Green
Singh 2015	Red	Yellow	Green	Green	Green	Green	Green
Valizadeh 2012	Green	Yellow	Green	Green	Green	Green	Green
Nasr 2010	Red	Yellow	Green	Green	Green	Green	Green
Arroyo Sebastián 2005	Green	Yellow	Green	Green	Green	Green	Green
Iqbal 2016	Green	Yellow	Green	Green	Green	Green	Green
Asgari 2010	Red	Yellow	Green	Green	Green	Green	Green
Brady 2017	Red	Yellow	Green	Green	Green	Green	Green
Arroyo 2005	Green	Yellow	Green	Green	Green	Green	Green
Alghaity 2008	Yellow	Yellow	Green	Green	Green	Green	Green
Alyanak 2022	Red	Yellow	Green	Green	Green	Green	Green
Ahmad 2014	Yellow	Yellow	Green	Green	Green	Green	Green
Imran Khan 2016	Green	Yellow	Green	Green	Green	Green	Green
Iswariah 2005	Green	Yellow	Green	Green	Green	Green	Green
Giral 2004	Red	Yellow	Green	Green	Green	Green	Green
Jeddi 2002	Red	Yellow	Green	Green	Green	Green	Green
Khryukin 2022	Yellow	Yellow	Green	Green	Green	Green	Green

Low risk	Green
Unclear	Yellow
High risk	Red

as pooled odds ratios (ORs) with a 95% confidence interval. Using the I² statistic, we assessed heterogeneity among the qualifying studies. a random effects model was applied when significant heterogeneity ($I^2 > 50\%$) was found. Additionally, we repeated the meta-analysis while removing one study at a time in a sensitivity analysis. We were able to guarantee the stability of our findings as a result. Last but not least, we used visual examination of funnel plot symmetry and Egger's regression analysis to look at the possibility of publication bias. A funnel plot was designed for the studies to assess publication bias, and Egger's test and Begg's test were also conducted.

Result

Study selection

Finally, 18 RCT articles with a total population of 1882 were reviewed. These studies compared botulinum toxin with LIS (Fig. 2).

Study characteristics

These researches were conducted in USA [15], Turkey [13, 16], Spain [17, 18], Australia [19], Saudi Arabia [20], Egypt

[21], Pakistan [22, 23, 24], Iran [25, 26, 27], India [28], Russia [29], Iraq [30, 31]. The average age of the patients varied from 30 to 52 years. The follow-up duration of these studies ranged from 2 weeks to 7 years. The percentage of females to males in the study varied from 18 to 100% (Table 2).

Botulinum toxin vs. LIS

This meta-analysis compared the efficacy of botulinum toxin vs. LIS in anal fissure patients. The results revealed a substantial effect of the LIS technique with an effect size of 0.87 (95% CI = [0.77, 0.94], $P < 0.01$), indicating a positive impact. However, the high heterogeneity of 91.85% suggests the need for careful interpretation. Similarly, botulinum toxin demonstrated a significant effect size of 0.65 (95% CI = [0.54, 0.75], $P < 0.01$) with a severe heterogeneity (89.11%).

The overall pooled effect size comparing botulinum toxin and LIS was 0.77 (95% CI = [0.69, 0.83]). The p-value less than 0.01 insisted on the significant results. Moreover, the heterogeneity of combined analysis remained considerable, with $I^2 = 90.95\%$, indicating an exceptionally high degree of variability among the studies (Fig. 3).

Fig. 2 PRISMA diagram of current systematic review and meta-analysis

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

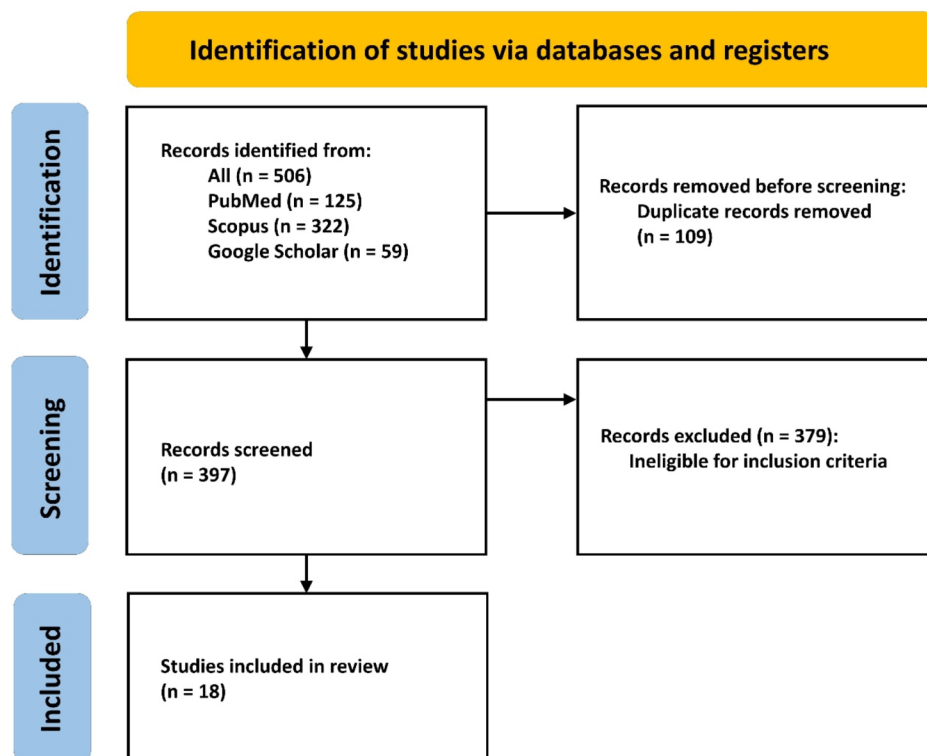


Table 2 Baseline characteristics of included studies

Author (year) [ref]	Country	Study design	Participants No. (LIS/BT)	Female (%)	Follow-up duration	Intervention	Mean age $\pm$ SD: Total (LIS/BT)
Zngana et al. (2021) [30]	Iraq	RCT	50 (25/25)	28	3 months	LIS BTA: Botulinum toxin A was diluted in 0.5 ml saline solution. Each patient received Botulinum toxin (for a total of 20 unit) administered as divided doses through the internal anal sphincter at 3, 9 and 12 o'clock and injection for an equal volume on each side of the fissure	39.52 (4.55)
Tawfeeq et al. (2019) [31]	Iraq	nRCT	60 (30/30)	58.3	3 months	LIS BTA: was diluted in saline to a concentration of 50 units/ ml. A 27-gauge needle syringe was used to introduce 10 units of BTA on each side of the midline anteriorly	(32.6/33.7)
Singh et al. (2015) [28]	India	RCT	60 (30/30)	31.6	1.5 month Follow-up duration was not clearly stated	LIS BTA: patients were injected with 5 units of Botulinum Toxin - single injections of Botulinum toxin type A purified neurotoxin complex	NR
Valizadeh et al. (2012) [27]	Iran	RCT	50 (25/25)	62	12 months	LIS BTA: A 100-U vial of type A lyophilized Botulinum stored at -20°C , diluted with saline to 50 U/ml on the day of injection. 25 U was injected into each side of the sphincter	(36.4 $\pm$ 8.5 / 34.8 $\pm$ 8.1)
Nasr et al. (2010) [21]	Egypt	RCT	80 (40/40)	65	4.5 month	LIS BT: 100 U vial of lyophilized botulinum toxin type stored at -8°C . The day of injection it was diluted with saline to 40 U/ml, and 10 U was injected into the internal anal sphincter on both sides of the fissure	33.8 $\pm$ 1.33
Sebastián et al. (2005) [18]	Spain	RCT	80 (40/40)	35	36 months	LIS BTA: 100-U vials of type A lyophilized botulinum were stored at a temperature of -20°C and diluted in saline to 0.1 ml/2.5 U the day of injection. With a 25 G needle, a total of 25 U were injected into the internal sphincter guided under direct vision and digital examination (8-U dose into each lateral side of the sphincter and 9-U into the anterior verge)	(40 $\pm$ 15 / 41 $\pm$ 15)
Asgari et al. (2010) [25]	Iran	RCT	36 (18/18)	41.66	6 months	- Injection of 50 units of botulinum toxin, 25 units of drugs in each side - LIS was done in surgery group by open method in left side	(33.3 $\pm$ 7.9 / 33.5 $\pm$ 7.8)
Brady et al. (2017) [15]	USA	RCT	94 (73/21)	53.2	NR	BT dosage varied between 50 and 100 units diluted in 5e10 ml of sterile saline based on surgeon preference	52 / 49
Arroyo et al. (2005) [17]	Spain	RCT	80 (40/40)	31.2	3-year	25 U botulinum toxin injected into the internal sphincter	(38 $\pm$ 14 / 41 $\pm$ 15)
Alyanak et al. (2022) [13]	Turkey	RCT	19 (11/8)	42.1	3-month	two insulin injectors each containing 0.5 ml of solution containing 100 IU Botulinum Toxin type A diluted with 1 ml of physiological saline solution	42.37 $\pm$ 5.96 (51.3 / 43)
Ahmad et al. (2014) [22]	Pakistan	RCT	100 (50/50)	22	two weeks	0.5 cc of Injection Neuronox injected in the sphincters under direct vision and digital examination	(32.9 $\pm$ 4.6 / 36.7 $\pm$ 3.1)
Iqbal et al. (2016) [23]	Pakistan	RCT	396 (198/198)	44.4	2 months	LIS 0.5 ml Botulinum toxin injection on each side of anal fissure especially posterior aspect of the internal anal sphincter under direct vision at 3 or 9 o'clock position of lithotomy	45.4 $\pm$ 13.8 (45.7 $\pm$ 14.3 / 45.1 $\pm$ 13.3)

Table 2 (continued)

Author (year) [ref]	Country	Study design	Participants No. (LIS/BT)	Female (%)	Follow-up duration	Intervention	Mean age $\pm$ SD: Total (LIS/BT)
Khan et al. (2016) [24]	Pakistan	RCT	396 (198/198)	44.4	2 months	LIS 0.5 ml Botulinum toxin injection on each side of anal fissure especially posterior aspect of the internal anal sphincter under direct vision at 3 or 9 o'clock position of lithotomy	45.4 $\pm$ 13.8 (45.7 $\pm$ 14.3 / 45.1 $\pm$ 13.3)
Iswariah et al. (2005) [19]	Australia	RCT	38 (21/17)	57.9	26 weeks	LIS 20 units Botox injected on either side of the fissure into the internal anal sphincter	NR
Giral et al. (2004) [16]	Turkey	nRCT	21 (11/10)	52.4	12 months	LIS 40 U/ml BT diluted in saline injected on both side on fissure	(39 $\pm$ 10 / 41 $\pm$ 11)
Jeddi et al. (2002) [26]	Iran	RCT	40 (20/20)	100	2 months	LIS 25 units BT injection	(32.3 $\pm$ 10.8 / 30.5 $\pm$ 7.1)
Khryukin et al. (2022) [29]	Russia	RCT	176 (88/88)	58.5	2 months	Close or open lateral subcutaneous sphincterotomy 10 units BTA in internal anal sphincter at 1,5,7 and 11 o'clock using insulin syringe for 100 divisions	-
Algaithy (2008) [20]	Saudi Arabia	RCT	100 (50/50)	100	3 Years	Close lateral sphincterotomy BTA: 100-IU vials of type A BTX was diluted in one ml of normal saline. 0.4 ml of diluted toxin injected and 0.2 ml in each side - LIS was done in surgery group by closed technique	33.10 (34.30 $\pm$ 9.9 / 31.90 $\pm$ 12.4)

NR: Not reported

Publication bias

The publication bias was evaluated using Begg's test and a visualized funnel plot. As a result, an insignificant Begg's test and symmetrical funnel plot (Fig. 4) indicated no publication bias. Moreover, the sensitivity analysis was done, and any study did not remove (data not shown).

Discussion

Various treatment choices exist for anal fissures, involving both medical and surgical options. Regardless of the selected method, the primary goal in the treatment of anal fissures is to decrease the internal sphincter pressure to a normal range, reducing the tension in the sphincter, enhancing local blood circulation, and, consequently, facilitating the healing process [19, 32, 33]. According to the findings of this systematic review, individuals who underwent LIS exhibited a 23% higher healing rate than those treated with botulinum toxin. The results of this meta-analysis are in keeping with previous studies comparing the healing rates of the two approaches [34, 35]

An anal fissure is marked by a vicious cycle characterized by spasms in the internal sphincter, resulting in pain and bleeding during bowel movements [36]. Conservative treatments such as warm-sitz baths and creams aimed at reducing internal sphincter pressure are employed for the management of acute anal fissures. In cases of chronic

conditions, options include LIS or botulinum toxin injections. Botulinum toxin impacts peripheral nerve endings by inhibiting sympathetic neural output, likely involving post-ganglionic action. This action reduces noradrenaline release at the neuromuscular junction, leading to flaccid paralysis and inducing a temporary state of weakness in the muscle of the internal anal sphincter [37].

LIS is deemed the gold standard for the treatment of chronic anal fissures. However, this option has potential downsides, Acar et al. conducted a retrospective study involving 417 patients who were treated for chronic anal fissure at the General Surgery Department between January 2010 and October 2017. The aim of the study was to evaluate the safety and adequacy of lateral internal sphincterotomy (LIS) as a treatment option for chronic anal fissure.

The study demonstrated that while LIS it remains the gold standard for treating chronic anal fissure is associated with potential complications, such as wound infection, hematoma, abscess, and anal fistula [38]. Hence, the risk of permanent damage to the anal sphincter has called for the application of alternative treatments such as botulinum toxin injection. Additionally, for patients with clinical risks for surgery, such as those undergoing chemotherapy, high cardiac risk, requiring blood diluents, or those who prefer to avoid surgical interventions, the injection of botulinum toxin into the internal sphincter may be selected [2, 8, 39].

Although this meta-analysis shows that LIS is superior in healing and recurrence rates, it does not analyze complications. Hospitalization and time away from work are

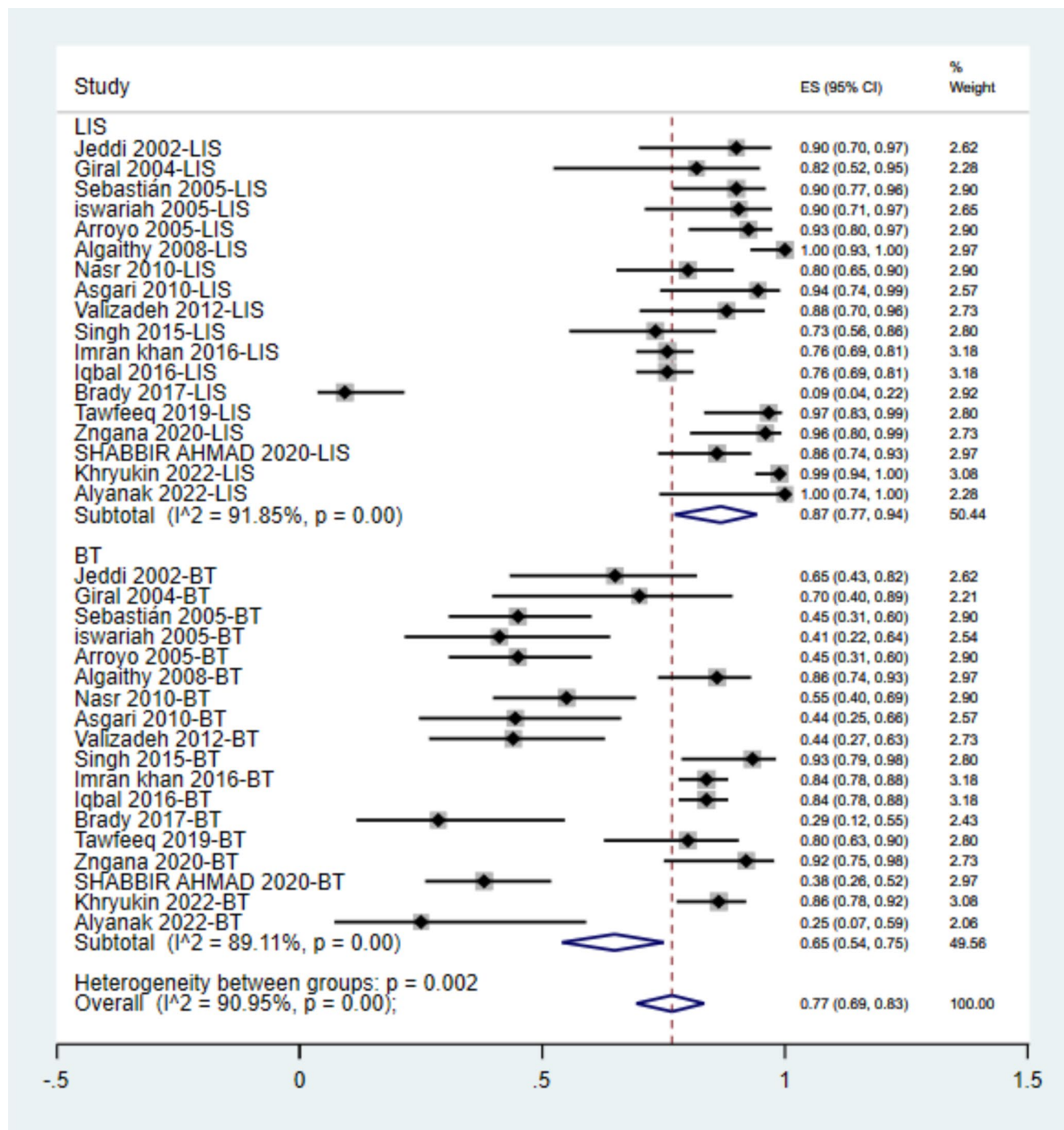


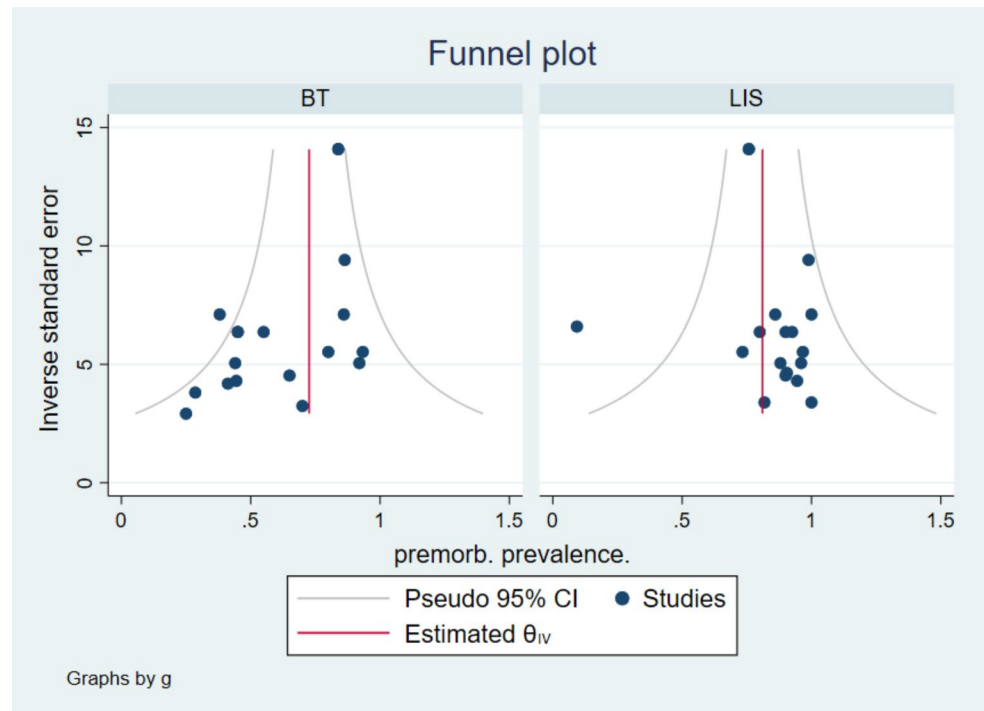
Fig. 3 Forest plot for Botulinum toxin injection (0.65 (0.54, 0.75)) versus lateral internal sphincterotomy (0.87 (0.77, 0.94)) and the overall effect (0.77 (0.69, 0.84))

necessary for LIS. Additionally, there is a potential for complications associated with general or spinal anesthesia [27]. In a meta-analysis by Chen et al., botulinum toxin injection demonstrated superiority over LIS in terms of overall complication rates and incontinence rates, therefore presenting several advantages for patients with chronic anal fissures, including a good tolerance of procedure, outpatient setting,

and a lower risk of incontinence. However, in the study above, LIS still had significantly better healing and lower recurrence rates [34].

In alignment with our findings, the study by Menten et al., which involved 111 patients, compared the effectiveness of botulinum toxin (BT) injection with LIS for chronic anal fissure (CAF). This study concluded that while BT achieved

Fig. 4 Funnel plot of the studies shows a symmetrical pattern for both Botulinum toxin (BT) injection and lateral internal sphincterotomy (LIS) indicating no publication bias



a high healing rate, particularly with a second injection for initial failures, its effects were slower and less stable compared to LIS. LIS provided a faster, more permanent solution with a lower recurrence rate. They highlighted BT's ease of administration and lower incidence of incontinence, making it a viable option for high-risk patients. This supports the idea that while LIS is highly effective, BT can be considered in specific cases where surgery might pose a greater risk [40].

Another study by Massoud et al. involved 50 patients comparing BT injection with surgical sphincterotomy. Their results comply with our findings, as they concluded that LIS was more effective in achieving healing, with all patients in the LIS group fully recovering, compared to only 22 out of 25 in the BT group. The study reported a higher recurrence rate with BT, aligning with our observations that LIS is superior in maintaining long-term healing. Despite these findings, Massoud et al. acknowledged BT as a practical nonsurgical alternative due to its ease of administration and favorable outpatient setting, making it a recommended first step in treatment [41].

In another comprehensive analysis, Sajid et al. conducted a meta-analysis that supports and emphasizes the work of previous studies. Their study found that LIS had better healing outcomes and lower recurrence rates compared to BT. Interestingly, Sajid et al. observed that complications, including fecal incontinence, were comparable between LIS and BT, suggesting that LIS may be considered a first-line therapy in the management of CAF. This observation reinforces our results, as it highlights the balance between

efficacy and safety that LIS offers, even in comparison to less invasive treatments like BT [34].

Shao et al. conducted a systematic review and meta-analysis comparing BT injection with LIS for CAF treatment. Their analysis, which included four studies with 279 patients, demonstrated that while BT injection was associated with a higher rate of recurrent disease, LIS was more effective in achieving complete healing. This conclusion is in direct compliance with our study, favoring LIS as the ideal treatment for CAF, particularly in cases where conservative measures have failed. Shao et al. further emphasized that while BT is suitable for patients at high risk of incontinence, LIS remains the preferred option for long-term resolution of the fissure. Shao's findings also support and emphasize the earlier work of Montes et al. and Massoud et al., reinforcing the conclusion that LIS is more effective overall, despite BT being a valuable alternative in selected cases [42].

We acknowledge the limitations of our study. Substantial heterogeneity was evident among the healing rates of randomized controlled trials included in our study. The lack of double-blind design in the trials and potential variations in surgical expertise among surgeons performing LIS or botulinum toxin injection may have contributed to the observed heterogeneity. Results could vary for the same patient depending on the surgeon's experience. Additionally, although the risk may be negligible for transient fecal incontinence [19, 41] the current study does not include a meta-analysis of complications.

Conclusion

LIS and botulinum toxin injection represent the primary choices of intervention in chronic anal fissures, which are not responsive to conservative medical management. LIS, recognized as the gold standard, is associated with better healing outcomes yet is invasive and carries higher risk complications compared to alternative methods. Botulinum toxin injection, considered a less invasive option, exhibits higher recurrence rates but may be viewed as an alternative treatment for specific patients due to its lower complication rates. Despite the acknowledged limitations of our study, the results suggest LIS is superior in healing chronic anal fissures. However, the significant heterogeneity among studies and the lack of complication analysis highlight the need for further research. Additionally, treatment should be individualized, taking into account patient-specific factors and preferences.

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Data availability Data is available upon request from corresponding author.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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