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Review

Comparison of doses and injection sites of botulinum toxin for chronic anal fissure: A systematic review and network meta-analysis of randomized controlled trials

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ABSTRACT

Background: There are no consensus guidelines on the optimal dose or injection site of botulinum toxin (BT) for chronic anal fissure (CAF). The objective of this study was to determine the appropriate dose and injection site of BT for CAF by comparing healing rate and adverse effects (incontinence and recurrence).

Methods: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and Scopus were searched from inception through May 31, 2021. Randomized controlled trials evaluating healing and adverse effects of BT injection for CAF published in any language were selected. Multiple treatment comparisons and ranking were performed using a two-stage network meta-analysis, and results were graded by Confidence in Network Meta-Analysis tool.

Results: Twenty-seven trials involving 1880 patients were included. The results demonstrated that high-dose-BT had significantly higher short-term healing when injected out of the fissure (OF) site than each side of the fissure (SF) site, with a risk ratio (RR) of 2.12 (1.08, 4.15); low-dose-BT did not show any difference across OF and SF site with RR of 1.20 (0.85, 1.68). High-dose-BT at the OF site showed similar healing to low-dose-BT at the same site (RR of 1.02 (0.79, 1.31)) but with a higher risk of incontinence with RR of 3.54 (0.85, 14.76). In contrast, high-dose-BT at the SF site showed lower healing compared to low-dose-BT at the same site with RR of 0.57 (0.29, 1.14). Both high-dose-BT and low-dose-BT at the OF site had higher recurrence than high-dose-BT or low-dose-BT at the SF site with RR of 2.08 (0.33, 13.11) and 1.89 (0.60, 5.94), respectively.

Conclusions: Given moderate level of evidence, low-dose BT is optimal; injection out of the fissure site improves short-term outcomes while injection each side of the fissure site tends to reduce recurrence in the longer term.

1. Introduction

Anal fissures are thought to result from trauma that stretches the anal canal, and although it is a common non-fatal disease, it can significantly decrease quality of life [1]. This condition may persist and become a chronic anal fissure (CAF); hypertonia and spasm of the internal anal sphincter leading to local ischemia have been suffered by these patients [2].

Surgery is the treatment of choice for CAF, with high cure rates of 88–100%, but carries an increased risk of incontinence ranging from 8 to 30% [3]. Since 1993, Botulinum toxin (BT) injection has been widely used for treatment of CAF [4] with a lower cure rate (60%–80%) but also a lower risk of incontinence [5]. BT injection inhibits the release of acetylcholine and causes the short-term paralysis of the internal sphincter muscle [6]. However, evidence indicates that BT efficacy depends on the appropriate dosage and injection site [7]. Only a few

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systematic reviews with meta-analyses (SRMA) have focused on dosage issues. The first SRMA [6] included 34 randomized controlled trials (RCTs) and non-RCTs, and indicated no relationship between BT dose, healing rate, and postoperative incontinence. The second SRMA [8] pooled 18 RCTs reporting increased incontinence and recurrence rates, but lower healing rates with higher BT dosage. However, BT efficacy depends not only on the dose, but also on the site of injection. To our knowledge, there are no current clinical practice guidelines advising the choice of BT dose or injection site for the treatment of CAF [3]. Therefore, a systematic review and network meta-analysis (NMA) was conducted to estimate the relative treatment effects of low/high dose and injection sites of BT in CAF patients.

2. Material and methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for network meta-analysis [9], updated PRISMA 2020 [10], and methodological quality complied with the AMSTART 2 [11]. The study review protocol was registered at PROSPERO (CRD42019145608).

2.1. Search strategy

Relevant studies were identified from MEDLINE, Scopus, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception through May 31, 2021. Search strategies were constructed based on patients, interventions, comparators, and outcomes, as described in more detail in Appendix Table 1. No language restrictions were applied. Reference lists of the review articles were also explored.

2.2. Selection of studies

Two reviewers (K.V. and P.I.) independently performed study selection. Disagreements were resolved by consensus within the review team. RCTs were eligible if they (a) included adult patients with CAF defined as symptoms present for more than 8 weeks or fissure with one or more stigmata of chronicity, including a hypertrophied anal papilla, sentinel tag, and exposed sphincter muscle [3]; b) compared BT or a BT combination therapy with any of other interventions; and c) had any of the outcomes of interest: healing, adverse events, or post-treatment anal pressure. Studies were excluded if patients had atypical anal fissures, insufficient data for pooling, and non-English publications which were untranslatable by Google Translate.

2.3. Interventions

The interventions included the BT dosage and injection site. AbobotulinumtoxinA (i.e., Dysport®) dosage was converted to onabotulinumtoxinA (Botox®) dosage using a ratio of 3:1 [12]. BT dose was categorized based on the median total dose of all included studies as low ($\leq$20 units) and high dose (>20 units). The injection sites were grouped as injected out of the fissure (OF) site, each side of the fissure (SF) site, or both sites (BS). The comparator could be any conservative treatment (CT, i.e., bulk-forming agents, topical anesthetics, topical corticosteroids, and placebo), sphincter relaxants (SR; i.e., topical nitrate and calcium-channel blockers), or surgery (i.e., internal sphincterotomy).

2.4. Outcomes of interest

The primary outcome was fissure healing defined as per the original study (e.g., complete epithelization of the fissure or absence of symptoms) and was assessed in the short-term ($\leq$3 months) or the long-term (>3 months) after randomizations.

The secondary outcomes were adverse events (i.e., incontinence and recurrence) and post-treatment anal pressure (i.e., resting anal pressure (RAP) and maximal squeeze anal pressure (MSAP)). Incontinence (absent vs. present) was evaluated in the short or long-term. Recurrence was defined as a previously healed fissure which subsequently relapsed and was clinically detectable on physical examination.

2.5. Data extraction

Two reviewers (K.V. and P.I.) independently extracted data including the characteristics of the study and patients (i.e., mean age,

Table 1
Characteristics of included studies.

Author	Year	Country	n	Mean age (yr.)	% Female	Symptom duration (months)	Intervention comparison
Maria [23]	1998	Italy	30	43.5	33.3	17.5	BT vs CT
Brisinda [24]	1999	Italy	50	42	50	12.1	BT vs SR
Maria [25]	2000	Italy	50	42.6	50	16.6	BT vs BT
Gecim [26]	2001	Turkey	57	NR	NR	NR	BT vs SR
Lysy [27]	2001	Israel	30	44.6	NR	19.7	BT vs BT + SR
Uluutku [28]	2001	Turkey	75	36.4	29.8	NR	BT vs SR
Brisinda [29]	2002	Italy	150	44	46.5	12.5	BT vs BT
Colak [30]	2002	Turkey	62	37.4	56.3	11.5	BT vs CT
Mentes [31]	2003	Turkey	111	39.1	NR	22.3	BT vs Surgery
Siproudhis [32]	2003	France	44	44.5	34	11.5	BT vs CT
Arroyo [33]	2005	Spain	80	39.5	31.3	19	BT vs Surgery
Iswariah [34]	2005	Australia	38	NR	NR	NR	BT vs Surgery
De nardi [35]	2006	Italy	30	44.5	43.5	NR	BT vs SR
Fruehauf [36]	2006	Switzerland	50	50	38	NR	BT vs SR
Jones [37]	2006	UK	30	45.5	43	16.5	BT vs BT + SR
Brisinda [38]	2007	Italy	100	44.1	53	15.8	BT vs SR
Abd Elhady [39]	2009	Egypt	160	34.4	NR	NR	BT vs Surgery vs SR
Festen [40]	2009	Netherland	73	40	48	3.4	BT vs SR
Nars [41]	2010	Egypt	80	33.8	65	7.6	BT vs Surgery
Sahakitrungruang [42]	2011	Thailand	40	34.2	72.5	NR	BT vs Surgery
Samim [43]	2012	Netherland	134	46	52.2	13.3	BT vs SR
Valizadeh [44]	2012	Iran	50	35.6	62	10.2	BT vs Surgery
Asim [45]	2014	New Zealand	41	42.5	62	NR	BT vs BT + SR
Berkel [46]	2014	Netherland	60	44	44.9	8.1	BT vs SR
Dinc [49]	2014	Turkey	60	36.3	36.7	NR	BT vs Surgery
Gandomkar [47]	2015	Iran	99	37.9	33.5	12.5	BT + SR vs Surgery
Nour [48]	2020	Egypt	96	32.9	39.6	5.9	BT vs Surgery

percentage of females, duration of symptoms), type of BT, dose and injection site, comparator, outcomes, and definitions. Frequency data or summary statistics with standard errors (SE) and 95% confidence interval (CI) were extracted for dichotomous outcomes, whereas mean and standard deviations were extracted for continuous outcomes. Any disagreement was discussed and resolved by a third reviewer (A.T.).

2.6. Risk of bias assessment

Risk of bias was assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB2) consisting of five domains: randomization process, deviations from intended intervention, missing data, measurement of outcomes, and selection of the reported results [13]. Each domain was classified as low, high, or of some concern. Disagreements were resolved by consensus with the team.

2.7. Statistical analysis

2.7.1. Direct meta-analysis (DMA)

DMA of each comparison was performed for all outcomes if there were at least three studies. The risk ratio (RR), mean difference (MD), and 95% CIs were estimated for dichotomous and continuous outcomes, respectively. They were then pooled across studies using an inverse variance method if heterogeneity was low (i.e., $I^2 < 25\%$ and Q test p-value > 0.1); otherwise, the Der-Simonian and Laird method was applied. Meta-regression was used to explore source(s) of heterogeneity (i.e., age, sex, symptom duration, type of BT). Publication bias was assessed using funnel plots, Egger's tests [14], and contour-enhanced funnel plots as required [15].

2.7.2. NMA

Treatments were numerically coded from 1 to 11 for surgery, CT, SR, LowBTOF, LowBTSF, HighBTOF, HighBTSF, HighBTBS, LowBTOF + SR, LowBTSF + SR, and HighBTOF + SR using surgery as the reference treatment. A 2-stage NMA using a multivariate meta-analysis with a consistency model and a common between-study variance was applied to assess relative treatment effects across the network [16]. Multiple treatment comparisons were estimated and tested accordingly. The consistency assumption was assessed using the design-by-treatment interaction model, and transitivity was explored by comparing patient characteristics between the treatment and comparison groups. Publication bias was assessed using comparison-adjusted funnel plots.

All treatments were ranked according to their probability of being the best treatment with the highest efficacy and adverse events using the rankogram and surface under the cumulative ranking curve (SUCRA). Clustered ranking plots that demonstrated efficacy and adverse effects simultaneously were constructed. All analyses were performed using Stata version 16.1 (Stata Corp, College Station, Texas, USA). Statistical significance was set at $P < 0.05$.

2.8. Level of evidence

The level of certainty of evidence of the network meta-analysis results were assessed using the Confidence in Network Meta-Analysis (CINeMA) [17], which considered 6 domains including within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.

3. Results

Of the 2934 studies identified, 32 met the inclusion criteria (Fig. 1). Of these, 6 studies were excluded for the following reasons: 1 [18] was a duplicate of another [19]; 2 [20,21] had insufficient data even after the authors were contacted; and 3 [12,19,22] had treatment pairs that were

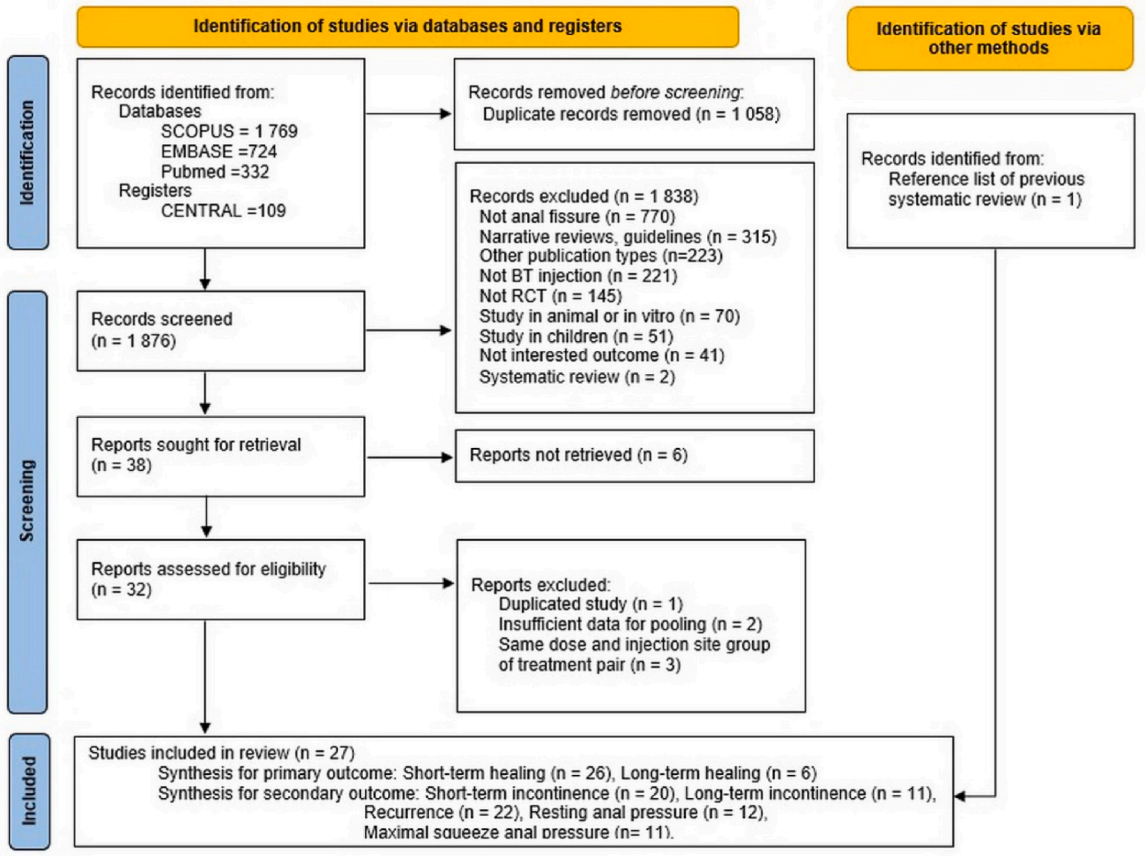

Fig. 1. Flow chart for study selection.

classified into the same dose and injection site group. Finally, 26 studies [23–48] plus one study [49] identified from the reference list were included in the analyses.

3.1. Characteristics of included studies

Among twenty-seven RCTs (n = 1880), the mean age ranged from 32.9 to 50 years, the percentage of females ranged from 22.0% to 72.5%, and the duration of pretreatment symptoms ranged from 3.4 to 22.3 months (Table 1). Three studies [27,34,37] included patients who previously failed to respond to topical treatment. SRs and surgery were common comparators. Outcomes of short- and long-term healing, short- and long-term incontinence, recurrence, RAP, and MSAP were reported in 26, 6, 20, 11, 22, 12, and 11 studies, respectively.

OnabotulinumtoxinA was more commonly used (23/27 = 85%) [23–31,33–35,37–41,43–45,47–49] with a median total dose of 20 units (range: 5–80 units). BT was injected bilaterally in two equally divided doses (94%). The median dilution and injected BT volume was 50

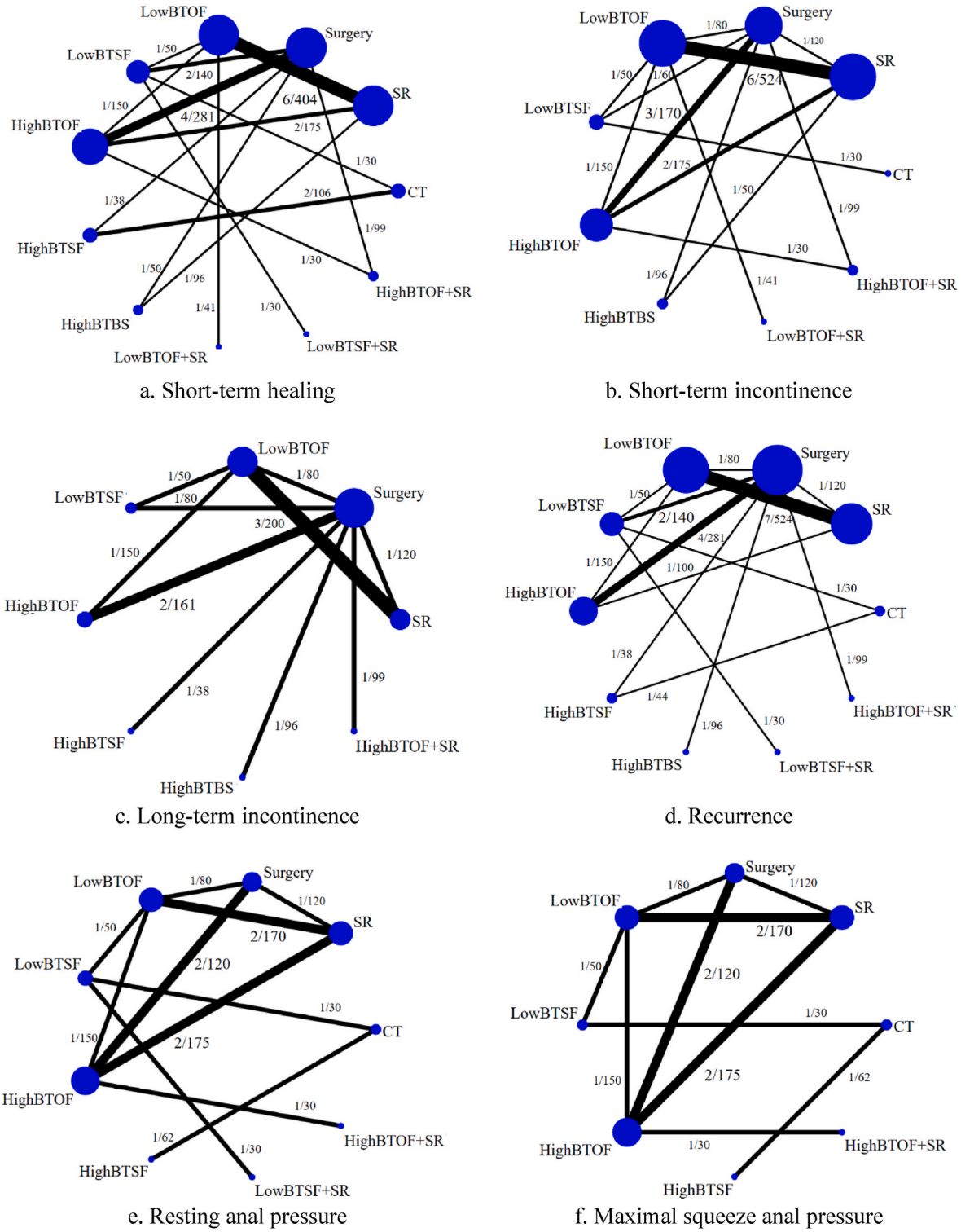

Fig. 2. Network maps of all outcomes.

units/ml (range: 12.5–100 units/ml) and 0.4 ml (range: 0.2–2.0 ml), respectively. The injection sites were grouped as follows: OF (66%), SF (29%), and BS (5%). Four RCTs evaluated the combination of BT and topical SRs [27,37,45,47] (Appendix Table 2).

3.2. Risk of bias assessment

Overall, most studies (74.1%) were considered to have some risk of bias, mainly because of the lack of information on the sequence generation process and treatment deviation (Appendix Table 3). Only 7.4% of the studies had a high risk of bias.

3.3. DMA

The data for all direct comparisons and outcomes were provided in Appendix Table 4. When compared with SR, LowBTOF had higher healing, but also higher incontinence with pooled RRs (95% CI) of 1.8 (0.78, 1.50), 1.25 (0.60, 2.61), and 1.25 (0.13, 11.76) for short-term healing, and short-term and long-term incontinence, respectively; and there was a lower risk of recurrence (RR 0.81 (0.62, 1.05)). Conversely, HighBTOF showed significantly lower short-term healing (0.82 (0.75, 0.89)) and significantly higher recurrence (4.18 (1.99, 8.81)) rates than surgery. Heterogeneity was present only when pooling LowBTOF vs. SR for short-term healing (Appendix Table 5), but none of heterogeneity sources was detected (Appendix Table 6). The funnel plots showed no evidence of publication bias (Appendix Fig. 1).

3.4. NMA

3.4.1. Healing

Twenty-six studies (n = 1720) with 11 treatments were included in the NMA for short-term healing (Fig. 2A). Most interventions had lower short-term healing than surgery, but only LowBTSF and HighBTSF were significant, with pooled RRs of 0.70 (0.53, 0.92) and 0.40 (0.21, 0.77), respectively, see Table 2 and Appendix Table 7.

Considering the injection sites, HighBTOF had significantly higher short-term healing than HighBTSF with a RR of 2.12 (1.08, 4.15); and LowBTOF vs. LowBTSF was not significant, with a RR of 1.20 (0.85, 1.68). Injection at both sites showed that HighBTBS had lower short-term healing than HighBTOF [RR = 0.84 (0.52, 1.36)], but it had higher healing than HighBTSF [RR = 1.77 (0.84, 3.75)]. Considering the BT dose, HighBTOF and LowBTOF effects in short-term healing were very similar, with a RR of 1.02 (0.79, 1.31). In contrast, HighBTSF appeared to reduce the effect compared to LowBTSF with RR of 0.57 (0.29, 1.14). Combining BT with topical SR did not improve short-term healing relative to without topical SR with RRs of 0.88 (0.44, 1.73) and 0.94 (0.60, 1.48) for Low- and HighBTOF, respectively.

In contrast, LowBTSF + SR significantly improved short-term healing relative to LowBTSF, with a RR of 3.33 (1.12, 9.91). Ranking according to SUCRA indicated that the highest probability of short-term healing was LowBTSF + SR, followed by surgery, HighBTOF, and LowBTOF (Table 2). There was no evidence of inconsistency (global chi-squared = 10.55, p = 0.159) or publication bias (Appendix Fig. 2A).

Only 6 studies (n = 377), including 7 treatments, were available for long-term healing. The NMA could not be performed because one study [35] (LowBTOF vs. SR) was disconnected and violation of the consistency assumption (global chi-square = 6.08, p = 0.014).

3.4.2. Incontinence

Twenty studies (n = 1458) with 9 treatments were included in the NMA for short-term incontinence (Fig. 2B). All interventions, except HighBTBS, had lower short-term incontinence than surgery, particularly for SR and LowBTOF, which were significant, with RRs of 0.13 (0.03, 0.54) and 0.15 (0.04, 0.64), see Table 3 and Appendix Table 8.

Considering the injection site regardless of dosage, the risk of incontinence was similar between LowBTOF and LowBTSF, with a RR of 1.09 (0.09, 13.38). Injection at both sites had a higher short-term risk of incontinence than injection at a single site; comparing HighBTBS vs. HighBTOF had a RR of 2.49 (0.66, 9.44). When considering the BT dose at the OF site, the HighBTOF group had higher incontinence than the LowBTOF group [RR = 3.54 (0.85, 14.76)]. Combining BT with SR did not appear to have any consistent benefit, (i.e., LowBTOF + SR vs. LowBTOF with a RR of 0.15 (0.01, 2.73) and HighBTOF + SR vs. HighBTOF with a RR of 1.73 (0.46, 6.59)). SUCRA ranking indicated that HighBTBS had the highest rate of short-term incontinence, followed by surgery, HighBTOF + SR, and HighBTOF (Table 3). There was no evidence of inconsistency (global chi-squared = 3.41, p = 0.756) or publication bias (Appendix Fig. 2B).

Eleven studies (n = 914) were evaluated for long-term incontinence with 8 treatments (Fig. 2C). All treatments, except HighBTSF, had lower

Table 2
Estimation of relative treatment effects of network meta-analysis for short-term healing.

Reference treatment	Risk ratio (95% CI)								
	Surgery	LowBTOF	LowBTSF	HighBTOF	HighBTSF	HighBTBS	LowBTOF +SR	LowBTSF +SR	HighBTOF +SR
Surgery	***84.3***	0.84 (0.62,1.13)	**0.70 0.53,0.92)**	0.86 (0.70,1.04)	**0.40 (0.21,0.77)**	0.72 (0.46,1.11)	0.74 (0.35,1.55)	2.34 (0.73,7.52)	0.81 (0.53,1.24)
LowBTOF	1.19 (0.88,1.60)	***62.4***	0.84 0.60,1.17)	**1.02 (0.79,1.31)**	0.48 (0.24,0.98)	0.85 (0.49,1.47)	**0.88 (0.44,1.73)**	2.78 (0.85,9.09)	0.96 (0.59,1.56)
LowBTSF	1.42 (1.08,1.87)	**1.20 (0.85,1.68)**	***38.2***	1.22 (0.89,1.66)	**0.57 (0.29,1.14)**	1.02 (0.60,1.73)	1.05 (0.49,2.24)	**3.33 (1.07,10.36)**	1.15 (0.70,1.88)
HighBTOF	1.17 (0.96,1.42)	0.98 (0.76,1.27)	0.82 (0.60,1.12)	***64.2***	0.47 (0.24,0.92)	**0.84 (0.52,1.36)**	0.86 (0.42,1.78)	2.74 (0.85,8.86)	**0.94 (0.60,1.48)**
HighBTSF	2.48 (1.30,4.70)	2.08 (1.02,4.25)	1.74 (0.88,3.44)	**2.12 (1.08,4.15)**	***13.5***	1.77 (0.84,3.75)	1.82 (0.68,4.88)	5.80 (1.54,21.79)	2.00 (0.91,4.40)
HighBTBS	1.40 (0.90,2.16)	1.17 (0.68,2.03)	0.98 0.58,1.66)	1.19 (0.74,1.94)	0.56 (0.27,1.19)	***43.6***	1.03 (0.43,2.46)	3.27 (0.94,11.41)	1.13 (0.57,2.21)
LowBTOF +SR	1.36 (0.65,2.86)	1.14 (0.58,2.26)	0.95 (0.45,2.04)	1.16 (0.56,2.40)	0.55 (0.20,1.47)	0.97 (0.41,2.33)	***48.2***	3.18 (0.81,12.46)	1.10 (0.48,2.53)
LowBTSF +SR	0.43 (0.13,1.37)	0.36 (0.11,1.17)	0.30 (0.10,0.93)	0.37 (0.11,1.18)	0.17 (0.05,0.65)	0.31 (0.09,1.07)	0.31 (0.08,1.23)	***96.2***	0.34 (0.10,1.19)
HighBTOF +SR	1.24 (0.81,1.90)	1.04 (0.64,1.69)	0.87 (0.53,1.43)	1.06 (0.68,1.66)	0.50 (0.23,1.10)	0.89 (0.45,1.74)	0.91 (0.40,2.10)	2.90 (0.84,10.0)	***54.8***

Inconsistency assumption checking: Number of studies = 26, Chi-square = 10.55, p-value = 0.159.
CI = confidence interval, CT = conservative treatment, SR=Sphincter relaxant, SUCRA=Surface under the cumulative ranking curve.
Each diagonal cell contains SUCRA, percentage probability of being **highest healing**, having highest healing rate of each treatment.
Each cell contains the risk ratio of treatment in column over treatment in row.

Table 3
Estimation of relative treatment effects of network meta-analysis for short-term incontinence.

Reference treatment	Risk ratio (95% CI)						
	Surgery	LowBTOF	LowBTSF	HighBTOF	HighBTBS	LowBTOF +SR	HighBTOF +SR
Surgery	***80.4***	**0.15 (0.04,0.64)**	0.14 (0.01,1.54)	0.54 (0.22,1.34)	**1.35 (0.49,3.72)**	0.02 (0.00,0.58)	0.94 (0.21,4.27)
LowBTOF	6.51 (1.56,27.18)	***33.4***	0.92 (0.07,11.23)	**3.54 (0.85,14.76)**	8.80 (1.63,47.35)	**0.15 (0.01,2.73)**	6.13 (0.90,41.60)
LowBTSF	7.10 (0.65,77.54)	**1.09 (0.09,13.38)**	***33.7***	3.86 (0.32,46.87)	9.60 (0.73,126.67)	0.16 (0.00,7.56)	6.69 (0.41,108.41)
HighBTOF	1.84 (0.75,4.52)	0.28 (0.07,1.18)	0.26 (0.02,3.14)	***61.7***	**2.49 (0.66,9.44)**	0.04 (0.00,1.07)	**1.73 (0.46,6.59)**
HighBTBS	0.74 (0.27,2.03)	0.11 (0.02,0.61)	0.10 (0.01,1.37)	0.40 (0.11,1.53)	***88.7***	0.02 (0.00,0.49)	0.70 (0.11,4.24)
LowBTOF +SR	43.47 (1.71,1104.81)	6.68 (0.37,121.71)	6.12 (0.13,283.23)	23.64 (0.93,600.39)	58.79 (2.05,1683.90)	***9.3***	40.94 (1.26,1325.40)
HighBTOF +SR	1.06 (0.23,4.81)	0.16 (0.02,1.11)	0.15 (0.01,2.42)	0.58 (0.15,2.20)	1.44 (0.24,8.74)	0.02 (0.00,0.79)	***77.9***

Inconsistency assumption checking: Number of studies = 20, Chi-square = 3.41, p-value = 0.756.
CI = confidence interval, CT = conservative treatment, SR=Sphincter relaxant, SUCRA=Surface under the cumulative ranking curve.
Each diagonal cell contains SUCRA, percentage probability of being **highest incontinence**, having highest incontinence rate of each treatment.
Each cell contains the risk ratio of treatment in column over treatment in row.

long-term incontinence than surgery, particularly HighBTOF, with a significant RR of 0.14 (0.02, 0.94). Injection at both sites was not significantly worse than injection at a single site; HighBTBS vs. HighBTOF with RR = 1.46 (0.04, 52.35). The SUCRA ranking indicated that surgery had the highest risk of long-term incontinence, followed by HighBTSF, see Appendix Table 9. There was no evidence of inconsistency (global chi-squared = 0.84, p = 0.840) or publication bias (Appendix Fig. 2C).

3.4.3. Recurrence

Twenty-two studies (n = 1622) were pooled for recurrence with 10 treatments (Fig. 2D). All treatments had higher recurrence than surgery, particularly SR, and LowBTOF, LowBTSF, and HighBTOF had RR of 8.79 (3.77, 20.50), 7.13 (3.01, 16.85), 3.77 (1.70, 8.33), and 3.29 (1.62, 6.66), respectively, see Appendix Table 10. Regarding injection site, the OF site had a higher recurrence rate than SF site (i.e., HighBTOF and LowBTOF had higher recurrence than HighBTSF and LowBTSF with RR of 2.08 (0.33, 13.11) and 1.89 (0.60, 5.94), respectively), but paradoxically, injection at both sites had less recurrence (i.e., HighBTBS had more recurrence than both HighBTOF and HighBTSF with RR of 1.52 (0.16, 14.06) and 3.16 (0.21, 47.53)). Higher doses showed less recurrence, i.e., lower recurrence in both HighBTOF and HighBTSF than LowBTOF and LowBTSF with RR of 0.46 (0.16, 1.30) and 0.42 (0.07, 2.59), respectively. The SUCRA ranking indicated that SR had the highest risk of recurrence, followed by HighBTOF + SR, and LowBTOF. There was no evidence of inconsistency (global chi-squared = 4.68, p = 0.456) or publication bias (Appendix Fig. 2D).

3.4.4. Post-treatment anal pressure

Twelve studies (n = 817) with 9 treatments and 11 studies (n = 787) with 8 treatments were pooled for RAP and MSAP, respectively. All BT injection sites had a higher RAP than surgery, especially in LowBTOF, LowBTSF, HighBTOF, and HighBTSF, with MD of 6.88 (0.93, 12.82), 21.15 (7.54, 34.76), 10.92 (4.60, 17.24), and 30.06 (12.09, 48.04), see Appendix Table 11. Regardless of dose, OF injections had significantly lower RAP than SF injections, that is, High- and LowBTOF vs. High- and LowBTSF yielded MDs of −19.14 (−36.84, −1.45) and −14.27 (−26.61, −1.93). Paradoxically, high-dose BT had higher RAP than low-dose BT (i.e., HighBTOF and HighBTSF vs. LowBTOF and LowBTSF showed MDs of 4.04 (−0.61, 8.70) and 8.91 (−2.91, 20.73), respectively), but these were not significant. The SUCRA ranking indicated that CT had the highest RAP, followed by HighBTSF, LowBTSF, and LowBTSF + SR.

Similarly, almost all treatments had higher MSAPs than surgery, that is, LowBTOF, LowBTSF, HighBTOF, and HighBTSF had MDs of 8.72 (1.05, 16.40), 3.19 (−21.74, 28.13), 7.40 (−2.31, 17.11), and 59.96 (30.33, 89.58), respectively, see Appendix Table 12. The OF injection site had a lower MSAP than the SF site (i.e., HighBTOF had a significantly lower MSAP than HighBTSF with a MD of −52.56 (−82.36, −22.76)), but this was not consistent (i.e., LowBTOF had a higher MSAP than LowBTSF with a MD of 5.53 (−18.25, 29.30)). Paradoxically, higher BT doses were not consistently associated with lower MSAP. The SUCRA ranking indicated that HighBTSF had the highest probability of having a high MSAP, followed by CT and SR. There was no evidence of inconsistency, for either RAP (global chi-square = 5.53, p = 0.137) or MSAP (global chi-square = 6.12, p = 0.106), and publication bias (Appendix Fig. 2E and F).

3.5. Clustered ranking plots of healing and adverse events

Cluster ranks were constructed by plotting the SUCRA of short-term healing (x-axis) versus adverse effects (i.e., incontinence and recurrence) (y-axis) (Appendix Fig. 3). Surgery was ranked second for short-term healing and incontinence, but lowest for recurrence. HighBTOF ranked moderately for short-term healing, incontinence, and recurrence. LowBTOF was still good in terms of short-term healing, with low incontinence, but high recurrence.

3.6. Evaluation of level of evidence

The CINeMA tool was used to evaluate levels of evidence for the primary outcomes indicating 58%, 11%, and 33% out of total comparisons were graded as moderate for short-term healing, incontinence, and recurrence outcomes, respectively. Evidence of LowBTAF and HighBTAF relative to surgery were in moderate level.

4. Discussion

We conducted a systematic review and NMA to determine the optimal injection site (OF, SF, and BS) and BT dose (low and high) for CAF. We found that surgery is the best option for healing, with the lowest risk of recurrence; although it increases short-term incontinence. BTOF, regardless of dose, generally produces better results than BTSF but also increases adverse effects. Combining BTOF/BTSF, that is, injection at both sites, does not appear to enhance efficacy, but does increase adverse effects.

Maria (2000) compared BT injected on each side of the fissure vs injected on the opposite site without fissure [25]. BTOF had a higher healing rate than injecting on either side of the fissure with RR of 1.47 (0.30, 2.08), a significantly lower RAP and unchanged MSAP. Likewise, our results showed that BTOF had better short-term healing than BTSF, particularly at higher doses. Fibrosis of the internal sphincter is more prominent at the base of the fissure than at other sites and injecting BT

out of the fissure should have a greater physiological effect [7]. Previous RCTs [4,29] have investigated the effects of BT doses on healing rates by comparing 40 units vs. 20 units of Dysport® and 30 units vs. 20 units of Botox®, indicating no significant difference. Our results support previous findings indicating that higher doses did not necessarily increase short-term healing, but could increase incontinence and recurrence. Combining LowBTSF + SR significantly improved efficacy, but this estimate was based on only a single primary study [27], reducing the precision of the estimate. Further studies are required to confirm these findings.

Our results suggest that LowBTOF is a good choice in the short term, whereas LowBTSF is better in the long term because of less recurrence and incontinence. Paradoxically, simultaneous injection at both sites did not show any benefit. In clinical practice, it is not unusual for the temporary sphincter-relaxing effects of BT to be assessed in the short term, with another treatment added within 6 weeks to 3 months. Therefore, it is possible that sequential injections might combine the best of both effects, but such protocols would be complex and supporting data are sparse, warranting further investigation. The risks and benefits were assessed simultaneously using a cluster rank plot. Considering healing and incontinence, HighBTOF and LowBTOF were clustered within the same area indicating that both treatments were reasonable options, whereas surgery had better healing but also higher incontinence. LowBTOF was favored over HighBTOF because of the lower risk of short-term incontinence.

This study is the first NMA to evaluate the efficacy of BT according to dose and injection site in CAF. All relevant clinical outcomes were considered in both the short -and long-term. However, some treatments were indirectly estimated from a small number of studies, resulting in low precision. Long-term healing outcomes could not be assessed due to network inconsistencies. BT dosage was dichotomized based on summary data as low and high; more granular effects of dosage levels may prove more informative if individual patient data were available. Some aspects of the injection technique (e.g., volume and dilution of BT and number of injection sites) could not be evaluated due to a lack of data.

5. Conclusion

Pooled evidence from RCTs suggest that BT injection out of the fissure site offered improved outcomes in the short term compared to injections on both sides for the treatment of CAF with evidence of low to moderate level. Low-dose patients had a lower risk of short-term incontinence and a better RAP. Injection on either side of the fissure may offer some advantages in reducing recurrence in the longer term and could be further explored in a sequential protocol.

Ethical approval

Ethical approval was not given because we conducted systematic reviews that did not collect personal information from patients.

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None.

Author contributions

Kasidin Vitoopinyoparb: Conceptualization, Design of the study, Data extraction, Data analysis, Interpretation of results, Writing-Original Drafting the article.

Putsarat Insin: Data extraction.

Kunlawat Thadanipon: Design of the study, Interpretation of results, Writing-Review and Editing.

Sasivimol Rattanasiri: Design of the study, Data analysis, Interpretation of results, Writing-Review and Editing.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2022.106798.

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