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Acupuncture for the treatment of trigeminal neuralgia: A systematic review and meta-analysis

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ABSTRACT

Background and purpose: Few systematic reviews have examined the effects of acupuncture on trigeminal neuralgia. This review aims to provide up-to-date evidence on the efficacy of acupuncture for managing pain in patients with trigeminal neuralgia.

Methods: Eleven databases were searched from inception until November 2022 for relevant articles Two researchers independently conducted study selection, data extraction, and evaluation. The present review solely targeted randomized controlled trials (RCTs). The Cochrane risk of bias assessment tool 2.0 was employed to assess the risk of bias. Data were compiled using RevMan 5.4.1 software, and the quality of the evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

Results: Thirty studies involving 2295 patients were included in this review. Compared with carbamazepine, acupuncture led to improvements in pain scores (15 RCTs, mean difference (MD) - 1.40, 95% confidence interval (CI)-1.82 to −0.98 [95% prediction interval, −3.137,0.343], $p < 0.00001$, low certainty of evidence (CoE)), response rates (29 RCTs, risk ratio (RR) 1.20, 95% CI 1.15 to 1.25 [95% prediction interval, 1.067, 1.346], $p < 0.00001$, low CoE), frequency of pain attacks (2 RCTs, MD -2.53, 95% CI -4.11 to −0.96, $P = 0.002$, low CoE), and adverse effects (13 RCTs, risk difference (RD) −0.15, 95% CI -0.19 to −0.11 [95% prediction interval, −0.193, −0.108], $P < 0.00001$, very low CoE).

Conclusion: Although the quality of evidence is low, compared with carbamazepine, acupuncture may improve trigeminal neuralgia-related pain. Further rigorously designed studies are warranted to confirm the effects of acupuncture on patients with trigeminal neuralgia.

1. Introduction

Trigeminal neuralgia is a form of severe and persistent pain characterized by intermittent electric shock-like sensations in one or more divisions of the trigeminal nerve [1]. Pain attacks gradually escalate in frequency, duration, and severity, and may become unresponsive to medication [2]. As a result, the condition may become chronic, significantly impacting the quality of life of most individuals with trigeminal neuralgia and resulting in cognitive impairments, including anxiety and depression [3]. The prevalence of trigeminal neuralgia ranges from 0.03% to 0.3%, with females being predominantly affected. This condition primarily occurs between the ages of 37 and 67 years and primarily affects the maxillary and mandibular branches of the trigeminal nerve [4].

Antiepileptic medications, such as carbamazepine, are the primary treatment option for trigeminal neuralgia. However, these drugs are frequently ineffective in providing pain relief and may cause severe side effects, including bone marrow suppression, memory loss, and cognitive

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impairment [5,6]. Among surgical treatments, microvascular decompression may be an effective option for trigeminal neuralgia [7]. Nonetheless, this procedure is typically reserved for treating trigeminal neuralgia caused by vascular compression of the trigeminal nerve root in young adults or healthy elderly patients, and approximately 50% of patients may experience recurrent pain after the procedure [2,8]. Therefore, acupuncture may be considered an alternative treatment option for pain management in patients with trigeminal neuralgia.

Acupuncture is a widely used practice in Asia for treating various conditions, including cardiovascular disease, infertility, pain, and mental health disorders [9–11]. Acupuncture have been employed to alleviate different types of pain. A recent meta-analysis of 11 clinical trials involving 707 patients showed that acupuncture was effective in managing pain [12]. Acupuncture may exert its therapeutic effects through mechanical stimulation that transmits signals to the spinal cord via sensory ganglia, modulating the activity of motor neurons in the brainstem network via intermediate neurons, thereby activating various opioid receptors and inducing analgesic effects through descending inhibition in the supraspinal central nervous system (CNS) region [13–15]. Furthermore, the analgesic effect associated with endogenous opioid peptides linked with acupuncture is long-lasting [16]. Additionally, acupuncture produces immediate analgesic effects, and diffuse noxious inhibitory control (DNIC) may be a possible mechanism underlying this effect [17]. According to the theory of DNIC, noxious stimuli can immediately inhibit pain transmission in neurons of the trigeminal caudate and/or spinal horn [18,19].

Acupuncture has been used as a treatment for primary trigeminal neuralgia in China for a prolonged period, and several studies have shown its effectiveness in managing this condition [20,21]. A longitudinal study indicated that acupuncture may be a viable option for treating trigeminal neuralgia due to its analgesic effects on both trigeminal neuralgia and myofascial pain [22]. Additionally, a clinical trial demonstrated that acupuncture can enhance cognitive function and quality of life in individuals with trigeminal neuralgia [23]. Furthermore, a recent literature review concluded that acupuncture, either alone or in combination with standard medications, may reduce the frequency and intensity of pain episodes associated with trigeminal neuralgia [24].

Currently, there is insufficient reliable evidence on the efficacy of acupuncture as an alternative therapy for trigeminal neuralgia. As there are now new randomized controlled trials (RCTs) available, it is imperative to incorporate these studies into existing evidence. The objective of this review is to conduct a comprehensive assessment of all existing evidence regarding the effectiveness and safety of acupuncture for pain management in patients with trigeminal neuralgia.

2. Methods

The systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 (PRISMA) statement. Additionally, the review protocol was registered on PROSPERO with the identifier CRD42018087594. (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018087594).

2.1. Search strategy

We conducted a comprehensive search of electronic databases, including PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL), as well as six Korean databases (KoreaMed, Korean Traditional Knowledge Portal, the Oriental Medicine Advanced Searching Integrated System [OASIS], DBpia, Research Information Service System [RISS], and Korean Studies Information Service System databases), and two Chinese databases (China National Knowledge Infrastructure [CNKI] database and Wanfang database), from their inception until November 2022, without any restrictions on publication status. Moreover, we manually searched the reference lists of relevant systematic reviews and included studies to identify additional eligible articles. The search strategy employed keywords such as 'acupuncture,' 'trigeminal neuralgia,' and 'randomized controlled trial,' along with their equivalent terms as per the respective databases (see Supplement 1).

2.2. Inclusion and exclusion criteria

2.2.1. Participants

The participants were patients diagnosed with trigeminal neuralgia, regardless of age, sex or diagnostic criteria.

2.2.2. Interventions

The inclusion criteria for this study were limited to randomized controlled trials (RCTs) that utilized manual acupuncture, which involves the insertion of penetrating needles into specific acupuncture points. Other forms of acupuncture, such as auricular acupuncture, electroacupuncture, and warm acupuncture, were not considered eligible. Similarly, interventions that did not involve needle insertion, such as acupressure or moxibustion, were also excluded. Furthermore, studies that used combined interventions of different acupuncture types or involved other alternative modalities, such as acupuncture combined with herbal medicine or acupuncture plus cupping, were also excluded from the study.

2.2.3. Controls

Control interventions only included conventional treatments (medication alone). Other types of control interventions were not eligible for inclusion.

2.2.4. Outcomes

The primary endpoint for this study was the measurement of pain severity using a validated pain measurement tool. The secondary endpoints included the response rate, which was defined as the number of patients who experienced an improvement in their trigeminal neuralgia symptoms, the frequency of pain attacks, and the occurrence of any adverse effects (AEs).

2.2.5. Study design

This study only included RCTs. Other clinical studies such as cohort studies, observational studies, quasi-RCTs, case-control studies, case series, qualitative and laboratory studies, and uncontrolled trials were not eligible for inclusion. There were no limitations with regard to the publication type or language.

2.3. Data collection, extraction, and assessment

2.3.1. Study selection

Two reviewers (HJK and TYC) independently screened the titles and abstracts of the retrieved studies, evaluating them against pre-established selection criteria and recording their decisions accordingly. In cases where there were discrepancies in study selection, a third reviewer (JIK) was consulted to reach a consensus. The entire study selection process was meticulously documented and presented in a PRISMA flow diagram.

2.3.2. Data extraction

Two independent reviewers (LA and HJK) read all the articles and extracted relevant data according to predetermined criteria. The extracted data included information such as the authors' names, year of publication, sample size, age and gender of participants, details about the acupuncture intervention, the control intervention, acupuncture points utilized during the intervention, number of treatment sessions, outcome measures, and main results. This extracted data was tabulated for future analysis. To ensure adherence to the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)

[25], information about the acupuncture method and control interventions was carefully extracted. In cases where the reported data were inadequate or unclear, the authors reached out to the study's corresponding author or first author via email or phone to request missing or clarifying data.

2.3.3. Assessment of risk of bias

The quality of the studies included in this review was evaluated using version 2 of the Cochrane risk of bias assessment tool (RoB 2) [26]. The tool was used to assess the following biases: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) outcome measurements, (5) selection of reported results, and (6) overall bias. The evaluations were categorized as 'Low,' 'High,' or 'Some concerns,' where 'Low' indicated a low risk of bias, 'Some concerns' indicated an uncertain risk of bias, and 'High' indicated a high risk of bias. Any disagreements among the authors were resolved through discussion. A summary of the risk of bias assessment for each included study was provided, along with a critical discussion of the results and their implications.

2.4. GRADE evaluation

The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system [27–29]. Initially, each RCT was awarded four points for each outcome, which was then downgraded for deficiencies in risk of bias, inconsistency, indirectness, imprecision, and publication bias. The risk of bias included incorrect randomization methods, lack of allocation concealment, inadequate blinding, and excessive loss of follow-up data. Inconsistencies mainly referred to differences in interventions or evaluation metrics. Indirectness was evaluated based on two categories: (1) direct comparison of the two groups, and (2) whether the outcome indicators directly evaluated efficacy. Imprecision was determined by assessing the width of the confidence interval (CI). Publication bias was assessed according to the GRADE handbook [29]. The quality of evidence was classified as high, moderate, low, or very low quality.

2.5. Data analysis

The statistical analysis was performed using the Cochrane Collaboration Review Manager (RevMan) software, v.5.4.1 for Windows (Nordic Cochrane Center, Copenhagen, Denmark). For categorical data, risk ratios were calculated, and for continuous data, mean difference (MD) was calculated. Categorical and continuous variables were reported as efficacy values with 95% confidence intervals (CIs). If outcome variables had different scales, a standardized MD was used. The heterogeneity of the studies was evaluated using the Chi-square test and Higgins $I^2 \geq 50\%$. Due to the diversity of interventions, study designs, and other conditions, substantial clinical heterogeneity was anticipated across the included studies, and therefore, a random effects model was used to determine combined effect sizes from efficacy variables. Subgroup analysis was not performed due to the lack of comparable subsamples. To estimate true effect values, the prediction interval was calculated since the I^2 index shows the variation in effect size across studies [30,31]. Albatross plots were generated to display the effects of direction and size range by p value, and for high heterogeneity cases, a sample size was generated for each included study [32,33]. Publication bias was evaluated using funnel plots if more than ten studies were available [34].

3. Results

3.1. Search results

Of the 4952 articles retrieved from the 11 databases, 970 duplicates were removed. After screening the titles and abstracts of the remaining 3982 articles, 33 articles were selected for full-text review. Following the inclusion criteria described in Fig. 1, three articles were excluded, and 30 studies [35–64] were finally included in the meta-analysis. A PRISMA flowchart (Fig. 1) outlines the entire search process.

3.2. Characteristics of the included studies

All of the included studies [35–64] were conducted in China with parallel study designs. The sample size was 2295 in total (ranging from 30 to 192), with a mean age of 48.8 years. All the studies used manual acupuncture as an intervention and carbamazepine (conventional medicine alone) as a comparator. For outcome measures, 15 studies [35–49] reported pain outcomes using the visual analog scale (VAS), 29 studies [35–44,46–64] reported on response rate, 2 studies [37,41] reported on frequency of pain attack, and 13 studies [35,37,38,40,41,44,50–56] reported on AEs. The details of the included studies are presented in Table 1.

The majority of the included studies in the analysis chose acupuncture points based on traditional Chinese medicine (TCM) theory, with study personnel commonly selecting points such as *Hegu* (LI4), *Xiaguan* (ST7), *Taiyang* (EX-HN5), and *Fengchi* (GB20), followed by *Yintang* (EX-HN3), *Shenting* (GV24), *Renzhong* (GV26), and other points. Table 2 provides further information on the specifics of the acupuncture regimens used.

3.3. Risk of bias in the included studies

The risk of bias in the included studies was assessed using the RoB 2 tool (Fig. 2). Out of the 30 studies, only one [47] was judged to have a low risk of bias in the randomization process domain, while the other 29 studies were considered to have a concerning risk of bias. Among the included studies, eight studies [35–37,40,41,46,53,62] employed a random number table, four studies [44,47,57,59] utilized computerized randomization, one study [54] used dice, and one study [64] employed a coin flip. The remaining 16 studies [38,39,42,43,45,48–52,55,56,58,60,61,63] only mentioned that they were randomized without specifying the methods of randomization. Only one study [47] reported using sealed envelopes for allocation concealment, while the other studies did not provide any details on allocation concealment.

In terms of deviations from intended interventions, all studies were judged to have a concerning risk of bias. None of the studies reported blinding of both participants and investigators, although appropriate statistical analysis was performed in all studies. Regarding missing outcome data, all studies were evaluated as having a low risk of bias, with most studies having complete data for all participants. While two studies [37,46] had dropouts, the low percentage of dropouts indicated no effect on the results.

Regarding the measurement of outcome domain, all included studies were judged to have a low risk of bias. Although most studies did not report on outcome assessor blinding, two studies did [37,47]. For the selection of reported results domain, all studies were assessed as having a concerning risk of bias. No studies had publicly available protocols or mentioned trial registration. Overall, the bias for all studies was determined to be concerning.

3.4. Effect of interventions

3.4.1. Pain (VAS)

Fifteen studies [35–49] reported pain using VAS scores. Fourteen studies [35–48] showed a positive effect of acupuncture on improving pain scores compared to that of carbamazepine, and only one study [49] failed to observe this effect. The meta-analysis showed positive effects of acupuncture on reducing pain (MD - 1.40, 95% CI -1.82 to −0.98 [95% prediction interval, −3.137,0.343], $p < 0.00001$, $I^2 = 96\%$, Fig. 3A). The albatross plot illustrated that the points were spread out throughout the contour lines (Supplement 2). However, all the points were

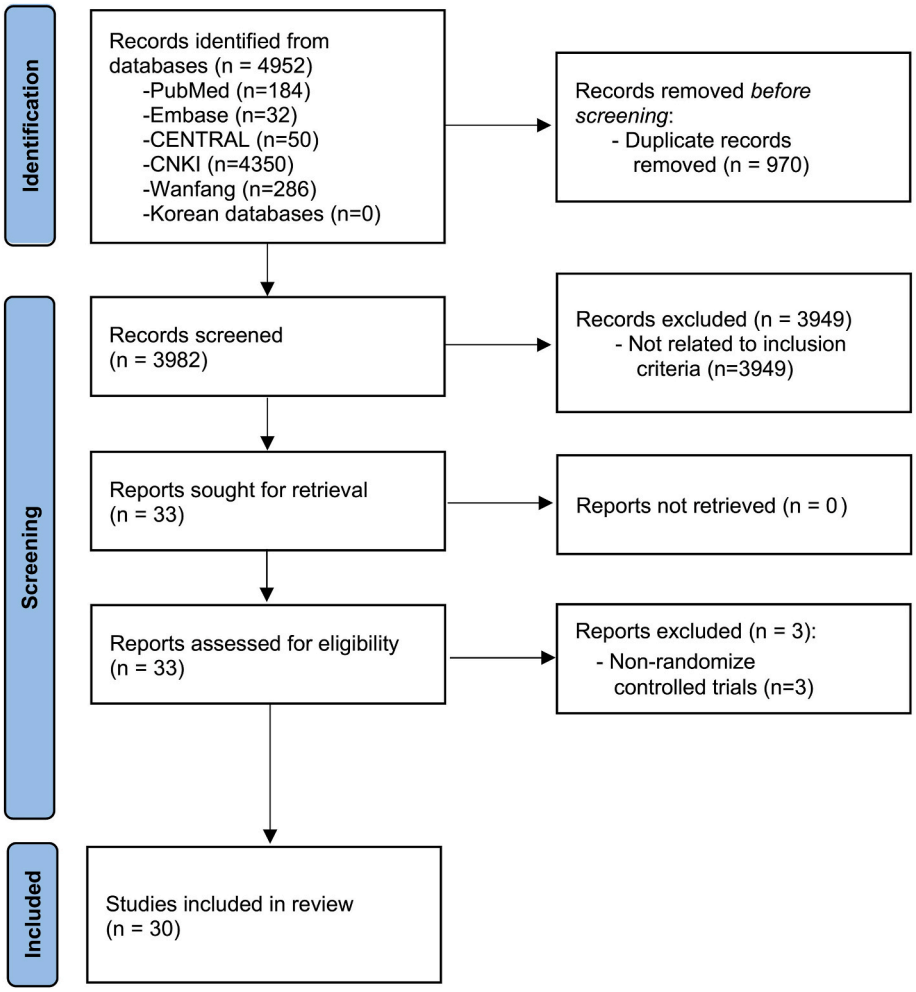

Fig. 1. Flow chart of the study selection process.

concentrated on the positive association side of the plot, implying that acupuncture is a beneficial treatment option for alleviating pain among individuals with trigeminal neuralgia.

3.4.2. Response rate

Response rates were reported in 29 studies [35–44,46–64]. Of these, 18 studies [35,36,38–40,43,44,47,50–52,54–56,58,59,61,64] showed positive effects, while 11 studies [37,41,42,46,48,49,53,57,60,62,63] demonstrated that acupuncture had similar effects as carbamazepine on response rates. According to the meta-analysis, acupuncture had favorable effects on enhancing the response rate (RR 1.20, 95% CI 1.15 to 1.25 [95% prediction interval, 1.067, 1.346], $p < 0.00001$, $I^2 = 24\%$, Fig. 3B).

3.4.3. Frequency of pain attacks

Only two studies [37,41] reported on the frequency of pain attacks. Both studies reported positive effects of acupuncture, compared with carbamazepine, on reducing the frequency of pain attacks (MD -2.53, 95% CI -4.11 to −0.96, $P = 0.002$, $I^2 = 84\%$).

3.4.4. Adverse events

Thirteen studies provided information regarding adverse events. Out of these, ten RCTs [35,37,38,40,41,51–53,55,56] demonstrated no difference in the occurrence of adverse events between the two groups, while three RCTs [44,50,54] illustrated a lower incidence of adverse events with acupuncture compared to carbamazepine. As per the meta-analysis, acupuncture resulted in a lower occurrence of adverse events than carbamazepine (RD -0.15, 95% CI -0.19 to −0.11 [95% prediction interval, −0.193, −0.108], $P < 0.00001$, $I^2 = 0\%$, Fig. 3C).

3.5. Publication bias across studies

Funnel plots were utilized to examine potential publication bias concerning the outcome measures (Fig. 4). A visual assessment of the funnel plots suggested that there was no significant asymmetry in pain (VAS) scores, indicating comprehensive publication coverage (Fig. 4A). Nonetheless, funnel plots for the response rate and adverse events revealed slight asymmetry, suggesting the potential existence of publication bias (Fig. 4B and C).

3.6. Certainty of evidence

The validity of evidence for both primary and secondary outcomes was assessed using the GRADEpro software. Regarding the effect of acupuncture on pain compared to carbamazepine, the certainty of evidence was downgraded from high to low due to substantial heterogeneity and serious concerns about the risk of bias. For the effect of acupuncture on response rate compared to carbamazepine, the certainty of evidence was downgraded from high to very low due to the risk of bias, substantial heterogeneity, and suspicion of publication bias. Similarly, the certainty of evidence for the effect of acupuncture on the frequency of pain attacks was downgraded from high to low due to inconsistencies and the risk of bias. The certainty of evidence for the effect of acupuncture on adverse events compared to carbamazepine was

Table 1
Summary of the characteristics of the included studies.

Author (Year)	Sample size (M/F) Age (years)	Intervention Group (Regimen)	Comparison Group	Outcome Measures	Main Results
Chen (2021) [35]	80 (34/46) A: 43.3; B: 43.8	(A) AT (25 min, once daily for 28 days, n = 40)	(B) Carbamazepine (0.4–0.8 g daily, n = 40)	1) Pain (VAS) 2) Response rate 3) AEs	1) MD -2.41 [-2.77, −2.05], P < 0.0001 2) RR 1.15 [1.00, 1.32], P < 0.05 3) RR 0.17 [0.02, 1.32], P < 0.05
Ti (2021) [36]	60 (25/35) A: 57.3; B: 58.4	(A) AT (30 min, 5 times weekly for 5 weeks, n = 30)	(B) Carbamazepine (0.2–0.4 g daily, n = 30)	1) Pain (VAS) 2) Response rate	1) MD -1.16 [-1.99, −0.33], P < 0.01 2) RR 1.27 [1.01, 1.61], P < 0.05
Zhang (2019) [37]	64 (23/41) A: 47.3; B: 45.8	(A) AT (40 min, 6 times weekly for 4 weeks, n = 33)	(B) Carbamazepine (0.3–0.6 g daily, n = 29)	1) Pain (VAS) 2) Frequency of pain attack 3) Response rate 4) AEs	1) MD -0.89 [-1.11, −0.67], P < 0.0001 2) MD -1.62 [-2.82, −0.42], P < 0.01 3) RR 1.20 [0.95, 1.51], NS 4) RR 0.38 [0.11, 1.32], NS
Liu (2019) [38]	88 (36/52) A: 48.7; B: 48.3	(A) AT (20 min, once daily for 30 days, n = 44)	(B) Carbamazepine (0.4–0.8 g daily, n = 44)	1) Pain (VAS) 2) Response rate 3) AEs	1) MD -2.42 [-2.80, −2.04], P < 0.0001 2) RR 1.16 [1.01, 1.33], P < 0.05 3) RR 0.17 [0.02, 1.33], P < 0.05
Mu (2019) [39]	100 (45/55) A: 42.6; B: 43.1	(A) AT (30 min, once daily for 30 days, n = 50)	(B) Carbamazepine (0.2 g daily, n = 50)	1) Pain (VAS) 2) Response rate	1) MD -1.40 [-1.76, −1.04], P < 0.001 2) RR 1.31 [1.08, 1.57], P < 0.01
Huang (2018)a [40]	63 (23/41) A: 44.9; B: 43.6	(A) AT (30 min, once daily for 30 days, n = 32)	(B) Carbamazepine (0.4–0.8 g daily, n = 31)	1) Pain (VAS) 2) Response rate 3) AEs	1) MD -2.25 [-2.67, −1.83], P < 0.0001 2) RR 1.24 [1.03, 1.48], P < 0.01 3) RR 0.16 [0.02, 1.26], P < 0.05
Huang (2018)b [41]	86 (50/36) A: 42.5; B: 41.9	(A) AT (20 min, once daily for 30 days, n = 43)	(B) Carbamazepine (0.3–0.6 g daily, n = 43)	1) Pain (VAS) 2) Frequency of pain attack 3) Response rate 4) AEs	1) MD -0.33 [-0.58, −0.08], P < 0.05 2) MD -3.24 [-3.65, −2.83], P < 0.0001 3) RR 1.14 [0.98, 1.32], NS 4) RR 0.08 [0.00, 1.32], P < 0.05
Zhang (2018) [42]	60 (34/26) A: 58.2; B: 58.5	(A) AT (20 min, once daily for 90 days, n = 30)	(B) Carbamazepine (0.2 g daily, n = 30)	1) Pain (VAS) 2) Response rate	1) MD -1.40 [-1.92, −0.88], P < 0.0001 2) RR 1.17 [0.95, 1.43], NS
Shen (2016) [43]	80 (45/35) A: 59.8; B: 59.6	(A) AT (30 min, once daily for 30 days, n = 40)	(B) Carbamazepine (0.4–0.8 g daily, n = 40)	1) Pain (VAS) 2) Response rate	1) MD -1.62 [-2.42, −0.82], P < 0.001 2) RR 1.26 [1.06, 1.50], P < 0.01
Xiao (2016) [44]	100 (28/72) A: 54.4; B: 54.2	(A) AT (30 min, 6 times weekly for 4 weeks, n = 50)	(B) Carbamazepine (0.2–0.6 g daily, n = 50)	1) Pain (VAS) 3) Response rate 4) AEs	1) MD -0.84 [-1.16, −0.52], P < 0.0001 3) RR 1.21 [1.02, 1.42], P < 0.05 4) RR 0.08 [0.01, 0.62], P < 0.001
Meng (2014) [45]	100 (56/44) A: 53.2; B: 54.2	(A) AT (30 min, once daily for 30 days, n = 50)	(B) Carbamazepine (0.2–1.2 g daily, n = 50)	Pain (VAS)	MD -1.99 [-2.77, −1.21], P < 0.0001
Wang (2013) [46]	40 (8/32) A: 54.5; B: 53.9	(A) AT (30 min, 5 times weekly for 6 weeks, n = 19)	(B) Carbamazepine (0.2–1.2 g daily, n = 20)	1) Pain (VAS) 2) Response rate	1) MD -1.59 [-2.97, −0.21], P < 0.05 2) RR 1.26 [0.96, 1.66], NS
Zheng (2010) [47]	120 (55/65) A: 52; B: 56	(A) AT (3 sessions [30 min, once daily for the first 10 days, rest 2 days per session], n = 60)	(B) Carbamazepine (1.5 g daily, n = 60)	1) Pain (VAS) 2) Pain (MPQ) 3) Response rate	1) MD -2.18 [-2.30, −2.06], P < 0.0001 2) MD -0.91 [-0.97, −0.85], P < 0.0001 3) RR 1.12 [1.00, 1.24], P < 0.05
Li (2009) [48]	64 (33/31) A: 26–69; B: 27–67	(A) AT (3 sessions [30 min, once daily for the first 10 days, rest 3 days per session], n = 33)	(B) Carbamazepine (0.6 g daily, n = 31)	1) Pain (VAS) 2) Response rate	1) MD -0.71 [-1.42, −0.00], P < 0.05 2) RR 1.17 [0.94, 1.46], NS

(*continued on next page*)

Table 1 (*continued*)

Author (Year)	Sample size (M/F) Age (years)	Intervention Group (Regimen)	Comparison Group	Outcome Measures	Main Results
Jiao (2008) [49]	192 (71/121) A: 53.4; B: 51.5	(A) AT (40 min, 6 times weekly for 4 weeks, n = 96)	(B) Carbamazepine (0.3 g daily, n = 96)	1) Pain (VAS) 2) Response rate	1) MD 0.31 [-0.35, 0.97], NS 2) RR 0.94 [0.83, 1.06], NS
Yan (2018) [50]	72 (25/47) A: 43.1; B: 44.1	(A) AT (30 min, once daily for 30 days, n = 36)	(B) Carbamazepine (0.6 g daily, n = 36)	1) Response rate 2) AEs	1) RR 1.31 [1.05, 1.63], P < 0.01 2) RR 0.38 [0.11, 1.32], P < 0.05
Li (2018) [51]	88 (41/47) A: 42.0; B: 41.2	(A) AT (30 min, once daily for 30 days, n = 44)	(B) Carbamazepine (0.4–0.8 g daily, n = 44)	1) Response rate 2) AEs	1) RR 1.28 [1.05, 1.56], P < 0.01 2) RR 0.14 [0.02, 1.11], P < 0.05
Liu (2016) [52]	60 (21/39) A: 42.9; B: 42.7	(A) AT (n.r., once daily for 30 days, n = 30)	(B) Carbamazepine (0.6 g daily, n = 30)	1) Response rate 2) AEs	1) RR 1.20 [1.01, 1.42], P < 0.05 2) RR 0.40 [0.08, 1.90], NS
Li (2016) [53]	50 (31/19) 60.1	(A) AT (20 min, once daily for 30 days, n = 25)	(B) Carbamazepine (0.6 g daily, n = 25)	1) Response rate 2) AEs	1) RR 1.20 [0.97, 1.48], NS 2) RR 0.20 [0.03, 1.59], NS
Liu (2015) [54]	84 (37/47) A: 54.3; B: 53.7	(A) AT (20 min, once daily for 28 days, n = 42)	(B) Carbamazepine (0.6 g daily, n = 42)	1) Response rate 2) AEs	1) RR 1.27 [1.02, 1.57], P < 0.05 2) RR 0.25 [0.08, 0.82], P < 0.01
Wang (2015) [55]	70 (30/40) 51.3	(A) AT (20 min, once daily for 30 days, n = 35)	(B) Carbamazepine (0.5 g daily, n = 35)	1) Response rate 2) AEs	1) RR 1.37 [1.12, 1.66], P < 0.001 2) RR 0.25 [0.06, 1.11], P < 0.05
Xia (2015) [56]	60 (31/29) n.r.	(A) AT (30 min, once daily for 30days, n = 30)	(B) Carbamazepine (0.6 g daily, n = 30)	1) Response rate 2) AEs	1) RR 1.45 [1.12, 1.88], P < 0.01 2) RR 0.20 [0.02, 1.61], NS
Wang (2019) [57]	30 (15/15) A: 45.8; B: 44.8	(A) AT (20 min, once daily for 90 days, n = 15)	(B) Carbamazepine (0.5–0.8 g daily, n = 15)	Response rate	RR 1.27 [0.91, 1.78], NS
Zhou (2016) [58]	65 (39/26) A: 42.2; B: 43.5	(A) AT (20 min, once daily for 30 days, n = 33)	(B) Carbamazepine (0.6 g daily, n = 32)	Response rate	RR 1.29 [1.05, 1.59], P < 0.01
Shangguan (2016) [59]	80 (34/46) A: 40.7; B: 40.5	(A) AT (20 min, once daily for 30 days, n = 40)	(B) Carbamazepine (0.6 g daily, n = 40)	Response rate	RR 1.23 [1.01, 1.51], P < 0.05
Chen (2014) [60]	112 (58/54) 44.2	(A) AT (20 min, once daily for 30 days, n = 76)	(B) Carbamazepine (0.6 g daily, n = 36)	Response rate	RR 1.11 [0.94, 1.30], NS
Sun (2014) [61]	70 (33/37) A: 47.5; B: 46.5	(A) AT (20 min, once daily for 30 days, n = 35)	(B) Carbamazepine (0.6 g daily, n = 35)	Response rate	RR 1.50 [1.15, 1.96], P < 0.001
Wang (2014) [62]	38 (23/15) 59.3	(A) AT (20 min, once daily for 30 days, n = 19)	(B) Carbamazepine (0.6 g daily, n = 19)	Response rate	RR 1.13 [0.86, 1.50], NS
Zou (2011) [63]	70 (25/45) 35–68	(A) AT (3 sessions [30 min, once daily for the first 10 days, rest for 6 days per session], n = 40)	(B) Carbamazepine (0.6 g daily, n = 30)	Response rate	RR 1.32 [0.92, 1.90], NS
Zhou (2004) [64]	49 (14/35) A: 42.9; B: 42.7	(A) AT (n.r., 6 times weekly for 4 weeks, n = 31)	(B) Carbamazepine (0.3 g daily, n = 18)	Response rate	RR 1.33 [1.10, 1.61], P < 0.001

A, intervention group; AEs, adverse effects; AT, acupuncture; B, control group; F, female; g, grams M, male; MD: mean difference; min, minutes; MPQ: McGill Pain Questionnaire; n.r., not reported; NS, not significant; RR: risk ratio; VAS, visual analog scale.

Table 2
Descriptions of the acupuncture interventions.

First author (year) (Ref)	Acupuncture rationale	Names of acupoints (Unilateral/Bilateral)	Response sought	Needle retention time	Treatment regime (Total sessions)
Chen (2021) [35]	TCM theory	EX-HN5, GB20, LI4, GV26, EX-HN3 (unclear)	de qi	25 min	28 D (28)
Ti (2021) [36]	TCM theory	GV20, CV17, LR14, CV6, LI4, LR3, ST44 (unclear)	de qi	30 min	5 W, 5/W (25)
Zhang (2019) [37]	TCM theory	S118, GB34, ST40 Additional points: V1- EX-HN4; V2- ST2; V3- ST7 (unclear)	de qi	40 min	4 W, 6/W (24)
Liu (2019) [38]	TCM theory	GB20, GV24, LI4, EX-HN3, GB12, BL10, GV26 (unclear) V1-BL2, GB14, TE23; V2- EX-HN5, ST2, GB3; V3- ST7, ST9, ST4 (unclear)	de qi	20 min	1 M, 1/D (30)
Mu (2019) [39]	Nerve stimulation	EX-HN3, GV26, GV24, GB12, BL10, SJ5 (unclear)	n.r.	30 min	1 M, 1/D (30)
Huang (2018a) [40]	TCM theory	EX-HN5, ST7, GB20, ST6, LI4, ST4 (unclear)	de qi	30 min	1 M. 1/D (30)
Huang (2018b) [41]	TCM theory	EX-HN5 (U), ST7 (B), LI4 (B), LI7, GV20, EX-HN3 (unclear) LI7 (B), GB20	de qi	20 min	1 W, 1/D (30)
Zhang (2018) [42]	TCM theory	EX-HN5, LI4, ST7, EX-HN3, GV20 (unclear), EX-HN5, ST7	de qi	20 min	3 M, 1/D (90)
Shen (2016) [43]	TCM theory	EX-HN5, ST7 (B), LI4, LI7, GV20, EX-HN3 (unclear), GB20	de qi	30 min	1 M. 1/D (30)
Xiao (2016) [44]	TCM theory	LI4, SP10, BL17, GB20, GB14, TE17, EX-HN5, ST8, TE23, TE17, ST2, L120, SI18, ST7, ST6, ST4, CV24, Ashi points (unclear)	de qi	40 min	4 W, 6/W (24)
Meng (2014) [45]	TCM theory	EX-HN5, LI4, LI7, GB4, GB20, ST7, ST3, EX-HN3, GV23, GV20	de qi	30 min.	1 M, 1/D (30)
Wang (2013) [46]	TCM theory	EX-HN5, Trigger points, GV23, EX-HN3, ST3, ST7, GB20, GB4, LI4	de qi	30 min	6 W, 5/W (30)
Zheng (2010) [47]	TCM theory	Local acupuncture (affected side)-ST9(U); V1-GB14, BL2, EX-HN4; V2-ST2, LI20, ST7; V3-ST4, ST6, CV24	de qi	30 min	1 M, 1/D (30)
Li (2009) [48]	TCM theory	ST7, LI11, LI14, ST36	de qi	30 min	1 M, 1/D (30)
Jiao (2008) [49]	TCM theory	SI18; Local (affected): S118 (U); Distant (B): GB34, ST40	de qi	40 min	4 W,6/W (24)
Yan (2018) [50]	TCM theory	ST7, GB20, ST6, LI4, ST4 (unclear), EX-HN5	n.r.	30 min	1 W, 1/D (30)
Li (2018) [51]	TCM theory	EX-HN3, GV24, LI4 (B) GB12, BL10, GB20, SJ5, EX-HN5, ST7	de qi	30 min	1 M, 1/D (30)
Liu (2016) [52]	TCM theory	GB20, LI4, SJ5, EX-HN3, GV24, GV26, GB12, BL10, Local-GB20, ST7, ST4, ST6 (unclear); Distant-LI4 (B), EX-HN5	de qi	n.r.	30 D. 1/D (30)
Li (2016) [53]	TCM theory	GB20, LI4, TE5, GV24, EX-HN3, GB12, GV26, BL10 V1-GB14, BL2, TE23, GB15; V2-ST2, EX-HN5, GB3; V3-ST7, ST4, ST5	de qi	20 min	1 M, 1/D (30)
Liu (2015) [54]	TCM theory	GB20, LI4, SJ5, EX-HN3, GV24, GV26, GB12, BL10 Local acupuncture (affected side)-GB20, GV29, GV26, GV24, BL10, GB12 (U); V1-TE23, GB14, BL2, GB15; V2-GB3, EX-HN5, ST2; V3-ST5, ST4, ST2; Distant acupuncture-TE5, LI4 (B)	de qi	20 min	4 W, 1/D (28)
Wang (2015) [55]	TCM theory	GB20, LI4, SJ5, EX-HN3, GV24, GV26, GB12, BL10 V1-GB15, BL2, GB14, TE23; V2-EX-HN5, ST2, GB3; V3-ST7, ST9, ST4 (unclear)	de qi	20 min	1 M, 1/D (30)
Xia (2015) [56]	TCM theory	GB20, LI4, SJ5, EX-HN3, GV24, GV26, GB12, BL10 Local acupuncture (affected side)-GV29, GV26, GV24, GB20, GB12, BL10 (U); V1- GB14, BL2, GB15, TE23; V2-ST2, EX-HN5, GB3; V3-ST7, ST4, ST5; Distant acupuncture-LI4, TE5 (B)	de qi	30 min	1 M, 1/D (30)
Wang (2019) [57]	TCM theory	LI4, EX-HN3, ST7, EX-HN5, GV20 (unclear), GB20, LI4	n.r.	20 min	3 M, 1/D (90)
Zhou (2016) [58]	TCM theory	GB20, LI4, EX-HN3, GV24, GV26, GB12, BL10 (unclear); V1-GB15, BL2, GB14, TE23; V2-EX-HN5, ST2, GB3; V3-ST7, ST9, T4 (unclear)	de qi	20 min	1 M, 1/D (30)
Shangguan (2016) [59]	TCM theory	Local acupuncture (affected side)-GV24, GB20, EX-HN3, GV29, GV26, GB12, BL10 (U); V1-GB14, GB15, TE23, BL2; V2-EX-HN5, GB3, ST2; V3-ST7, ST4, ST5; Distant acupuncture-TE5 (B)	de qi	20 min	1 M, 1/D (30)
Chen (2014) [60]	TCM theory	Local acupuncture (affected side): V29, GV24, GV20, GB12, BL10, GV26 (U); V1-GB14, BL2, GB15, TE23; V2-EX-HN5, ST2, GB3; V3-ST4, ST7, ST5; Distant acupuncture: LI4, TE5 (B)	de qi	20 min	1 M, 1/D (30)
Sun (2014) [61]	TCM theory	Local acupuncture (affected side)-GV24, GB20, EX-HN3, GB12, BL10, GV26 (U); V1-GB14, BL2, GB15, TE23; V2-EX-HN5, GB3, ST2; V3-ST7, ST4, ST5; Distant acupuncture-LI4, TE5 (B)	de qi	20 min	1 M, 1/D (30)
Wang (2014) [62]	TCM theory	GB20, LI4, SJ5, GV24, GV26, BL10 (unclear); V1-GB15, BL2, GB14, TE23; V2-EX-HN5, ST2, GB3; V3-ST7, ST9, ST4 (unclear)	de qi	20 min	1 M, 1/D (30)
Zou (2011) [63]	TCM theory	LI11, LI14, ST36, ST3, LI20; Local (affected): ST3, LI20 (U); Distant (B): LI11, LI4, ST43 (B)	de qi	30 min	1 M, 1/D (30)
Zhou (2004) [64]	TCM theory	SI18, GB34, ST40	de qi	40 min	4 W, 6/W (24)

* Number of papers adequately reporting values and their total percentage. B, bilateral; D, day(s); M, month(s); min, minutes; n.r., not reported; Ref, reference; TCM, traditional Chinese medicine; U, unilateral; W, week(s).

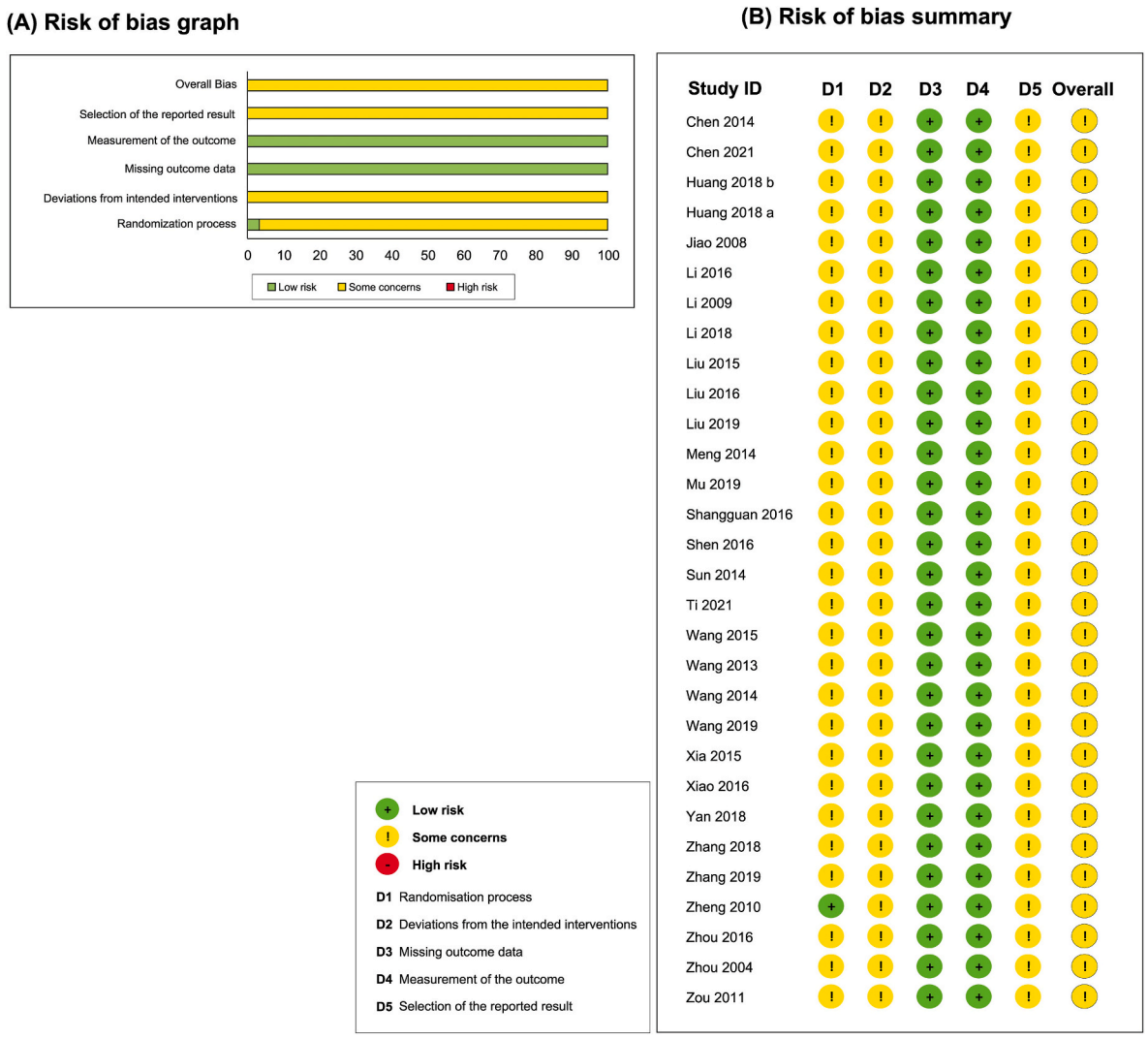

Fig. 2. (A) Risk of bias graph and (B) risk of bias summary: review authors' judgments on each item's risk of bias for all included studies.

downgraded from high to very low due to the risk of bias, inconsistency, and publication bias. More information regarding the certainty of evidence can be found in Table 3.

4. Discussion

4.1. Summary of findings

Our findings show that compared with carbamazepine (the gold standard treatment for trigeminal neuralgia), acupuncture has beneficial effects on pain reduction (very low CoE), response rates (very low CoE) and a reduction in the number of AEs (very low CoE). Evidence on the effectiveness of acupuncture for patients with trigeminal neuralgia is currently limited to provide recommendations for its usage.

4.2. Quality of the evidence

Our evaluation indicated that the risk of bias in each of the included studies was high, which could lead to false-positive results. The assessment of blinding is a crucial factor in determining a study's risk of bias, but the majority of the studies did not provide relevant information on blinding. Furthermore, all of the studies were conducted in China. Therefore, additional independent studies conducted in different countries are necessary to determine the generalizability of the findings.

4.3. Agreements and disagreements with other studies or reviews

Two systematic reviews have examined the effectiveness of acupuncture intervention in treating trigeminal neuralgia [20,21]. One of the systematic reviews [20] included RCTs published up to 2016, and it is out of date. This review used odds ratios instead of relative risks in the meta-analysis, which may have exaggerated the effects. The second review employed network meta-analysis to compare the effects of different types of acupuncture for trigeminal neuralgia [21]. Our review comprehensively searched broader databases and identified more eligible studies than previous reviews. We successfully updated the evidence for manual acupuncture compared to carbamazepine, and the CoE for each outcome was evaluated using GRADE. Our findings were similar to those of a previous review, which suggested that acupuncture may be beneficial for treating trigeminal neuralgia.

4.4. Limitations

This review has several limitations. Firstly, there was insufficient data on clinical outcomes such as pain, which hindered the pooling of results. Additionally, most studies utilized the response rate as the primary outcome, which may vary depending on the practitioner. Therefore, future studies should utilize appropriate outcomes. Secondly, the quality of the included RCTs was concerning, which may reduce the

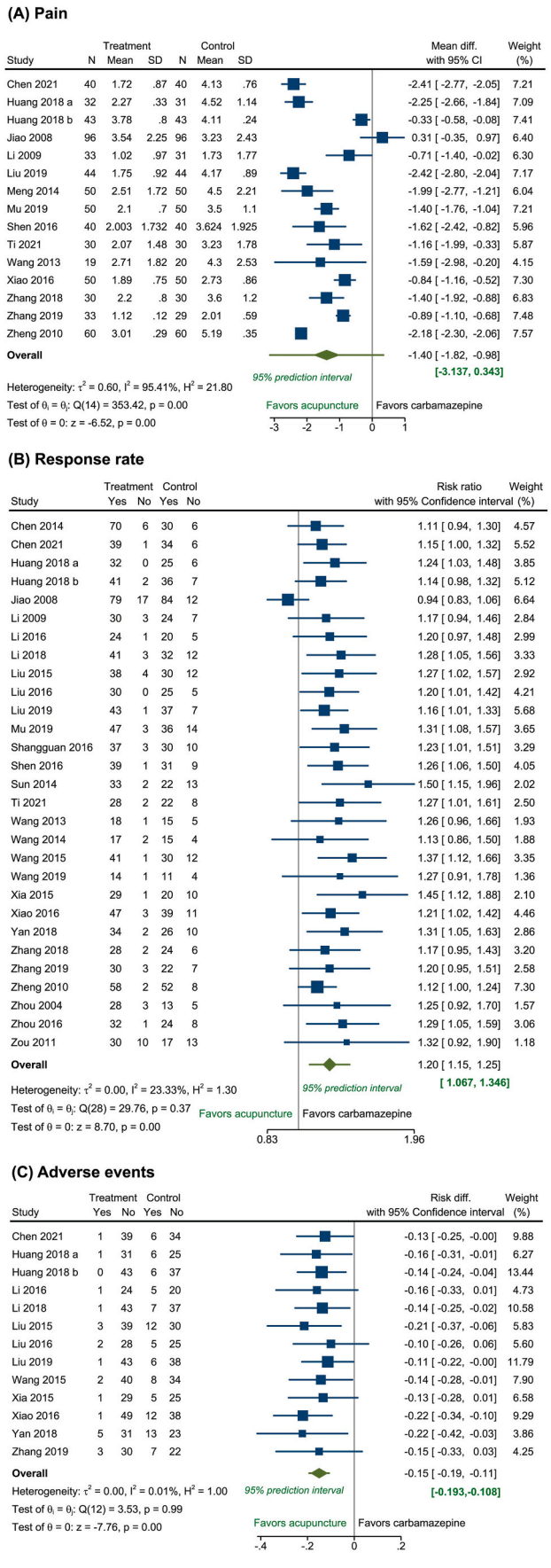

Fig. 3. Forest plot of acupuncture for (A) pain, (B) response rate and (C) adverse events compared with carbamazepine.

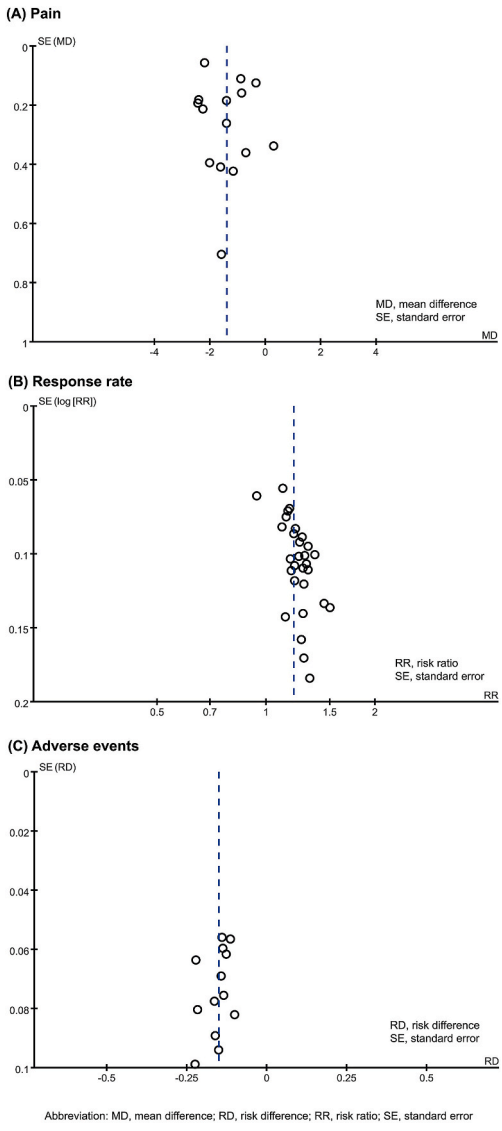

Fig. 4. Funnel plot of the comparison between acupuncture and carbamazepine for the outcomes of (A) pain, (B) response rates and (C) adverse effects. MD, mean difference; RD, risk difference; RR, risk ratio; SE, standard error.

validity of positive findings. Many of the included studies were rated as having "Some concern" in the ROB. Thirdly, clinical heterogeneity related to the participants, intervention, outcomes, or trial settings that cannot be managed by statistical approaches was observed, which means that the results of our study should be interpreted with caution. Although over half of the included studies did not report serious acupuncture-related AEs, more than half of the included studies did not evaluate the incidence of AEs. Thus, future acupuncture studies should investigate the incidence of adverse events and their potential relationship with acupuncture treatment.

4.5. Potential mechanisms

If we assume that acupuncture is an effective treatment for trigeminal neuralgia, it is worth exploring its underlying mechanisms. Acupuncture is believed to activate pain afferents located in the dorsal horn of the spinal cord, which, in turn, stimulates the descending pain suppression mechanism and leads to pain relief [65]. Additionally, acupuncture not only inhibits the supraspinal CNS region but also

Table 3
Summary of findings.

Patient or population: Trigeminal neuralgia patients					
Intervention: Acupuncture					
Comparison: Carbamazepine					
Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with carbamazepine	Risk difference with acupuncture
Pain (VAS)	1294 (15 RCTs)	⨁⨁◯◯ Low[a,b]	–	The mean pain was 0	MD 1.4 lower (1.85 lower to 0.95 lower)
Response rate	2206 (29 RCTs)	⨁◯◯◯ Very low[a,b,c]	RR 1.19 (1.15–1.23)	773 per 1000	147 more per 1000 (116 more to 178 more)
Frequency of pain attack	148 (2 RCTs)	⨁⨁◯◯ Low[a,b]	–	The mean frequency of pain attack was 0	MD 2.53 lower (4.11 lower to 0.96 lower)
Adverse events	977 (13 RCTs)	⨁◯◯◯ Very low[a,b,c]	RR 0.19 (0.12–0.32)	202 per 1000	163 fewer per 1000 (177 fewer to 137 fewer)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; MD: mean difference; VAS: Visual Analog Scale; RR: risk ratio; RCTs: randomized controlled trials.
GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Explanations.
a. Lack of allocation concealment and blinding.
b. Substantial heterogeneity yielding a large I2.
c. Asymmetry in funnel plot.

induces the combined action of the endocrine system and pain control system. Furthermore, acupuncture affects local nerves, reducing the degree of direct pain sensitivity of the nerves [66]. These findings provide sufficient evidence for acupuncture analgesia.

4.6. Implications for future studies

Future studies on the treatment of trigeminal neuralgia with acupuncture should emphasize the use of appropriate methods to allow for RCTs, including the use of pilot trials to help design appropriate RCTs. The trial design, implementation, and reporting of the studies should adhere strictly to the Consolidated Standards of Reporting Trials (CONSORT) and STRICTA. Other factors such as acupuncture point selection, treatment duration, intervention time, frequency of treatment sessions, and dose of intervention that can impact clinical heterogeneity should also be considered during trial design. Long-term studies are also necessary to determine the longevity of treatment effects. Longitudinal trials should be conducted to investigate the long-term effects and safety of acupuncture for trigeminal neuralgia.

5. Conclusion

This review suggests that there is insufficient evidence to support the use of acupuncture as a treatment for trigeminal neuralgia compared to carbamazepine. Nonetheless, the level of evidence is low or very low due to the high risk of bias. Consequently, further well-designed studies are required to substantiate the efficacy of acupuncture for the management of trigeminal neuralgia.

Authors' contributions

H.J.K. and J.I.K. conceptualized and designed the study; L.A. and J.W.H. administrated the project and data collection; H.J.K. and T.Y.C. coordinated and supervised data collection; H·W.L. and J.W.H. performed data analysis; M.S.L. acquired funding support; L.A., H.J.K., M.S.L. and J.I.K. drafted the initial manuscript; and H.J.K., T.Y.C. and H·W.L. critically reviewed and revised the manuscript. All the authors read and approved the final version of the manuscript.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2023.101763.

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