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Tolerability and efficacy of botulinum toxin injection in the treatment of bromhidrosis: a systematic review and meta-analysis of clinical trials

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Abstract

This review evaluates the risks and benefits of botulinum toxin (BTX) therapy for treating bromhidrosis. A search was conducted across six databases, including clinical trials comparing BTX therapy with BTX-free controls. The analyzed outcomes included pooled adverse events (AEs), treatment success, ≥ 50% overall improvement, and recurrence rates. Subgroup and sensitivity analyses were performed. Fourteen trials involving 1,293 participants were eligible. The BTX group experienced significantly fewer AEs than controls (relative risk [RR], 95% confidence interval [CI]: 0.33 [0.20–0.54]). Subgroup analysis indicated that the AE reduction was significant only when compared to small skin incision procedures. Overall, BTX did not show significant treatment success (RR [95% CI]: 1.06 [0.85–1.34]) or ≥ 50% improvement (RR [95% CI]: 0.98 [0.93–1.03]). However, BTX demonstrated superior treatment success compared to electrocauterization (RR [95% CI]: 1.45 [1.15–1.83]) and ethanol injection (RR [95% CI]: 2.27 [1.49–3.45]). Against placebos, BTX significantly reduced odor intensity (mean difference [95% CI]: 1.39 [–2.63 to –0.16]). Nevertheless, the recurrence rate was significantly higher in the BTX group (RR [95% CI]: 3.80 [1.06–13.67]). Notably, most studies ($n = 9$) were of low quality. In conclusion, although BTX is safe, it is not effective for the treatment of bromhidrosis.

Keywords: body odor, bromhidrosis, botulinum, botulinum toxin, systematic review

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Introduction

Bromhidrosis, also known as osmidrosis, is a condition characterized by an overabundance of body malodor emanating from the integumentary system (1). The pathophysiology is complex, incorporating multiplex constellations of abnormal bacterial skin microbiota, abnormally excessive secretion of sweat, metabolic imbalance, and apocrine sweat that contains lipocalins, as well as socioeconomic and environmental factors (2, 3). A variety of treatment modalities to manage bromhidrosis have been explored, including botulinum toxin therapy (BTX), microwave-based therapy, laser therapy, and surgical intervention; of them, BTX has been by far the most studied minimally invasive treatment (4). Other treatment modalities such as topicals are commonly used due to the ease of use and cost effectiveness (5, 6). However, it is crucial to mention that they act by mechanically blocking the sweat glands' openings and preventing sweat secretion, and they do not treat the underlying cause of excessive sweat secretion (6, 7).

BTX, a neurotoxin extracted from the bacterium *Clostridium botulinum*, has been investigated for its therapeutic effect against several dermatological conditions, such as hyperhidrosis, rosacea, Frey's syndrome (gustatory sweating), acne vulgaris, and hypertrophic scarring (8, 9). It has been postulated that BTX disrupts cholinergic neuronal activity at autonomic receptors (10, 11). Because acetylcholine is a known potent stimulator of the sweat glands, BTX theoretically exerts its denervating properties to be effective (10, 11).

The impact of bromhidrosis is frequently overlooked. Despite its inapparent effects on physical health, its impact on one's psychological, social, and professional life can be detrimental. A recent observational study by Kataoka et al. involving 34 patients with bromhidrosis revealed that 67% of them experienced severe depression attributed to bromhidrosis (12). Most psychological symptoms were caused by isolation and fear of negatively perceived social stigma (12). Another cross-sectional survey conducted in China by Zhang et al. suggested significant pathopsychological impacts of bromhidrosis in various domains, including somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, phobic anxiety, paranoid ideation, psychoticism, and hostility (13).

Beginning in 2003, Heckman et al. pioneered a successful clinical trial of BTX for managing bromhidrosis (14), which demonstrated its safety and efficacy in alleviating body odor. Several other clinical trials have been conducted to support its implementation (4, 15–22). Most published trials have generally demonstrated consistent safety of BTX with good tolerability, no or minimal reported non-serious adverse events (AEs) / serious adverse events (SAEs), and no reported all-cause mortality (15, 18, 21–26). Nevertheless, the evidence of its benefits is inconsistent. A study by Xie et al. of BTX therapy for bromhidrosis demonstrated a non-significant cure rate for mild bromhidrosis and a significantly inferior cure rate for severe bromhidrosis compared to small skin incision surgery (23). A similar result was reported by Li et al. (18). In contrast, Wang et al. revealed a significantly better cure rate of BTX therapy when compared to small skin incision surgery (4). The majority of available trials comparing BTX with other existing modalities as control arms (i.e., ethanol injection and electrocauterization) also produced conflicting results.

Our review of the available literature found no study that pooled the available evidence on the efficacy and safety of BTX in

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the treatment of bromhidrosis. This meta-analysis thus serves to fill the gap by analyzing pooled data from clinical trial studies that examined the role of BTX in the management of bromhidrosis.

Methods

Protocol and registration

This systematic review and meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol and registered with the International Prospective Register of Systematic Reviews (PROSPERO) registry (CRD42023491985).

Literature search strategy and eligibility criteria

The authors searched available records from inception to December 2023 on the following databases: Cochrane CENTRAL, Google Scholar, ProQuest, PubMed/MEDLINE, ScienceDirect, and SinoMed. The search incorporated both MeSH keywords and a field-text input, which was combined through the Boolean connector model. The keywords included "bromhidrosis," "osmidrosis," "bad odor," or "body odor" to represent our population, and "botulinum" or "botulinum toxin" to represent the intervention of interest. The keywords were input and restructured according to the individual database's search format.

The retrieved records were screened for predefined eligibility criteria that included 1) an interventional study; 2) a sample population with a diagnosis of bromhidrosis or unpleasant body odor; 3) an intervention arm receiving BTX injection; 4) a control arm that did not receive BTX injection; 5) data on relevant outcomes; and 6) written in either English or Chinese. Any records that did not meet these criteria were considered ineligible for this study.

Following the database search, the retrieved records were imported into a single Excel sheet and distributed to three reviewers for a thorough independent screening. The reviewers shared decision-making, and any discrepancy in opinion was resolved through group discussion and the involvement of other authors.

Data extraction

The required data were extracted following the selection of relevant studies: name of the first author, type of clinical trial, year of publication, study location (country), sample size for each arm, sex and mean age of participants, type of intervention of both arms, types of BTX delivered, anatomical area of injection, route of injection, dose of injection, and time to follow-up. Data on safety outcomes and efficacy outcomes were also collected. Subsequently, the data were imported and recoded into SPSS software version 28 for statistical analysis.

Quality assessment

The Jadad scale was used to assess study quality and the risk of biases (27). The Jadad scale has demonstrated good validity and reliability, and it is frequently used to assess the quality of clinical trials (28). The scoring criteria encompass randomization (scored 0, 1, and 2), double-blinding techniques (scored 0, 1, and 2), and comprehensive reporting of withdrawals and dropouts (scored 0 and 1). The total possible score for each study ranges between 0 and 5. The cutoff for a high-quality study was set at ≥ 3 out of 5 if blinding was feasible, and ≥ 2 out of 5 if blinding was not feasible (29, 30). The quality assessment of the included studies was independently evaluated by two reviewers.

Definition of outcome measures

Our study endpoints included the safety and efficacy outcomes of BTX in the treatment of bromhidrosis. The safety outcome was defined as overall AEs. We excluded both SAEs and all-cause mortality from the safety analysis because none of the trials demonstrated any SAEs or mortality in any of the arms. Efficacy outcomes were defined as total treatment success, overall improvement, and recurrence. Malodor was evaluated by either 1) a questionnaire answered by the patient and independent raters that evaluated blinded T-shirt samples, or 2) one or more relatives, the physician, and the patient himself or herself rating the degree of malodor. However, due to inconsistency in how the published trials defined treatment success and the unavailability of objective tools to determine the scale of malodor, binary outcomes were set for both categorical and ordinal outcomes. Total treatment success was defined as a 100% resolution of malodorous symptoms, or the highest score on each Likert satisfaction scale used. Overall improvement was defined as ≥ 50% improvement from the baseline score. However, all studies that included placebo-treated control arms used continuous variables to assess the reduction in odor intensity; thus, the treatment success for placebo-treated control arms was defined and performed separately. The rate of recurrence was indicated by the return of bromhidrosis symptoms usually between 6 and 12 months after treatment.

Statistical analysis

All outcome variables, apart from the treatment success analysis for placebo-treated control arms, were regarded as binary outcomes; the analysis was reported as relative risk (RR). For the reduction in odor intensity among the placebo-treated control arms with continuous data, mean difference analysis was performed using Hedges' *g* subgroup analysis based on control arms and quality of studies. Leave-one-out sensitivity analysis was also carried out to delineate the effect of each individual study in certain study endpoints. Heterogeneity was assessed using the I^2 measure. Publication bias risk was assessed using both a funnel plot and Egger's regression test. All statistical analyses were performed using both IBM SPSS Statistics for Mac (Version 28.0, IBM Corp., Armonk, NY) and Stata (Stata Statistical Software: Version 17, College Station, TX: StataCorp LP), with statistical significance determined at $p < 0.05$ and a 95% confidence interval (CI).

Results

Literature search results

A total of 644 records were retrieved from the six databases: Cochrane CENTRAL (n = 8), PubMed/MEDLINE (n = 14), Google Scholar (n = 488), ScienceDirect (n = 52), ProQuest, (n = 19), and SinoMed (n = 63). Screening for duplicates excluded 91 records, and title/abstract screening excluded a total of 529 records due to being observational studies (n = 39), book chapters (n = 29), review articles (n = 154), unavailable abstracts (n = 55), case reports/series (n = 24), irrelevant interventions (n = 78) and irrelevant populations (n = 87), and non-English or non-Chinese articles (n = 36).

Further full-text screening excluded articles with single-arm trials (n = 9) and those with both arms receiving BTX (n = 1). A total of 14 studies were included in our study for qualitative and quantitative analyses. The PRISMA flow diagram is summarized in Figure 1.

Characteristics of studies included

Table 1 outlines the characteristics of the 14 studies included. All studies were clinical trials, eleven of which were randomized controlled trials (RCTs). The pooled studies included 1,293 participants with bromhidrosis, with 681 receiving BTX therapy. The estimates for mean age across the studies included were between 18 and 33, with most studies at the lower end. Women accounted for approximately 61.3% of the pooled sample. Most studies were conducted in China (n = 11), followed by Germany (n = 2) and Taiwan (n = 1). All treatment arms received BTX-A serotype injections, whereas the control arms varied and included small skin incision (n = 8), placebo (n = 3), electrocauterization (n = 2), and ethanol injection (n = 1). The site of injection was invariably in the axilla, with intradermal routes being the most common injection method (n = 10). The BTX was manufactured by various manufacturers: Lanzhou (Lanzhou Institute of Biological Products, Lanzhou, China) (n = 9), Dysport (Ipsen, Wrexham, UK) (n = 2), and Allergan (Allergan, Westport, Ireland) (n = 2). The follow-up period in the studies ranged from 1 week to 24 months.

Quality of studies

Among the 14 studies, five were considered high quality (14, 15, 19, 22, 25); two high-quality studies scored 2 out of 5 owing to unfeasible blinding (Table 2) (19, 25). The remaining nine studies were classified as low quality (4, 16–18, 20, 21, 23, 24, 26). Among these, one study attained a score of 0, seven achieved a score of 1, and one received a score of 2. Subgroup analysis for all study endpoints based on the quality of studies was performed and is displayed in the Supplementary Materials.

Safety outcome analysis

Overall, there was a significantly decreased risk of AEs among the BTX-treated arm compared to the controls (RR [95% CI] = 0.33 [0.20–0.54], I^2 = 44.93%; Fig. 2). Subgroup analysis found a significantly lower risk of AEs after BTX treatment compared to small skin incision surgery (RR [95% CI] = 0.32 [0.19–0.54], I^2 = 51.20%). The leave-one-out analysis among small skin incision surgery-controlled studies showed a higher reduction in AE risk by removing the Wang et al. study. Among the low-quality studies, there was also a significant reduction in AEs (RR [95% CI] = 0.14 [0.06–0.34], I^2 = 0.00%). The lower dose subgroup (50 U/ml) showed a significantly lower risk of AEs (RR [95% CI] = 0.12 [0.04–0.33], I^2 = 0.00%; Supplementary Materials).

Efficacy outcome analysis

Ten studies analyzed treatment success (Fig. 3A). Overall, BTX showed a non-significant increase in total treatment success compared to the controls (RR [95% CI] = 1.06 [0.85–1.34], I^2 = 85.22%). Further subgroup analysis found no significant benefit

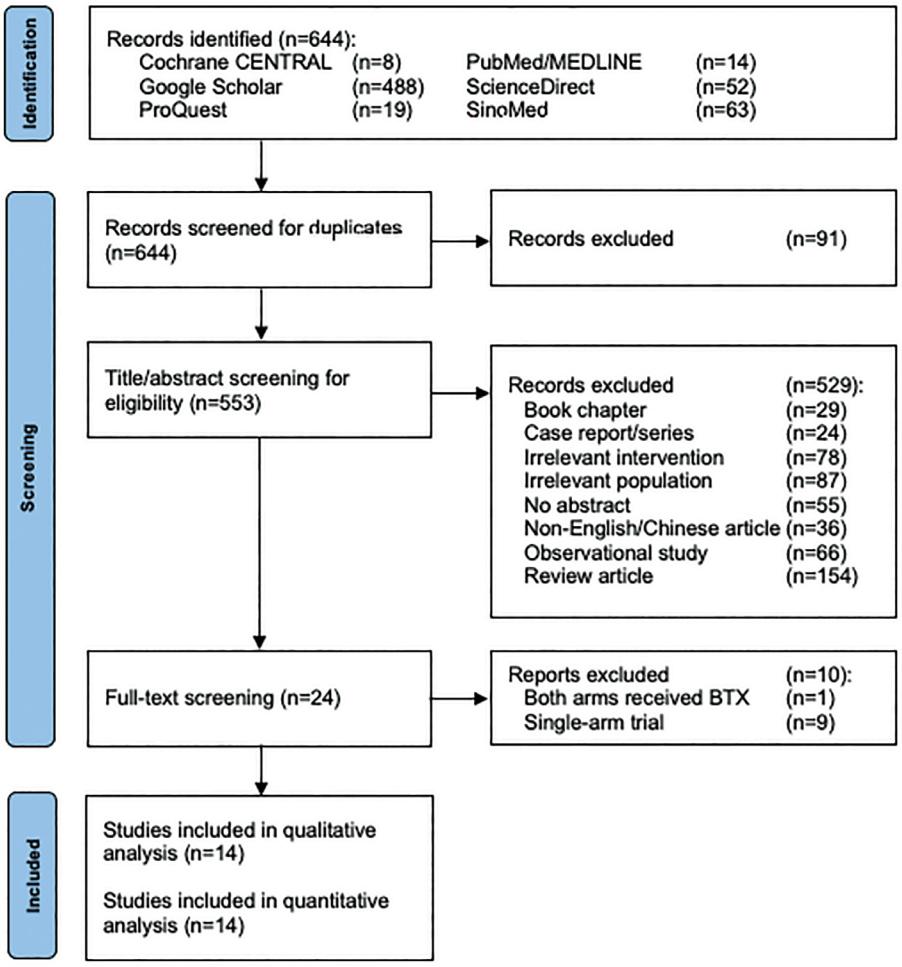

Figure 1 | Bromhidrosis. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the study. BTX = botulinum toxin.

Table 1 | **Baseline characteristics of the clinical trials included.**

Author (year)	Country	Study design	Arm	Sample size (*n*)		Sex		Age ± *SD*	Site	Intervention	Serotype of BTX	Manufacturer	RoA	Dose (U/ml)*	Follow-up
				Σ	Each arm	M	F								
Heckmann, et al. (2003) (10)	Germany	RCT	Tx	32†	16†	6	10	27.00 ± 9.92	Axilla	BTX	A	Dysport	ID	100	1 w
			Con		16†	6	10			Placebo	—	—	—	—	
Heckmann, et al. (2007) (11)	Germany	RCT	Tx	51†	51†	32	19	33.30 ± 13.37	Axilla	BTX	A	Allergan	ID	50	1 w, 3 mo
			Con		51†					Placebo	—	—	—	—	
Xie, et al. (2009) (12)	China	RCT	Tx	150	74	62	88	23.00 (NA)	Axilla	BTX	A	Lanzhou	SC	50	1–3 mo
			Con		76					Small incision	—	—	—		
Liu, et al. (2013) (13)	China	RCT	Tx	80	40	30	50	26.00 (NA)	Axilla	BTX	A	Lanzhou	ID	50	6 mo
			Con		40					Ethanol	—		—		
Xie, et al. (2014) (19)	China	RCT	Tx	150	74	27	47	23.00 ± 8.00	Axilla	BTX	A	Lanzhou	ID	100	1–3 mo
			Con		76	35	41	23.00 ± 9.00		Surgery	—	—	—	—	
Li, et al. (2017) (14)	China	NRCT	Tx	89	42	14	28	24.50 ± 8.20	Axilla	BTX	A	Lanzhou	NA	50	3–9 mo
			Con		47	16	31	22.70 ± 10.40		Small incision		—	—		
Qiu, et al. (2019) (16)	China	RCT	Tx	60	30	10	20	25.13 ± 3.42	Axilla	BTX	A	NA	ID	50	1–3 w
Shuai, et al. (2019) (20)	China	RCT	Tx	160	80	19	61	22.23 ± 6.64	Axilla	BTX + electrocauterization	A	Lanzhou	ID	75	3, 12 mo
			Con		80	21	59	23.47 ± 5.52		Electrocauterization			—		
Wang, et al.(2019) (15)	China	RCT	Tx	160	80	NA	NA	Range: 18–40	Axilla	BTX + small incision	A	Lanzhou	ID	100	12 mo
			Con		80	NA	NA	Range: 18–40		small incision	—		—		
Wu, et al. (2019) (3)	Taiwan	NRCT	Tx	38†	19	4	15	27.20 ± 14.00	Axilla	BTX	A	Dysport	ID	100	6–12 mo
			Con		19					Placebo	—	—	—	—	
			Con		30	11	19	24.89 ± 2 .31		Small incision			—		
Song, et al. (2020) (17)	China	RCT	Tx	122	62	32	30	24.00 ± 4.20	Axilla	BTX	A	Lanzhou	ID	50	6–24 mo
			Con		60	27	33	22.40 ± 3.60		Small incision	—	—	—	—	
Chen, et al. (2021) (18)	China	RCT	Tx	90	60	NA	NA	NA	Axilla	BTX ± electrocauterization	A	Allergan	SC	50	3, 6, 9, 12 mo
			Con		30	NA	NA	NA		Electrocauterization	—	—	—	—	
Tang, et al. (2021) (21)	China	RCT	Tx	40	20	7	13	25.37 ± 2.56	Axilla	BTX	A	Lanzhou	ID	50	6 mo
			Con		20	8	12	26.03 ± 3.27		Small incision			—		
Yang, et al. (2022) (22)	China	NRCT	Tx	71	33	15	18	27.20 ± 5.10	Axilla	BTX	A	Lanzhou	NA	70	3, 12 mo
			Con		38	17	21	25.70 ± 9.40		Small incision	—	—	—		

∑ = total participants in the study, BTX = botulinum toxin, Con = control arm, ID = intradermal injection, mo = month, NA = not available, NRCT = non-randomized controlled trial, RCT = randomized controlled trial, RoA = route of administration, SC = subcutaneous injection, *SD* = standard deviation, Tx = treatment arm, w = week, M = male, F = female.
*dose in each axilla; †number of axillae.

of BTX when compared to the controls receiving small skin incision surgery (RR [95% CI] = 0.91 [0.76–1.09], I^2 = 72.18%); however, BTX did significantly increase treatment success when compared to the controls receiving either ethanol injection (RR [95% CI] = 2.27 [1.49–3.45], I^2 = 0%) or electrocauterization (RR [95% CI] = 1.45 [1.15–1.83], I^2 = 0.00%). The subgroup analysis of quality of studies and doses showed no significant difference between subgroups. The leave-one-out analysis among small skin incision surgery-controlled trials showed higher treatment success by removing the Wang et al. trial (Supplementary Materials).

In addition, BTX significantly reduced odor intensity compared to placebos (mean difference [95% CI] = −1.39 [−2.63 to −0.16], I^2 = 90.97%; Fig. 3B). However, leave-one-out sensitivity analysis revealed an insignificant reduction in odor intensity when either study by Heckmann et al. was excluded from the analysis (Supplementary Materials).

The analysis of overall improvement (≥ 50%) was pooled from 10 studies (Fig. 4) and revealed an overall non-significant odor improvement (RR [95% CI] = 0.98 [0.93–1.03], I^2 = 63.66%). However, there was a significant improvement when BTX was compared to ethanol injection (RR [95% CI] = 1.23 [1.02–1.47]). No significant difference was seen between BTX and electrocauterization (RR [95% CI] = 1.03 [0.95–1.10], I^2 = 56.11%). When compared to small incision surgery, BTX showed a significantly lower probability of overall improvement (RR [95% CI] = 0.95 [0.90–1.00], I^2 = 47.29%). No significant differences were reported upon subgroup analysis based on either quality of studies or doses (Supplementary Materials).

With regard to recurrence (Fig. 5), BTX demonstrated a significant increase in the overall risk of recurrence at the last follow-up period compared to the controls (RR [95% CI] = 3.80 [1.06–13.67], I^2 = 81.85%). The significantly higher risk of recurrence was particularly apparent when compared to the controls receiving small incision surgery (RR [95% CI] = 10.56 [5.20–21.43], I^2 = 13.40%). There was no significant risk of recurrence when BTX was compared to electrocauterization (RR [95% CI] = 0.63 [0.24–1.63], I^2 = 0.00%). A significantly higher risk of recurrence was found among the low dose (50 U/ml) subgroup (RR [95% CI] = 3.21 [1.80–5.74], I^2 = 0.00%). However, no significant differences were reported upon subgroup analysis based on the quality of studies (Supplementary Materials).

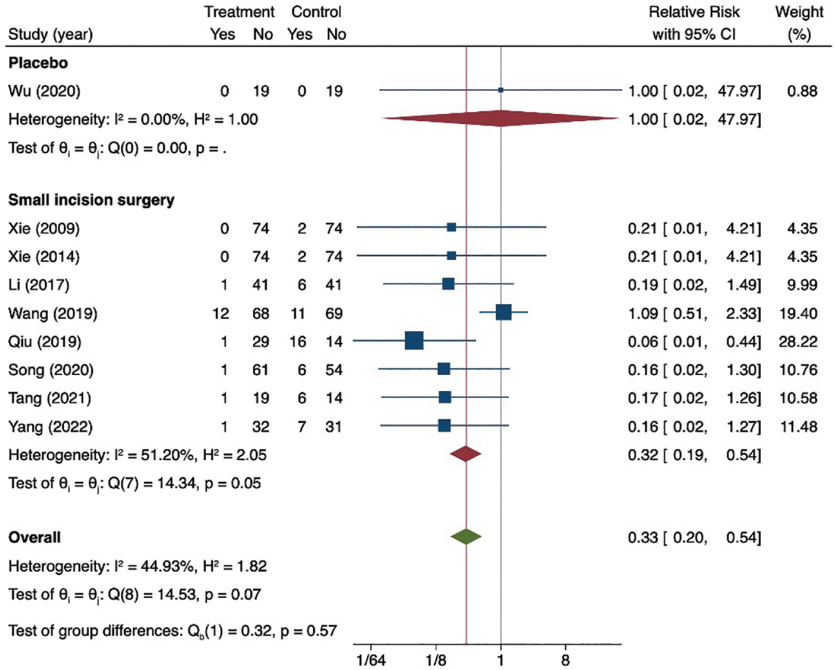

Figure 2 | Bromhidrosis. Forest plot of adverse events with subgroup analysis based on types of control arms. Treatment: botulinum toxin therapy for bromhidrosis. CI = confidence interval, RR = relative risk, I^2 = percentage of variability in effect estimates due to heterogeneity, H^2 = Cochran's Q statistic, Q(x) = Q statistic, p = *p*-value, θi = θj = test of homogeneity.

Table 2 | Jadad scores of the included randomized control trials.

Study (year)	Jadad score				Quality of study*
	R (0–2)	B (0–2)	D (0–1)	Total (0–5)	
Heckmann, et al. (2003) (10)	1	2	0	3	High
Heckmann, et al. (2007) (11)	2	2	0	4	High
Xie, et al. (2009) (12)	1	0	0	1	Low
Liu, et al. (2013) (13)	1	0	0	1	Low
Xie, et al. (2014) (19)	1	0	0	1	Low
Li, et al. (2017) (14)	0	0	0	0	Low
Qiu, et al. (2019) (16)	1	0	0	1	Low
Shuai, et al. (2019) (20)	1	0	0	1	Low
Wang, et al. (2019) (15)	2	0	0	2	High
Wu, et al. (2019) (3)	1	1	0	2	Low
Song, et al. (2020) (17)	0	0	0	1	Low
Chen, et al. (2021) (18)	2	0	1	3	High
Tang, et al. (2021) (21)	2	0	0	2	High
Yang, et al. (2022) (22)	0	0	1	1	Low

B = blinding, D = dropout, R = randomization.
*Studies were considered high quality when the Jadad score was ≥ 3 if blinding was feasible, or ≥ 2 if blinding was not feasible.

Publication bias analysis

Funnel plots for all study endpoints are displayed in the Supplementary Materials. Egger's regression analysis with either random-effect or fixed-effect models demonstrated high-risk publication bias for AEs (p = 0.01). Efficacy outcomes, on the other hand, demonstrated a low risk of publication bias in all endpoints, including total treatment success (p = 0.46), odor intensity among placebo control arms (p = 0.16), overall improvement (p = 1.54), and recurrence (p = 0.34).

Discussion

The evidence from pooled clinical trials of the safety and efficacy of BTX therapy in treating bromhidrosis has not previously been examined. This meta-analysis of 14 clinical trials was able to establish the safety of BTX as well as delineate the probability of total treatment success, overall improvement, and rate of recurrence in comparison to various control arms. Overall, BTX therapy demonstrated a good safety profile, especially when compared to invasive small skin incision surgery, but it did not significantly increase total treatment success or ≥ 50% improvement. Compared to placebos, ethanol injection, and electrocauterization, BTX therapy did have significantly higher treatment success (17, 22, 24). The ≥ 50% overall improvement after BTX treatment was also significant when compared to ethanol injection (17). However, when compared to controls receiving surgical intervention, BTX did not show a significantly different probability of total treatment success. The overall risk of recurrence was high, but only significantly higher compared to small skin incision surgery.

Our study found that BTX treatments were not associated with a higher risk of AEs when compared to placebos or small incision surgery. Comparison with other procedures (i.e., electrocauterization and ethanol injection) was not possible in our study due to limited data in the included trials. In addition, the placebo-controlled subgroup was analyzed from a single study. Nevertheless, our findings were consistent with a systematic review by Galadari

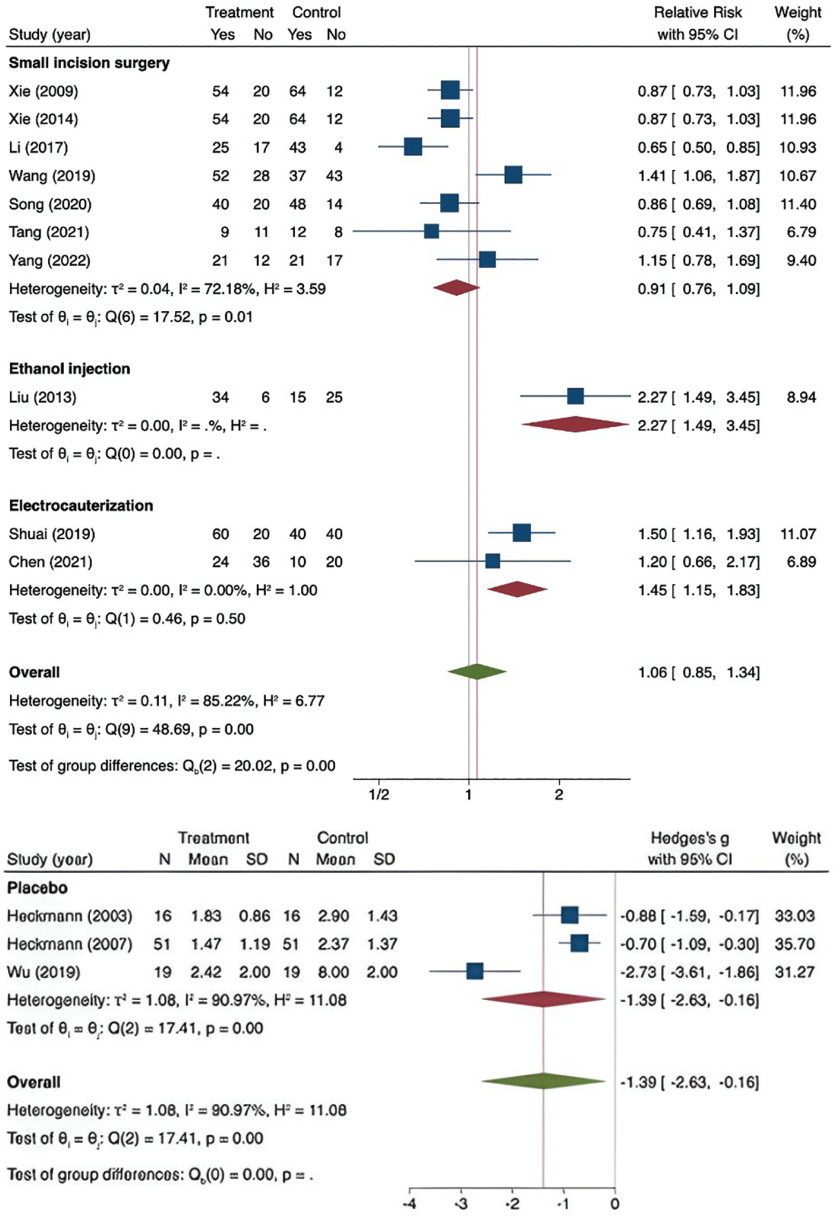

Figure 3 | Bromhidrosis. Forest plot of (A) the treatment success of botulinum toxin therapy for bromhidrosis compared with small skin incision, ethanol injection, and electrocauterization, and (B) reduction in odor intensity of botulinum toxin therapy compared with placebo controls.
CI = confidence interval, RR = relative risk, I^2 = percentage of variability in effect estimates due to heterogeneity, H^2 = Cochran's Q statistic, Q(x) = Q statistic, p = p-value, θi = θj = test of homogeneity.

et al. of pooled data from 11 studies, which reported no higher risk of AEs when BTX was used in the treatment of axillary hyperhidrosis (31). In the same study, the majority of reported AEs related to BTX in the treatment of palmar hyperhidrosis were mild to moderate in severity (31). In the Wang et al. trial, both small skin incision surgery and BTX were used in the intervention arm, which had a significantly higher risk of AEs compared to the arm receiving BTX therapy alone. Finally, our study found that no serious adverse events or all-cause mortality were reported by any of the included trials.

With regards to efficacy, BTX demonstrated no significant difference overall in total treatment success. Nevertheless, our subgroup analysis found that participants receiving BTX had significantly better treatment success compared to the controls receiving either ethanol injection or electrocauterization. The non-significant difference in the overall treatment success was largely attributed to the disproportionally high number of trials involving small skin incision surgery as the control, which did not demonstrate significantly better treatment success over placebos. These findings align with the study by Malik et al., which suggested that surgical treatment was the most effective method, but an aggressive one, among all treatment modalities (32). However, compared to placebos, BTX demonstrated significantly better performance in odor reduction. Regarding overall improvement, we found BTX

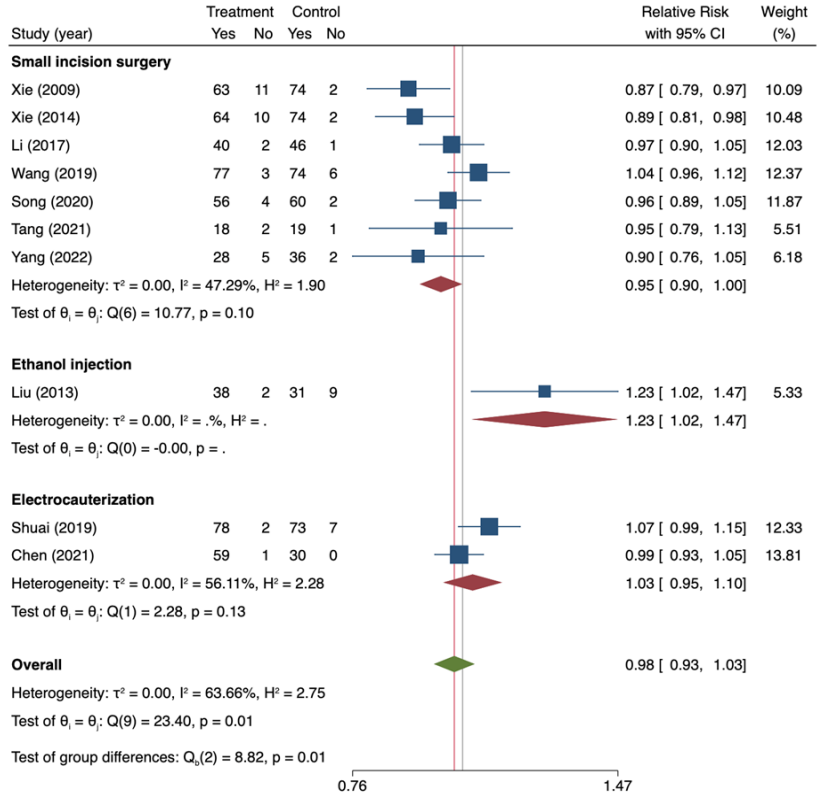

Figure 4 | Bromhidrosis. Forest plot of overall improvement; i.e., ≥ 50% improvement of bromhidrosis. Treatment: botulinum toxin therapy.
CI = confidence interval, RR = relative risk, I^2 = percentage of variability in effect estimates due to heterogeneity, H^2 = Cochran's Q statistic, Q(x) = Q statistic, p = *p*-value, θi = θj = test of homogeneity.

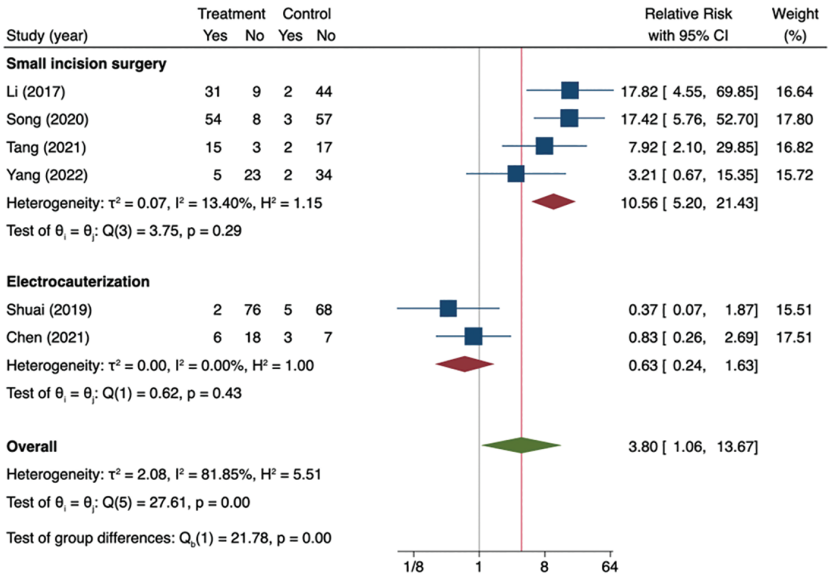

Figure 5 | Bromhidrosis. Forest plot of bromhidrosis recurrence events. Treatment: botulinum toxin therapy.
CI = confidence interval, RR = relative risk, I^2 = percentage of variability in effect estimates due to heterogeneity, H^2 = Cochran's Q statistic, Q(x) = Q statistic, p = *p*-value, θi = θj = test of homogeneity.

therapy was superior when compared to other non-surgical therapies. However, the efficacy benefits of BTX were compromised by the risk of recurrence, which was significantly higher when compared to surgical interventions. Thus, as a treatment for bromhidrosis, BTX demonstrated less efficacy than surgical intervention and exhibited a higher recurrence rate, necessitating repeated treatments. However, the advantage of BTX compared to surgical intervention lies in it being less invasive and safer.

We conducted a subgroup analysis based on BTX dosing categories, classified as high dose (100 U/ml) and low dose (50 U/ml) per axilla. The dosing did not influence the total treatment success outcome. Archawawat et al. and Darwish et al. had similar results when studying BTX doses in the treatment of hyperhidrosis (33, 34). On the other hand, we found that the lower dose subgroup resulted in a lower risk of AEs but a significantly higher risk of recurrence, whereas Archawawat et al. and Darwish et al. found that the risk of AEs did not differ between the two dosing regimens (33, 34).

Strengths and limitations

To the best of our knowledge, this is the first study that analyzed the safety and efficacy of BTX therapy in the treatment of bromhidrosis based on clinical trials. The comparison of BTX with other treatment modalities (i.e., electrocauterization, ethanol injection, and small skin incision) broadened our understanding of the safety and efficacy of BTX in clinical practice. Moreover, assessing the risk of recurrence can better influence treatment choice. Finally, the inclusion of a Chinese database resulted in a considerably greater pool of available literature; meta-analyses often miss these valuable data due to the language barrier because the studies are mostly published in Chinese, not English.

Despite our best efforts, this study has several limitations. The quality of available published data included in this study was generally low according to the Jadad scoring, which can compromise the quality of findings derived from this study. Furthermore, the majority of available studies compared BTX therapy with other interventions (only three trials had placebo control arms), which makes the overall findings less generalizable. This indicates a need for more trials, including trials with topical treatments. The disproportionately high number of surgically treated control arms may also have impacted the overall findings of our study.

Conclusions

This review established the safety of BTX injection therapy for the treatment of bromhidrosis. Despite the insignificant overall benefits, BTX therapy was significantly better than placebo, electrocauterization, and ethanol injection in treatment success. The efficacy of BTX therapy did not differ significantly when compared to small skin incision surgery; however, the risk of recurrence was significantly higher. Overall, this review strengthens the evidence of BTX's role as a valuable therapeutic modality in the treatment of bromhidrosis.

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