Botulinum toxin A treatment for post-herpetic neuralgia: A systematic review and meta-analysis

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Abstract. The present meta-analysis study aimed to investigate the safety and efficacy of local administration of botulinum toxin (BTX-A) vs. lidocaine in the treatment of post-herpetic neuralgia. A systematic search of the Cochrane Library, PubMed, Embase, Chinese National Knowledge Infrastructure, Wanfang, Chongqing VIP Information Co. and Chinese Biomedical Literature Database was performed to identify randomized controlled trials (RCTs) comparing BTX-A and lidocaine in the treatment of post-herpetic neuralgia. The primary outcomes were Visual Analogue Scale (VAS) pain scores at 1, 2 and 3 months after treatment and the effective rate. Secondary outcomes were scores on the McGill pain questionnaire and adverse event rate. A total of 7 RCTs comprising 752 patients were included. The VAS pain score was significantly lower at 1 month [mean difference (MD)=-2.31; 95% CI: -3.06, -1.56; P<0.00001)], 2 months (MD=-2.18; 95% CI: -2.24, -2.11; P<0.00001) and 3 months (MD=-1.93; 95% CI: -3.05, -0.82; P=0.0007) after treatment, the effective rate was significantly higher (odds ratio=2.9; 95% CI: 1.71, 4.13; P<0.0001) and scores on the McGill pain questionnaire were significantly lower (MD=-10.93; 95% CI: -21.02, -0.83; Z=2.12; P=0.03) in patients who received BTX-A for post-herpetic neuralgia compared to those who received lidocaine. There was no difference in the adverse event rate between treatments. In conclusion, BTX-A has potential as a safe and effective treatment option for post-herpetic neuralgia. Further large and well-designed RCTs are required to confirm this conclusion.

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Abbreviations: BTX-A, botulinum toxin A; RCT, randomized controlled trial

Key words: botulinum toxin-a, post-herpetic neuralgia, meta-analysis, efficacy, safety

Introduction

Post-herpetic neuralgia refers to pain that persists after an acute episode of herpes zoster and resolution of the rash (1). Post-herpetic neuralgia is a frequent complication of herpes zoster. Approximately 12.5% of patients with herpes zoster aged ≥50 years suffer from post-herpetic neuralgia at 3 months after the outbreak of herpes zoster and the risk of post-herpetic neuralgia increases sharply with age (1).

Post-herpetic neuralgia affects nerve fibers and skin and is characterized by a constant burning, stabbing sensation or pain triggered by light contact with non-painful stimuli. Pain associated with post-herpetic neuralgia is frequently refractory to treatment and may persist for years, negatively impacting patients' quality of life (2-4).

Numerous interventions are available for symptom control in patients with post-herpetic neuralgia, but there is currently no disease-modifying therapy. Oral medications are commonly used to treat post-herpetic neuralgia, including pregabalin, gabapentin, anti-depressants, anti-convulsants, carbamazepine, lamotrigine and opioids. However, these treatments may not provide effective pain relief in ~50% of patients with post-herpetic neuralgia and long-term use of these agents is associated with adverse effects, including dizziness, ataxia, nausea and dependence (1,5,6).

Botulinum toxin (BTX-A) is a neurotoxic protein produced by *Clostridium botulinum*. BTX-A is used in the clinic to treat muscle spasticity through blockade of neuromuscular transmission. BTX-A also has anti-nociceptive properties, as it inhibits the release of sensory inflammatory mediators and peripheral neurotransmitters and inactivates membrane sodium channels in central neurons (7-10).

A recent study demonstrated that BTX-A has an analgesic effect in post-herpetic neuralgia, trigeminal neuralgia and other types of neuropathic pain (11). Several meta-analyses have reported on the use of BTX-A in neuralgia, but these reviews investigated a range of neuropathies and included multiple interventions (lidocaine, saline, placebo) as comparators (11,12). Since these meta-analyses lack a subgroup analysis, they may have limited relevance regarding the effectiveness of BTX-A in post-herpetic neuralgia; as the inclusion of multiple neuropathies, each with a different underlying pathology, and several comparators, may introduce confounding variables that produce a biased effect.

The objective of the present systematic review and meta-narrative was to investigate the safety and efficacy of local administration of BTX-A vs. lidocaine in the treatment of post-herpetic neuralgia.

Materials and methods

Literature search. The present meta-analysis and systematic review was performed according to the recommendations of the Cochrane Collaboration (13). Two review authors independently searched the PubMed, Embase, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang, Chongqing VIP Information Co. and Chinese Biomedical Literature Database using the following keywords: 'Botulinum toxin type A', 'abobotulinumtoxinA', 'lidocain', 'botulinum toxin A', 'BTX-A', 'post-herpetic neuralgia' and 'placebo'. Searches were limited to studies published between 2005 and February 2019 in the English or Chinese languages. Additional articles were selected from manual searches of included studies and reviews.

Inclusion criteria. The inclusion criteria were as follows: i) Study design: Randomized controlled trials (RCTs); ii) population: Clinically diagnosed with post-herpetic neuralgia, lesions had crusted and healed, there was no new rash, but there was pain at the site of the original lesion (14); iii) intervention: Subcutaneous injection of BTX-A vs. lidocaine; patients may have been administered treatments in addition to BTX-A or lidocaine (15); iv) treatment duration: <3 injections during <6 days of hospitalization; and v) outcome measures, including the Visual Analogue Scale (VAS) pain scores, McGill pain questionnaire and the rate of adverse events.

Patients had been diagnosed with post-herpetic neuralgia according to the American Academy of Neurology 2004 or Chinese Medical Association criteria (16). BTX-A (total dose, ≤100 units) was administered by subcutaneous injection at the site of the herpes lesion and subsequent pain at the proximal end of the nerve branch in the damaged tissue. Efficacy was evaluated by pain scores on a Visual Analogue Scale (VAS; 0, no pain; 10, most severe pain); the effective rate, defined as the percentage of patients in which symptoms and signs had improved and the pain was at least 25% reduced; and the McGill pain questionnaire, which contains three questions: 'What Does Your Pain Feel Like?', 'How Does Your Pain Change with Time?' and 'How Strong is Your Pain?', with responses that may be scored to a maximum of 78 points (higher scores indicate stronger pain) (17). Safety was assessed from the adverse event rate, including those that were self-limiting.

Exclusion criteria were as follows: i) No full text available; ii) insufficient data; iii) models of induced neuralgia; and iv) case reports, reviews and abstracts.

Disagreements between review authors (XLL and HPH) on study selection were resolved by discussion mediated by LLP, until consensus was reached.

Primary and secondary outcomes. The primary outcomes were VAS pain scores at 1, 2 and 3 months after treatment and the effective rate. Secondary outcomes were scores on the McGill pain questionnaire at one month after treatment and the adverse event rate during follow-up.

Data extraction. Two review authors independently extracted the following information from each of the studies included: Name of first author, year of publication, demographic characteristics of the study population, intervention measures and follow-up. Disagreements among review authors on data extraction were resolved by discussion until consensus was reached.

Risk of bias. Two review authors independently assessed risk of bias in the studies included using the Cochrane Risk of Bias Tool for Randomized Controlled Trials, which evaluates the following domains: Sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. In each domain, risk of bias was judged as 'high', 'unclear' or 'low' (18). Disagreements among review authors on assessment of study quality were resolved by discussion until consensus was reached.

Statistical analysis. Data analyses were performed using Review Manager 5.3 (Cochrane Collaboration). Mean differences (MDs) with 95% CIs were calculated for continuous variables (VAS pain score and McGill pain questionnaire) and odds ratios (ORs) with 95% CIs were calculated for dichotomous variables (effective rate and adverse event rate). Heterogeneity was evaluated with the I^2-test. A fixed-effects model was used for outcomes with evidence of low heterogeneity (I^2<50%) between studies and a random-effects model was used for outcomes with evidence of significant heterogeneity (I^2>50%) between studies. P<0.05 was considered to indicate statistical significance (19).

Results

Study characteristics. The searches identified 570 articles. Titles and abstracts were screened, 259 duplicates were excluded and 33 articles were considered eligible for inclusion. After analyzing the full-text articles, 26 studies were excluded. Among these, 6 articles reported incomplete data, 11 were on non-randomized controlled trials, 8 studies did not use lidocaine as the intervention and 1 article was a case report. Finally, 7 RCTs (8 datasets) were evaluated in the meta-analysis (Fig. 1) (20-27).

The characteristics of the studies included are presented in Table I. The 7 eligible RCTs included 752 patients (367 patients in the BTX-A group and 385 patients in the lidocaine group) who were followed up for 3 months.

Risk of bias in the studies included. A total of 3 trials described random sequence generation (22,23,26,27). In addition, 1 trial adequately reported allocation concealment (22,23). Furthermore, 2 trials detailed the methods of blinding (22,23,25). All trials reported information on incomplete outcome data (20-27). Reporting bias was described by 5 trials (Fig. 2) (21-23,25-27). Funnel plots for publication bias were not evaluated due to the small number of trials included in the present meta-analysis.

Primary outcomes

VAS pain score. The VAS pain scores at 1 month of follow-up were provided by 4 trials (569 patients, including

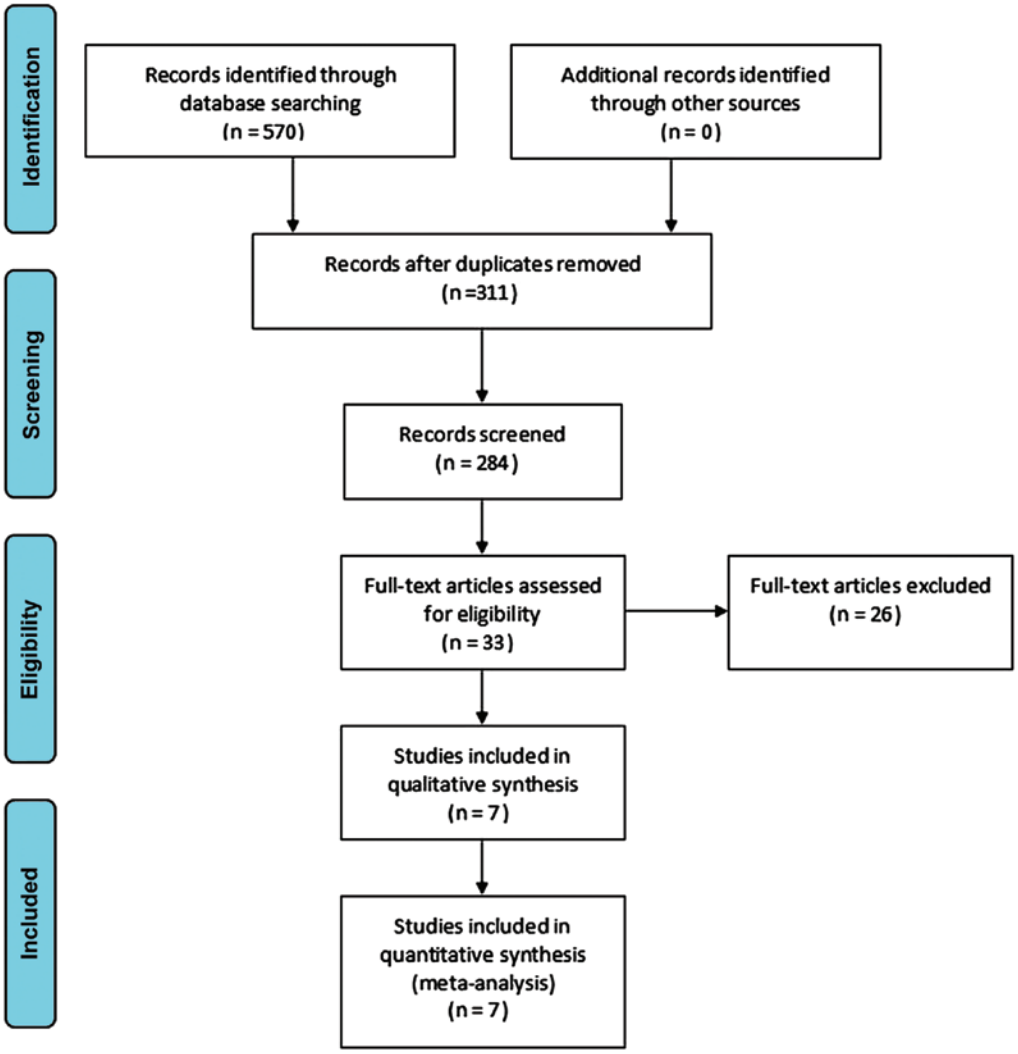

Figure 1. Flow chart of article screening and selection process.

289 patients in the BTX-A group and 307 patients in the lidocaine group) (20,21,24,27). There was evidence of heterogeneity between studies. The meta-analysis revealed a significantly lower VAS pain score in patients who received BTX-A for post-herpetic neuralgia compared to those who received lidocaine (MD=-2.31; 95% CI: -3.06, -1.56; Z=6.04; P<0.00001; Fig. 3). In a subgroup analysis, patients who received lidocaine were stratified by use of oral carbamazepine. At 1 month of follow-up, the VAS pain score was significantly lower in patients who received BTX-A for post-herpetic neuralgia compared to those who received lidocaine alone or lidocaine plus oral carbamazepine (lidocaine alone: MD=-0.87; 95% CI: -1.37, -0.38; P=0.0006; lidocaine plus oral carbamazepine: MD=-3.55; 95% CI: -3.59, -3.51; P<0.00001; Fig. 3).

The VAS pain scores at 2 months of follow-up were described in 3 trials (n=525 patients; 257 patients in the BTX-A group and 268 patients in the lidocaine group) (21,24,25). There was no evidence of heterogeneity between studies. The meta-analysis demonstrated a significantly lower VAS pain score in patients who received BTX-A for post-herpetic neuralgia compared to those who received lidocaine (MD=-2.18; 95% CI: -2.24, -2.11; P<0.00001; Fig. 4).

The VAS pain scores at 3 months of follow-up were described in 2 trials (n=98 patients; 49 patients in the BTX-A group and 49 patients in the lidocaine group) (22,23,27). There was evidence of heterogeneity between studies. The meta-analysis demonstrated a significantly lower VAS pain score in patients who received BTX-A for post-herpetic neuralgia compared to those who received lidocaine (MD=-1.93; 95% CI: -3.05, -0.82; Z=3.4; P=0.0007; Fig. 5).

Effective rate. Data reporting on the effective rate were included in 5 trials (n=623 patients; 306 patients in the BTX-A group and 317 patients in the lidocaine group) (21-23,25,27). There was no evidence of heterogeneity between studies. The meta-analysis demonstrated a significantly higher effective rate in patients who received BTX-A for post-herpetic neuralgia compared to those who received lidocaine (OR: 2.9; 95% CI: 1.71, 4.13; P<0.0001; Fig. 6).

Secondary outcomes

McGill pain questionnaire. Data from the McGill pain questionnaire at 1 month of follow-up were included in 2 trials (n=116 patients; 58 patients in the BTX-A group and 58 patients in the lidocaine group) (26,27). There was evidence of heterogeneity

Table I. Characteristics of trials included.

First author (year)	Patients, total (study completion)	Age (years)		Sex (male/female)		Interventions	Outcome measures	(Refs.)
		BTX-A group	Lidocain group	BTX-A group	Lidocain group			
Dai (2018)	71 (71)	64.5±8.9	66.2±8.4	18/14	21/18	BTX-A+gabapentin vs. Lidocain+gabapentin	VAS score, adverse events	(20)
Yang (2014)	400 (400)	56.32±5.69	56.34±4.88	120/80	115/85	BTX-A vs. Lidocain+carbamazepine	VAS score, effective rate	(21)
Xiao (2009) (2010)	40 (38)	70±15.41	65±14.20	11/9	8/12	BTX-A+gabapentin vs. Lidocain+gabapentin	VAS score, effective rate, adverse events	(22,23)
Zhu (2018)	65 (65)	/	/	/	/	BTX-A+Pregabalin+vitamin B1 vs. Lidocain+Pregabalin+vitamin B1	VAS score, effective rate	(24)
Xue (2017)	60 (60)	53.37±6.28	53.78±6.34	16/14	15/15	BTX-A+Pregabalin vs. Lidocain+Pregabalin	VAS score, effective rate	(25)
Yuan (2015)	56 (56)	58±3.5	57±4.3	16/12	11/17	BTX-A vs. Lidocain	Mcgill pain questionaire	(26)
Liu (2009)	60 (60)	56.36±0.9	56.8±0.9	13/17	14/16	BTX-A vs. Lidocain+carbamazepine	VAS score, effective rate, Mcgill pain questionaire	(27)

VAS, Visual Analogue Scale; BTX-A, botulinum toxin A.

Figure 2. Cochrane risk-of-bias assessment.

between studies. The meta-analysis demonstrated a significantly lower score on the McGill pain questionnaire in patients who received BTX-A for post-herpetic neuralgia compared to those who received lidocaine (MD=-10.93; 95% CI: -21.02, -0.83; Z=2.12; P=0.03; Fig. 7).

Adverse event rate. Adverse events during the follow-up period were described in 3 trials (n=169 patients; 81 patients in the BTX-A group and 88 patients in the lidocaine group). There was evidence of significant heterogeneity between studies. The meta-analysis revealed no significant difference in the adverse event rate in patients who received BTX-A for post-herpetic neuralgia compared to those who received lidocaine (OR: 0.57; 95% CI: 0.04, 7.93; P=0.67; Fig. 8).

Discussion

The present meta-analysis revealed that BTX-A has greater efficacy than lidocaine for post-herpetic neuralgia based on the VAS pain scores at 1, 2 and 3 months after treatment, the effective rate and the McGill pain questionnaire. There was no difference in the adverse event rate between treatments and BTX-A administration was not associated with any serious adverse events. Although the present meta-analysis was based on articles identified during a comprehensive search of seven databases, the results should be interpreted with caution. Of note, the results are based on a small sample size and risk of bias was unclear in five of the seven RCTs included (20,21,24,25,27).

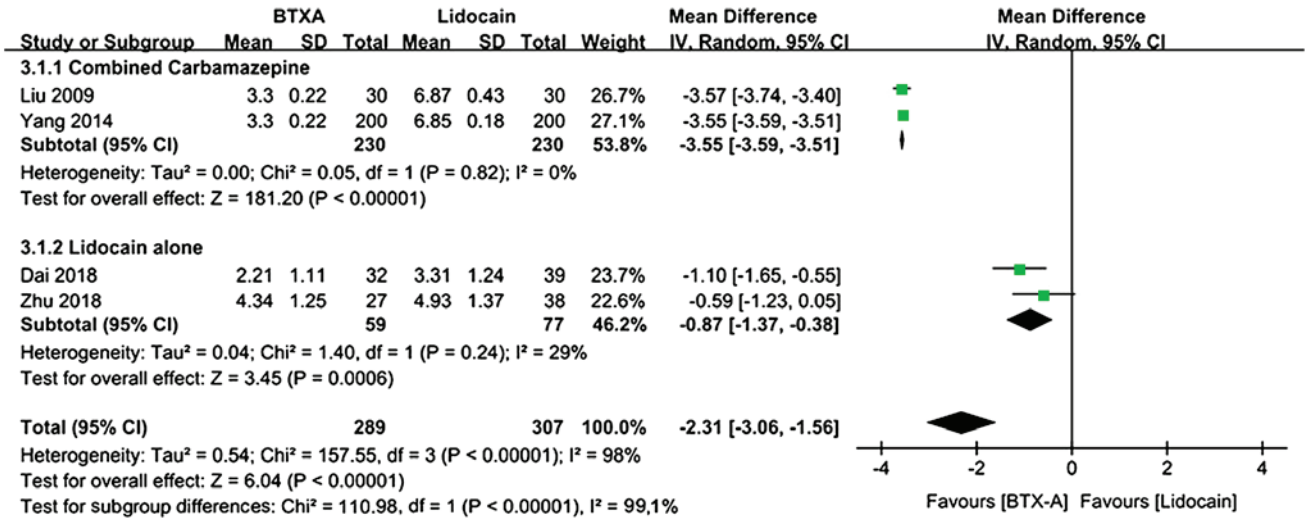

Figure 3. BTX-A vs. lidocaine for post-herpetic neuralgia: VAS pain score at 1 month of follow-up. VAS, Visual Analogue Scale; BTX-A, botulinum toxin A; df, degrees of freedom; IV, inverse variance; SD, standard deviation.

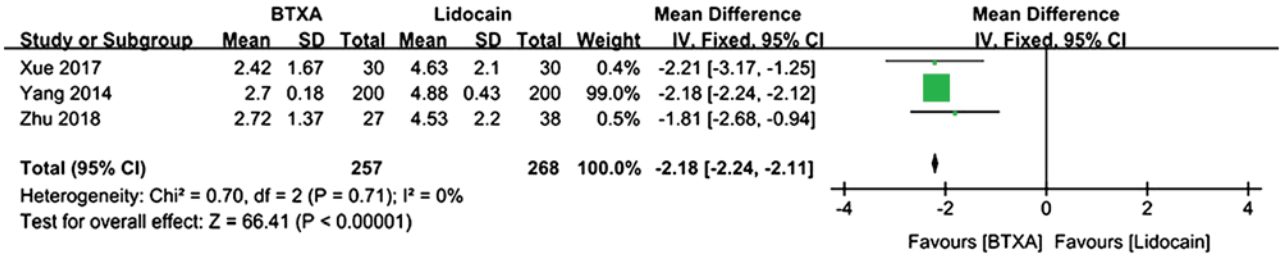

Figure 4. BTX-A vs. lidocaine for post-herpetic neuralgia: VAS pain score at 2 months of follow-up. VAS, Visual Analogue Scale; BTX-A, botulinum toxin A; df, degrees of freedom; IV, inverse variance; SD, standard deviation.

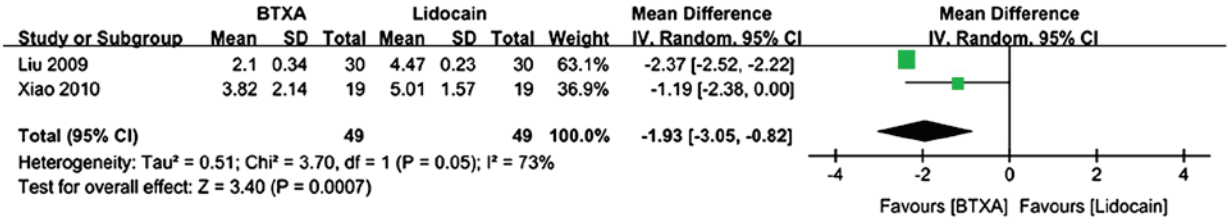

Figure 5. BTX-A vs. lidocaine for post-herpetic neuralgia: VAS pain score at 3 months of follow-up. VAS, Visual Analogue Scale; BTX-A, botulinum toxin A; df, degrees of freedom; IV, inverse variance; SD, standard deviation.

Previously, several meta-analyses have reported on the use of BTX-A in neuralgia. Meng *et al* (11) analyzed 12 RCTs and, consistent with the present results, their analysis suggested that BTX-A is a safe and more effective option than saline for alleviating neuropathic pain. They included studies investigating BTX-A for a range of neuropathies, including post-herpetic neuralgia, peripheral neuropathic pain, thoracic outlet syndrome, piriformis syndrome, spinal cord injury, trigeminal neuralgia and diabetic neuropathic pain, but did not perform a subgroup analysis investigating post-herpetic neuralgia alone. Shackleton *et al* (6) analyzed 6 RCTs and revealed that BTX-A was more effective than placebo for managing trigeminal neuralgia and post-herpetic neuralgia but did not perform any subgroup analysis investigating post-herpetic neuralgia alone. Yang *et al* (12) analyzed 4 RCTs and demonstrated the efficacy of BTX-A for post-herpetic neuralgia; however, their results may have been confounded by the inclusion of multiple interventions (lidocaine, saline, placebo) as comparators. The present meta-analysis did not include any RCTs comparing BTX-A to placebo or saline. Although such RCTs are considered rigorous high-quality studies (28), the clinical relevance of including saline or placebo as comparators is questionable.

Postherpetic neuralgia has a negative impact on patients' quality of life and represents an economic burden on individuals and the healthcare system (29). One study investigated the impact of post-herpetic neuralgia on quality of life in individuals

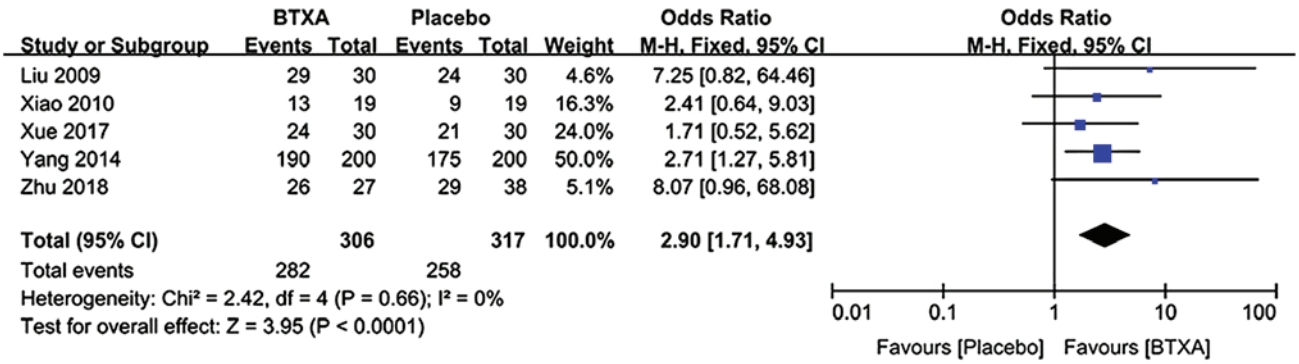

Figure 6. BTX-A vs. lidocaine for post-herpetic neuralgia: Effective rate. BTX-A, botulinum toxin A; df, degrees of freedom; M-H, Mantel-Haenszel.

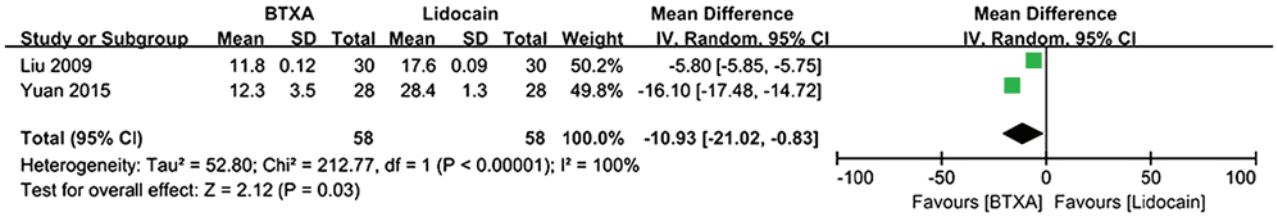

Figure 7. BTX-A vs. lidocaine for post-herpetic neuralgia: McGill pain questionnaire. BTX-A, botulinum toxin A; df, degrees of freedom; IV, inverse variance; SD, standard deviation.

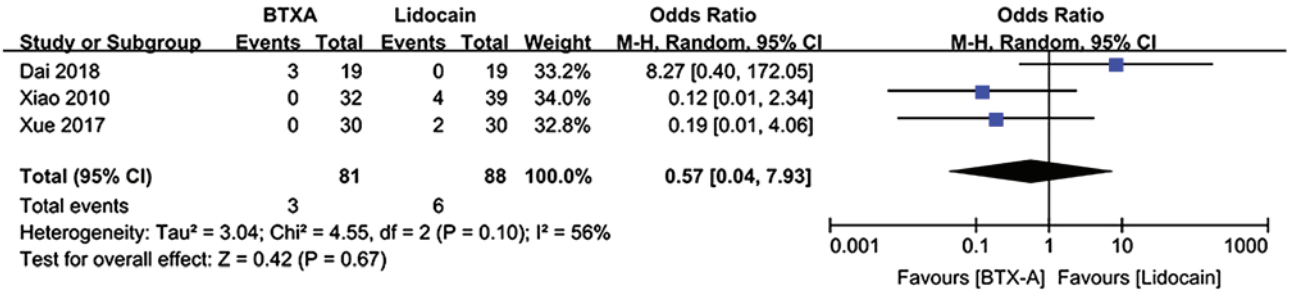

Figure 8. BTX-A vs. lidocaine for post-herpetic neuralgia: Adverse event rate. BTX-A, botulinum toxin A; df, degrees of freedom; M-H, Mantel-Haenszel.

aged ≥50 years in 6 European countries (Spain, Portugal, The Netherlands, Belgium, Sweden and Switzerland). In 37% of individuals, post-herpetic neuralgia had a high impact on quality of life, affecting enjoyment of life, general activity, mood, sleep and walking ability (30). A systematic review of published data investigating healthcare resource use and costs associated with herpes zoster in Europe revealed that post-herpetic neuralgia incurred outpatient costs (medical visits, diagnostic tests and medications), hospitalization and inpatient costs, as well as costs associated with sick leave (absenteeism) (31). Future research should include a comparison of the psychosocial and economic burden of post-herpetic neuralgia in patients treated with BTX-A vs. lidocaine.

The present meta-analysis had certain limitations. First, the numbers of clinical trials and patients included were small. Furthermore, certain studies were judged as having 'high risk' of bias and it was not possible to assess publication bias, as an insufficient number of studies was included. In addition, there were significant differences in the baseline characteristics of the patients treated with BTX-A or lidocaine in several of the included trials, representing a potential source of heterogeneity in the present analyses. As another limitation, certain patients were administered therapies in addition to BTX-A or lidocaine, which may make it difficult to draw conclusions about several outcomes. Furthermore, there is currently no gold standard measure of treatment success for neuralgia; therefore, the present study reports on a variety of outcomes. Finally, there was evidence of heterogeneity between trials. This will likely be reduced in the future as data from more RCTs become available and a gold standard measure of treatment success is established.

In conclusion, the present meta-analysis indicates that BTX-A has potential as an effective treatment for post-herpetic neuralgia. Large well-designed RCTs are required to substantiate this conclusion.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

XLL made substantial contributions to research concept, screening process, identification of eligible studies and manuscript preparation. SZ and XZ performed data analysis and prepared the manuscript. HPH screened, identified eligible studies and analyzed the data. ZZ and LLP performed the data extraction and quality evaluation. LGC conceived the research study and supervised the other authors to ensure integrity of the analysis. All authors reviewed, read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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