

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

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## Abstract

**Background** Although surgery is the gold standard treatment for anal fissure, the main concern remains its side effects and complications. Botulinum toxin injection and lateral internal sphincterotomy are technical options for patients suffering from chronic anal fissure. However, little is known about the efficacy of these two techniques. The aim of this meta-analysis was to compare the outcomes of botulinum toxin injection versus lateral internal sphincterotomy for chronic anal fissure.

**Methods** Original studies in English were searched from the MEDLINE database, PubMed, Web of Science, and the Cochrane Library database. Randomized control trials that compared botulinum toxin injection with lateral internal sphincterotomy were identified. Data were independently extracted for each study, and a meta-analysis was performed using fixed and random effects models.

**Results** Four hundred and eighty-nine patients from seven trials met the inclusion criteria. Patients undergoing lateral

internal sphincterotomy had a higher-healing and incontinence rate. No statistically significant differences were noted in total complications between botulinum toxin injection and lateral internal sphincterotomy. Patients treated with lateral internal sphincterotomy had a significantly lower recurrence rate than the patients treated with botulinum toxin injection. **Conclusions** Our meta-analysis shows that lateral internal sphincterotomy was superior to botulinum toxin injection in terms of healing rate and lower recurrence rate. Botox, however, is safe associated with a lower rate of incontinence and could be used in certain situations. Further studies with a long-term follow-up are required to confirm our observations.

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

## Introduction

Anal fissure is a common disease responsible for substantial morbidity in people who are otherwise healthy [1]. Many conservative or surgical treatments have been proposed even if the clinical management of chronic anal fissures is still controversial despite several reviews [2]. Surgical procedures, such as anal dilatation, posterior midline sphincterotomy, and lateral internal sphincterotomy (LIS), have been the gold standard treatment for anal fissure [3]. However, all surgical techniques may be accompanied by significant postoperative complications, such as pain, bleeding, incontinence, and recurrence. It has been found that patients undergoing lateral internal sphincterotomy had better relief of symptoms as well as a shorter hospital stay [4]. Recently, less invasive treatment options such as

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H.-L. Chen, X.-B. Woo, and H.-S. Wang are the co-first authors in this study.

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botulinum toxin injection (Botox), topical nitrates, and calcium antagonists have been proposed. Chemical sphincterotomy (CS) using botulinum toxin has been reported to be associated with a lower recurrence rate and fewer side effects than CS using nitrates [5, 6]. To establish the better technique, a meta-analysis was performed by comparing botulinum toxin injection with lateral internal sphincterotomy for chronic anal fissure with regard to postoperative outcomes.

## Materials and methods

### Data sources

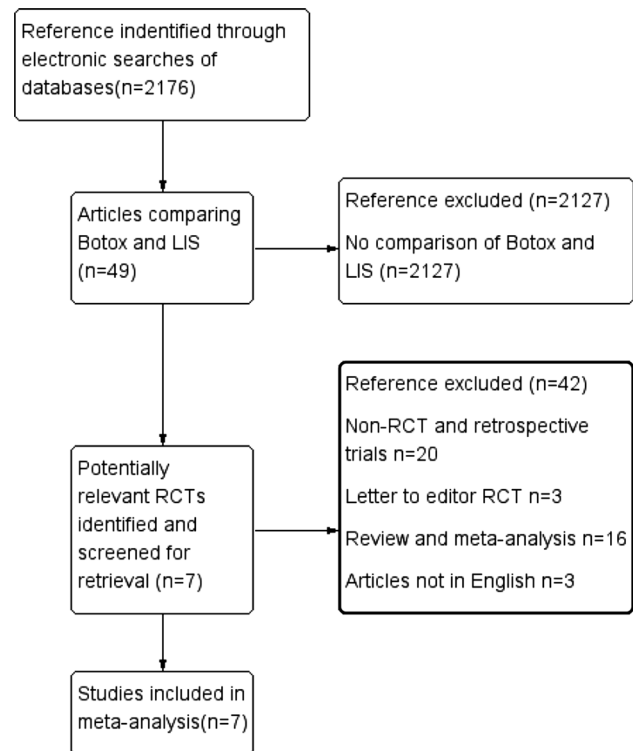
Randomized controlled trials (RCTs) that compared botulinum toxin injection with lateral internal sphincterotomy for chronic anal fissure were included in this meta-analysis. We used studies published from 1996 to August 31, 2013. A comprehensive search was performed in the MEDLINE database, PubMed, Web of Science, and the Cochrane Library database using the following search terms: “botulinum toxin,” “botulinum toxin injection,” “sphincterotomy,” “lateral internal sphincterotomy,” “anal fissure,” and “fissure-in-ano” combined with “randomized trials”. To identify all RCTs, we also included the reference list of the trials. Two independent observers (Huasheng Wang and Yijia Lin) separately identified and extracted the data.

### Inclusion and exclusion criteria

Studies were included if they met the following criteria: randomized trials; comparison between botulinum toxin injection and lateral internal sphincterotomy; and published full article. All studies were published in an English language format. The reference list of all trials that met the inclusion criteria and reference list of review articles were checked for more relevant articles. For estimation of the recurrence rate of anal fissure treated with botulinum toxin, clinical trials with a follow-up for at least 6 months were included. For duplicate publications, the most complete report was selected. Trials investigating the effects of botulinum toxin in children were excluded. Retrospective trials and studies without data for retrieval publications were excluded. Unpublished trials were not included (Fig. 1).

### Methodological quality

The Jadad scoring system, which evaluates studies based on appropriate randomization, proper blinding, and an adequate description of withdrawals and dropouts, was used to assess the quality of RCTs. The study was considered to be of high quality if the quality score was  $\geq 3$ .



**Fig. 1** Number of articles identified and evaluated during the review process

### Statistical analysis

Data analysis was performed using RevMan5.0 (The Cochrane Collaboration, Oxford, UK). For continuous variables, weighted mean difference (WMD) was calculated with a 95 % confidence interval (CI), and the odds ratio (OR) with a 95 % CI was calculated for all dichotomous variables. If mean values were not available for continuous outcomes, median values were used for meta-analysis. The standard deviation (SD) was calculated according to the guidelines of “The handbook Cochrane Collaboration.” The random effect model and the fixed effect model were used to calculate the overall effect of the combined outcomes. Heterogeneity was explored using the  $\chi^2$  test, with significance set at  $p < 0.05$ . If heterogeneity was present, only the random effects model results were reported. Heterogeneity was, respectively, qualified as low, moderate, or high for  $I^2$  values of 25, 50, and 75 %. The forest plot was then used to display the results from the meta-analysis.

## Results

Four hundred and eighty-nine patients from seven randomized controlled trials were qualified for the meta-analysis [7–13]. Patient characteristics extracted from these trials and quality scores are presented in Table 1. Table 2

**Table 1** General characteristics of the included studies

Trial	Year	Country	Type	Patients, n (F/M)	Mean age, years	Definition of fissure	Follow-up time	Quality score
Menteset et al. [10]	2003	Turkey	Botox	61 (44/17)	40 (19–70)	Not stated	12 months	3
			LIS	50 (32/18)	38 (18–70)			
Iswariah et al. [7]	2005	Australia	Botox	17	NA	Not stated	6 months	2
			LIS	21	NA			
Massoud et al. [6]	2005	Iran	Botox	25 (24/1)	33 ± 9.6	Evidence of circumscribed ulcer, with a large sentinel skin tag, indurations at the edges, and exposure of the horizontal fibers of the internal anal sphincter and symptoms lasting for more than 2 months	6 months	3
			LIS	25 (20/5)	35.5 ± 9.3			
Arroyo et al. [12]	2005	Spain	Botox	40 (14/26)	41 ± 15	Presence of a fibrous induration or exposed internal sphincter fibers	3 years	3
			LIS	40 (11/29)	38 ± 14			
Abd Elhady et al. [11]	2009	Egypt	Botox	40	34.4 ± 20.6	Having recurred if found on anatomical exploration, whether or not it caused symptoms	6 months	3
			LIS	40				
Nasr et al. [9]	2010	Egypt	Botox	40 (28/12)	33.8 ± 1.33	Based on evidence of a circumscribed ulcer in the anal canal, with indurations at the edges and exposure of the horizontal fibers of the internal anal sphincter at its base	18 weeks	2
			LIS	40 (24/16)				
Valizadeh et al. [8]	2012	Iran	Botox	25 (14/11)	34.8 ± 8.1	Evidence of a posterior or anterior circumscribed ulcer with a sentinel skin tag, indurations at the edges, and exposed internal sphincter fibers	12 months	3
			LIS	25 (17/8)	36.4 ± 8.5			

Botox botulinum toxin injection, LIS lateral internal sphincterotomy, NA not available

**Table 2** Results of meta-analysis comparing Botox with LIS

Outcome	No. of studies	No. of patients	Model	OR (95 % CI)	<i>p</i> value	$\chi^2$ test	<i>p</i> value for heterogeneity
Healing	6	409	Fixed	0.15 (0.08, 0.27)	<0.00001	4.36	0.50
Complications	6	451	Random	0.55 (0.15, 1.94)	0.35	20.28	0.001
Incontinence	7	489	Fixed	0.12 (0.05, 0.26)	<0.00001	5.24	0.53
Recurrence rate	7	489	Fixed	5.97 (3.51, 10.17)	<0.00001	6.26	0.39

LIS lateral internal sphincterotomy, OR odds ratio, CI confidence interval

displays the number of studies reporting on each outcome, the total number of patients in both Botox and LIS groups, the summary statistic, 95 % CIs, the calculated *p* values, and a test of heterogeneity between the studies.

#### Healing

Since data from six trials suggested that there were no significant heterogeneity among trials regarding healing ( $\chi^2 = 4.36$ ,  $df = 5$ ,  $p = 0.50$ ,  $I^2 = 0\%$ ), we used the fixed effect model. We observed a significant difference in the healing rate and hence concluded LIS is superior to Botox (OR 0.15; 95 % CI 0.08, 0.27;  $Z = 6.26$ ;  $p < 0.00001$ ; Fig. 2a).

#### Complications

There was a significant heterogeneity among trials regarding total complications ( $\chi^2 = 20.28$ ,  $df = 5$ ,  $p = 0.001$ ,  $I^2 = 75\%$ ). In the random models, there were no significant difference in the total complications between the Botox and LIS groups (OR 0.55; 95 % CI 0.15, 1.94;  $Z = 0.93$ ;  $p = 0.35$ ; Fig. 2b).

#### Incontinence

No significant heterogeneity was observed among trials regarding incontinence ( $\chi^2 = 5.24$ ,  $df = 5$ ,  $p = 0.53$ ,  $I^2 = 0\%$ ). In the fixed models, a significant difference was

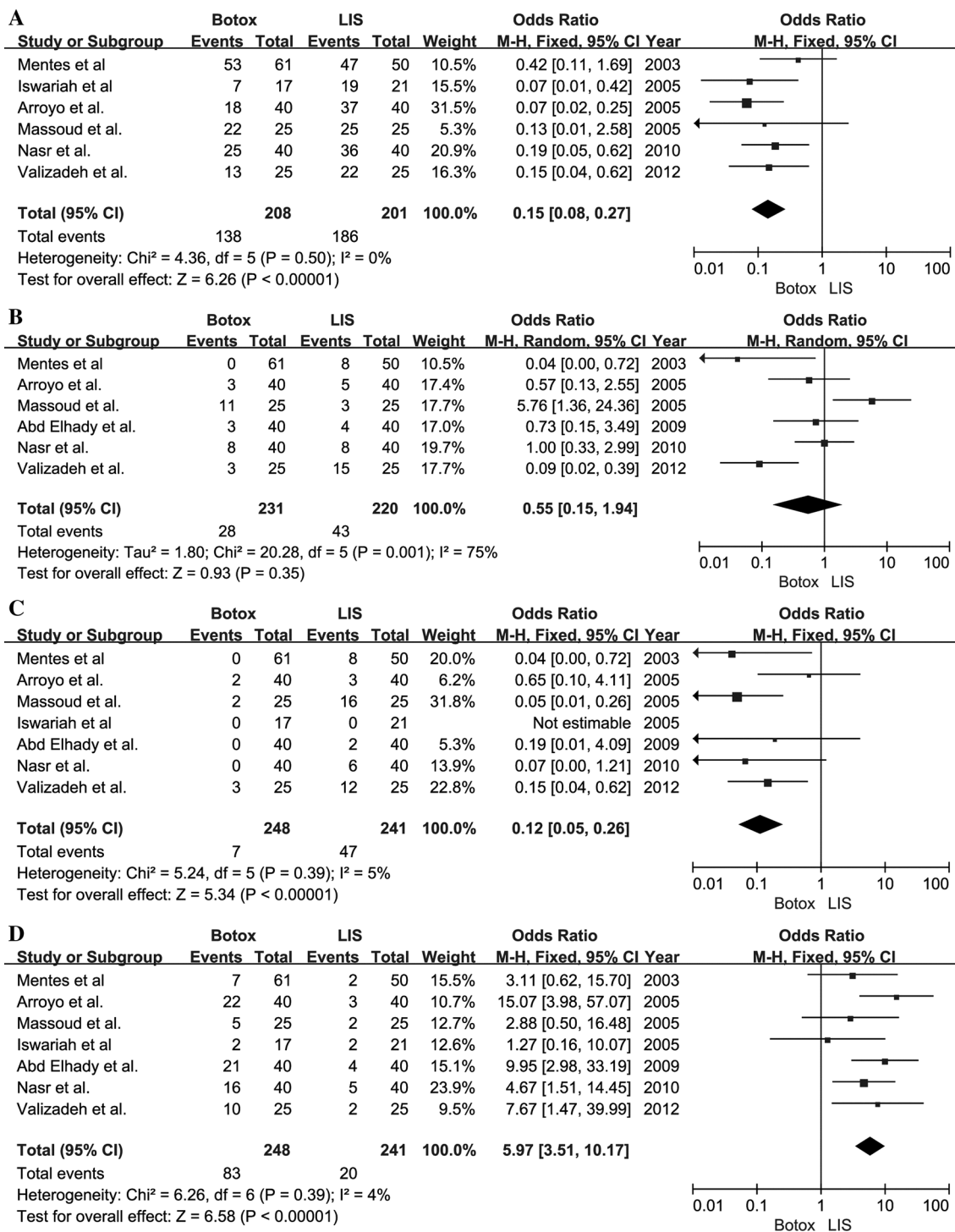


Fig. 2 Clinical outcomes: a healing; b total complications; c incontinence; d recurrence rate

found in the incontinence between Botox and LIS group (OR 0.12; 95 % CI 0.05, 0.26; Z = 5.34; p < 0.00001; Fig. 2c). Hence, our results show Botox is better than LIS as regards incontinence.

Recurrence rate

All of the trials presented data on recurrence. There was no significant heterogeneity among trials regarding recurrence

( $\chi^2 = 6.26$ ,  $df = 6$ ,  $p = 0.39$ ,  $I^2 = 4\%$ ). In the fixed models, the LIS group appeared to have a significantly lower recurrence rate than the Botox group (OR 5.97; 95% CI 3.51, 10.17;  $Z = 6.58$ ;  $p < 0.00001$ ; Fig. 2d).

## Discussion

Lateral internal sphincterotomy has been widely accepted as the treatment of choice for CAF [14]. However, the drawback of this surgery is potential fecal incontinence and complications such as bleeding, pain, anal abscess, or fistula [15]. Since Botox was introduced as a potential treatment for anal fissures [16], many studies have suggested encouraging results for the role of Botox in the treatment of anal fissures [17–20]. However, due to different results and unclear conclusions, controversy still exists on whether Botox is bound to replace LIS as the first-line treatment for CAF.

This meta-analysis showed that even though LIS is associated with a better healing rate and recurrence rate, Botox is superior to LIS in overall complication rates and incontinence rate. Thus, some advantages Botox offers to CAF patients include a good tolerance of the procedure, an outpatient setting, and a low risk of incontinence.

The results of this meta-analysis are in line with research from Sajid et al. and Shao et al. [21, 22]. However, our meta-analysis has some limitations. First, not only were various doses of botulinum toxin used in these studies, but various definitions of CAF were found; this suggests variability in methodology across studies and may impact interpretation of the measured pooled effect or  $z$  statistic. Secondly, none of the studies were double blinded. It is, hence, unavoidable that heterogeneity exists among studies in terms of the sample size and surgeon's experience. Thirdly, the results of the studies included in this meta-analysis were not consistent. The total complication rate varied from 0 to 64% among the trials, while the incontinence rate varied from 0 to 48%. Fourthly, although the Botox group may be associated with lower rates of incontinence and LIS group appeared to have a lower recurrence rate, the long-term follow-up data are limited which makes this determination uncertain. Finally, no multicentre randomized trial was found among these studies.

## Conclusions

This meta-analysis suggests that in regard to healing rate and recurrence rate, Botox is inferior to LIS for CAF. Botox may therefore be used as a first-line treatment for patients who refuse surgery, who have had previous

sphincter surgery, or who are at a particular risk of incontinence with sphincterotomy [7]. In further studies, large-scale, high-quality, multicenter trials based on commonly accepted end points with a long-term follow-up are required to confirm our observations.

**Conflict of interest** None.

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