

Bloodletting at EX-HN6 as an adjunctive therapy to eye drops for styne

A meta-analysis

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Abstract

Background: This study evaluated the effectiveness and safety of bloodletting (BL) at ear-apex (EX-HN6) as an adjunctive therapy to eye drops for styne.

Methods: This study systematically searched electronic databases from inception to March 1, 2020 in PUBMED, EMBASE, Cochrane Library, China National Knowledge Infrastructure, Chinese Scientific Journals Full-text Database, and WanFang Database. All potential randomized controlled trials (RCTs) investigating the effectiveness and safety of BL at EX-HN6 as an adjunctive therapy to eye drops for styne were included in this study. Study quality of all included studies was assessed by Cochrane Risk of Bias Assessment Tool. RevMan 5.3 software was used for statistical analysis and meta-analysis performance.

Results: A total of 11 RCTs, involving 1718 subjects, were included in this study. Results showed that BL at EX-HN6 as an adjunctive therapy to eye drops was superior to the eye drops alone in enhancing total effectiveness rate (risk ratio [RR] 1.21, 95% confidence intervals [CIs] [1.11, 1.32], $I^2 = 79\%$), and total cure rate (RR 1.28, 95% CIs [1.14, 1.43], $I^2 = 69\%$). After removing two studies, results of subgroup analysis still showed significant improvements in total effectiveness rate (RR 1.13, 95% CIs [1.08, 1.18], $I^2 = 0\%$), and total cure rate (RR 1.16, 95% CIs [1.08, 1.24], $I^2 = 0\%$). No data of adverse reactions was reported in primary trials, thus, this study did not analyze adverse reactions of BL at EX-HN6 as an adjunctive therapy to eye drops for styne.

Conclusion: BL at EX-HN6 as an adjunctive therapy to eye drops may benefit styne. However, high-quality RCTs addressing on this issue is still needed to warrant the findings of this study.

Abbreviations: BL = bloodletting, CIs = confidence intervals, EX-HN6 = Ear-apex, RCTs = randomized controlled trials, RR = risk ratio.

Keywords: styne, bloodletting, ear-apex, adjunctive therapy, eye drops, effectiveness

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The authors have no conflicts of interest to disclose.

Ethical consideration: Ethics approval and consent was unnecessary because no individual patient data was collected in this study.

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

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1. Introduction

Styne, also known as hordeolum, is a very common eye disorder.^[1–3] It is characterized as a painful, acute infectious condition at upper or lower eyelid.^[4,5] It has been estimated that there is an increasing incidence of styne in every age, especially in ages 30 to 50.^[6,7] Previous studies have reported that about 90% styne are associated with *Staphylococcus aureus*.^[8–13] People with seborrheic dermatitis, diabetes, and high serum lipids are more likely to be affected such disorder.^[6,7] Risk factors of poor eyelid hygiene and inflammatory eyelid diseases are more likely to cause styne.^[4,10,12]

Common treatments for styne consist of topical medications, antibiotics, steroids, massage, acupuncture and bloodletting (BL).^[14–24] Of those, BL is defined as withdrawal of blood from patients to prevent or treat disease, such as styne. It is reported to get rid of “Heat” and eradicate Qi/Blood stagnation that can help recover styne.^[25] Previously studies reported that BL at Ear-apex (EX-HN6, locates at the top region of the auricle, fold the auricle forward and it is at the apex of the auricle) as an adjunctive therapy to eye drops effectively treat styne.^[26–37] However, there are still inconsistent results, and no systematic review has specifically assessed the effectiveness and safety of BL at EX-HN6 as an adjunctive therapy for styne. Therefore, the present meta-analysis aimed to explore the effectiveness and safety of BL at EX-HN6 as an adjunctive therapy to eye drops for styne.

2. Methods

2.1. Eligibility criteria

2.1.1. Type of studies. All potential randomized controlled trials (RCTs) that assessed the effectiveness and safety of BL at EX-HN6 as an adjunctive therapy to eye drops for styne were included without language and publication status limitations. All other studies were excluded, such as animal study, review, case report, case series, uncontrolled trial, and non-RCTs.

2.1.2. Types of participants. All participants who were diagnosed with styne were included irrespective of age, sex, race, duration, and severity of styne.

2.1.3. Types of interventions. In the experimental group, all patients who received BL at EX-HN6 combined with eye drops were included.

In the control group, all patients received any forms of eye drops as their comparisons. We excluded studies involving BL at EX-HN6 or other acupoints.

2.1.4. Types of outcomes. The outcomes of this study included total effectiveness rate, total cure rate, and adverse events.

2.2. Search strategy

This study retrieved the following electronic databases (PUBMED, EMBASE, Cochrane Library, China National Knowledge Infra-

Table 1

Search strategy for PUBMED.

Number	Search terms
1	Hordeolum
2	Styne
3	Acute focal infection
4	External hordeola
5	Sty
6	Or 1–5
7	Blood letting therapy
8	Blood-letting therapy
9	Bloodletting therapy
10	Bloodletting intervention
11	Ear-apex
12	EX-HN6
13	Or 7–12
14	Randomized controlled trial
15	Controlled trial
16	Clinical trial
17	Random
18	Randomly
19	Blind
20	Concealment
21	Allocation
22	Or 14–21
23	6 and 13 and 22

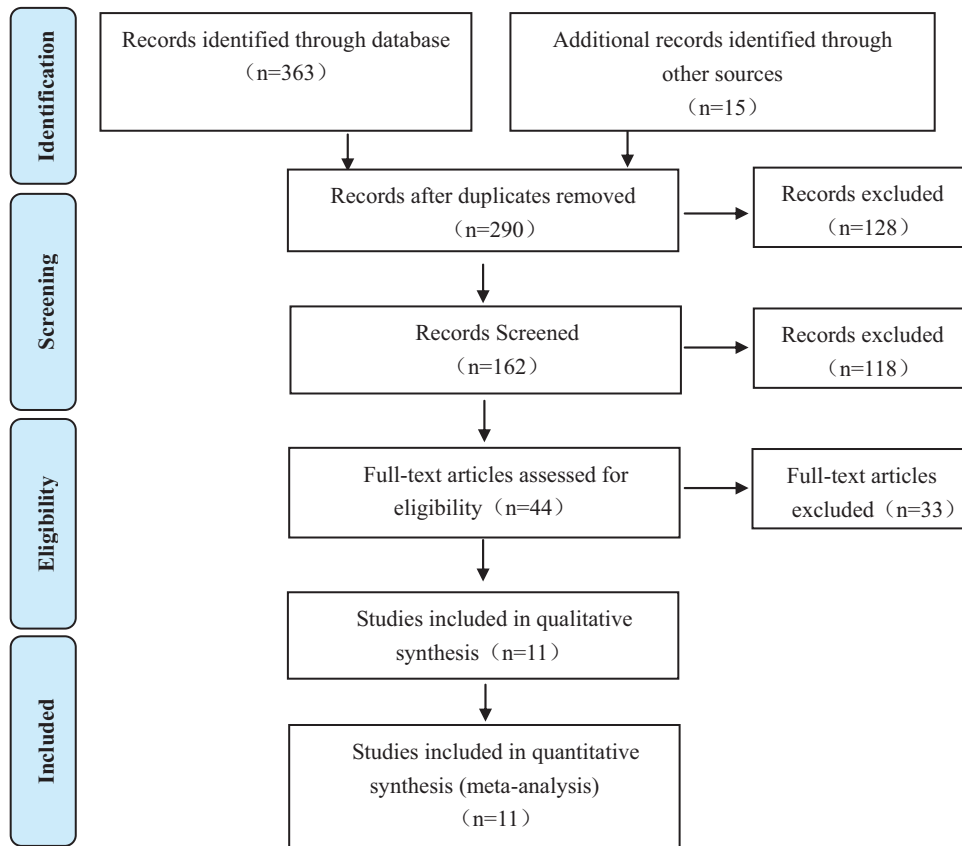


Figure 1. Flow chart of study selection.

Table 2
Basic characteristics of included studies.

Study	Sample size (EG/CG)	Sex (M/F)	Age (y, mean ± SD or range)	Interventions in EG	Interventions in CG	Outcomes	Course (d)
Zhang 2018 ^[27]	44/44	56/32	E:28.4 ± 2.6; C:27.4 ± 3.3	A+B	B	① ②	3
Yin 2003 ^[28]	148/148	67/81	E:3.0–56.0; C:NR	A+B	B	① ②	3
Yang 2014 ^[29]	54/54	60/48	23.2 ± 1.2	A+B	B	① ②	1–6
Yang 2011 ^[30]	200/186	215/171	NR	A+B	B	① ②	1–3
Xu 2007 ^[31]	32/30	33/29	2.0–60.0	A+B	B	① ②	1–3
Teng 2014 ^[32]	60/60	58/62	E:25.0 ± 6.2; C:24.0 ± 7.2	A+B	B	① ②	NR
Qi 2013 ^[33]	51/51	32/70	E:29.0 ± 10.0; C:27.0 ± 9.0	A+B	B	① ②	3
Pang 2009 ^[34]	30/30	32/28	E:27.6 ± 11.0; C:26.0 ± 12.0	A+B	B	①	NR
Ou 2017 ^[35]	100/100	112/88	23.06 ± 3.97	A+B	B	① ②	3
Mi 2015 ^[36]	60/60	72/58	32.0 ± 7.28	A+B	B	① ②	3
Chen 2000 ^[37]	111/120	136/95	E:1.0–55.0; C:1.0–48.0	A+B	B	① ②	3

A= bloodletting at Ear-apex, B=eye drops: including levofloxacin hydrochloride eye drops, chloramphenicol eye drops, gentamicin eye drops, erythromycin eye ointment, lomefloxacin hydrochloride gel, Tobramycin eye drops, ofloxacin eye drops, CG=control group, d=days, EG=experimental group, F=female, M= male, NR= unclear or not reported, Outcomes: ①=total effectiveness rate, ②=total cure rate, SD=standard deviation, y=years.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen 2000	?	?	?	?	+	+	?
Mi 2015	?	?	?	?	+	+	?
Ou 2017	+	?	?	?	+	+	?
Pang 2009	?	?	?	?	+	+	?
Qi 2013	+	?	+	?	+	+	?
Teng 2014	?	?	?	?	+	+	?
Xu 2007	?	?	?	?	+	+	?
Yang 2011	?	?	?	?	+	+	?
Yang 2014	+	?	?	?	+	+	?
Yin 2003	?	?	?	?	+	+	?
Zhang 2018	+	?	?	?	+	+	?

Figure 2. Risk of bias summary.

structure, Chinese Scientific Journals Full-text Database, and WanFang Database) from inception to March 1, 2020 without limitations to language and publication status. All potential RCTs that explored the effectiveness and safety of BL at EX-HN6 as an adjunctive therapy to eye drops for sty were considered for inclusion. The search terms include sty, hordeolum, acute focal infection, external hordeola, sty, blood letting, blood-letting, BL, therapy, intervention, Ear-apex, EX-HN6, RCT, controlled trial, clinical trial, random, blindly, blind, concealment and allocation. The detailed search strategy for PUBMED was summarized in Table 1. Similar search strategies for other electronic databases were adapted. In addition, this study searched other sources, such as conference proceedings, and reference lists of included studies

2.3. Study selection and data extraction

2.3.1. Study selection. Two researchers independently scanned titles and abstracts of searched records according to the predefined eligibility criteria. All irrelevant studies were excluded. Then, the full-texts of remaining studies were read cautiously based on the inclusion criteria. All excluded studies were recorded with specific reasons. Any disagreements between two researchers were solved by a third researcher through discussion.

2.3.2. Data extraction. Two researchers independently extract data from all included studies. Any divergences between two researchers were settled down by a third researcher via consultation. The extracted information includes study information (e.g., title, first author, and publication time), patient information (e.g., age, gender, race, inclusion, and exclusion criteria), study setting and methods, details of interventions and controls, outcomes, results and conclusions, and funding information.

2.4. Study quality assessment

Two investigators independently assessed study quality using Cochrane Handbook’s Bias Risk Tool, which covers 7 domains. Each domain is categorized into 3 levels: high, unclear, and low risk of bias. Different opinions were judged by a third researcher through discussion.

2.5. Statistical analysis

RevMan 5.3 software was used for statistical analysis. All dichotomous outcome data was calculated as risk ratio (RR) and 95% confidence intervals (95% CIs), and all continuous outcome data was expressed as standard mean difference and 95% CIs.

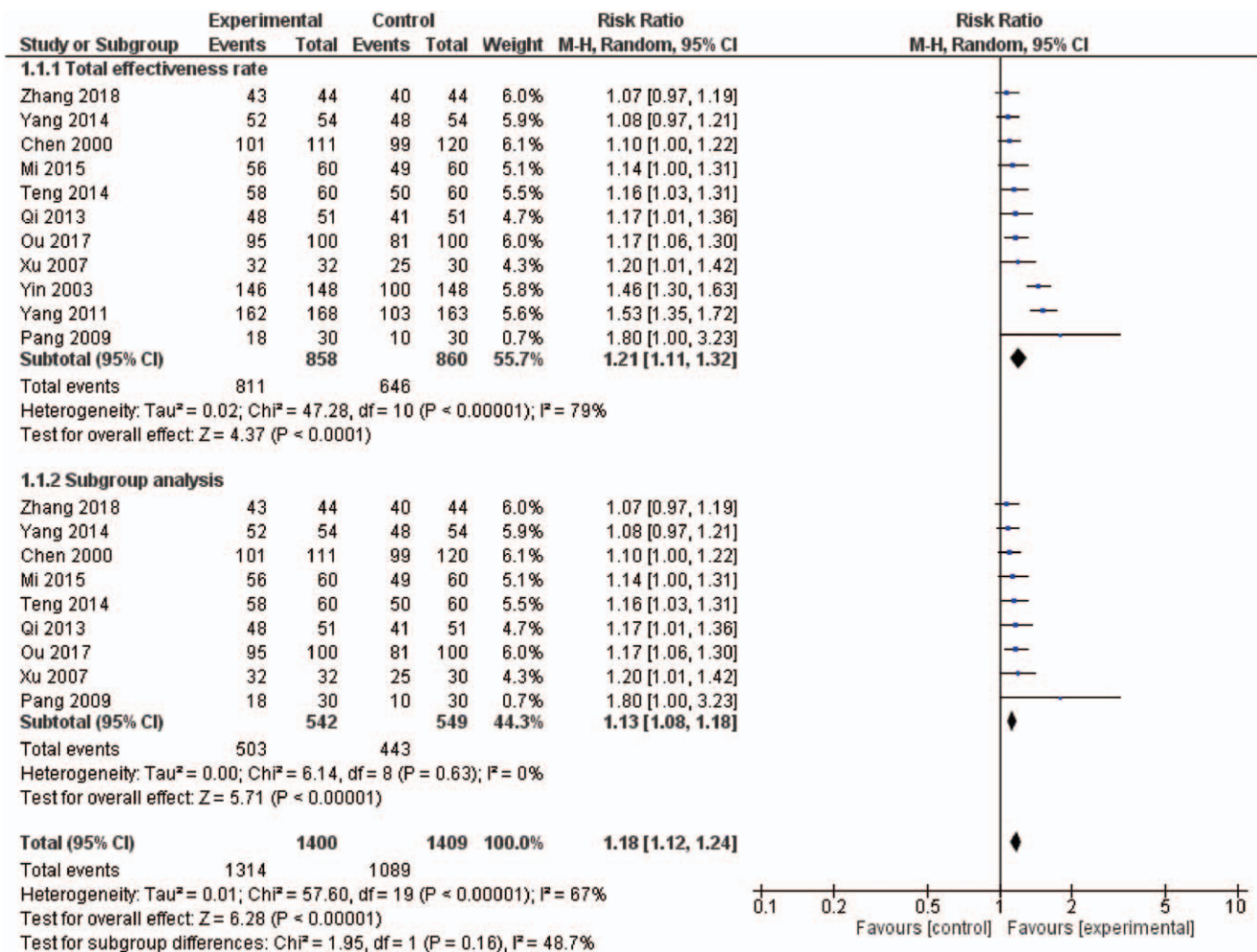


Figure 3. Meta-analysis of total effectiveness rate.

Statistical heterogeneity was identified by I^2 test. $I^2 \leq 50\%$ means low level of heterogeneity, and a fixed-effects model is used. $I^2 > 50\%$ suggests high level of heterogeneity, and a random-effects model is utilized. Significant heterogeneity was explored by subgroup analysis. Funnel plot was used to evaluate reporting bias if more than 10 studies were included.

3. Results

3.1. Literature selection

In this study, a total of 378 potential studies were examined (Fig. 1). A total of 334 studies were excluded based on the titles/abstracts identification. Full-texts of 44 eligible trials were subsequently read, and 33 studies were removed. Finally, 11 eligible trials involving 1718 patients met all inclusion criteria and were finally included in this study.^[27-37]

3.2. Characteristics of included studies

Characteristics of all included studies are shown in Table 2. All patients in the experimental group received BL at EX-HN6 plus eye drops, while the participants in the control group underwent

eye drops, including gentamicin, levofloxacin hydrochloride, chloramphenicol, tobramycin, and ofloxacin eye drops.^[27-37]

3.3. Study quality assessment

The results of study quality are summarized in Figure 2. Of 11 included RCTs, 4 studies reported details of randomization,^[27,29,33,35] while the other 7 studies did not provide specifics of randomization.^[28,30-32,34,36,37] None of 11 studies reported allocation, blinding of participants and personnel, and blinding of outcome assessment,^[27-37] except one study applied double blind to both patients and researchers.^[33] None of 11 RCTs reported incomplete data, selective reporting, and other bias.^[27-37]

3.4. Outcomes

3.4.1. Total effectiveness rate. For 11 studies, including 1718 patients, results of meta-analysis showed that BL at EX-HN6 as an adjunctive therapy to eye drops significantly enhanced total effectiveness rate in stye (RR 1.21, 95% CIs [1.11, 1.32], $I^2 = 79\%$)^[27-37] (Fig. 3). After excluding two trials,^[28,30] the remaining studies still exerted encouraging improvement in total effectiveness rate (RR 1.13, 95% CIs [1.08, 1.18], $I^2 = 0\%$)^[28,29,31-37] (Fig. 3).

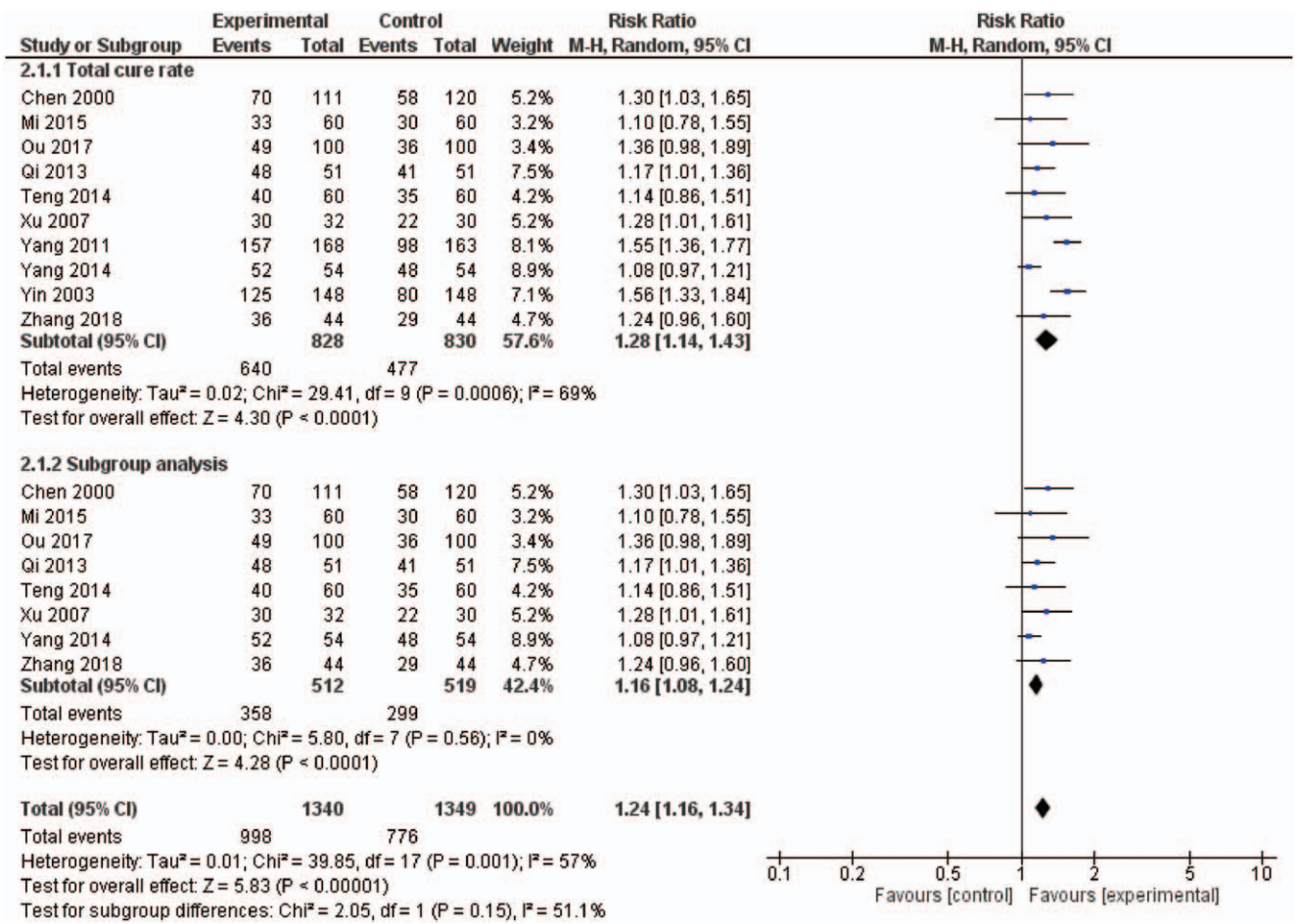


Figure 4. Meta-analysis of total cure rate.

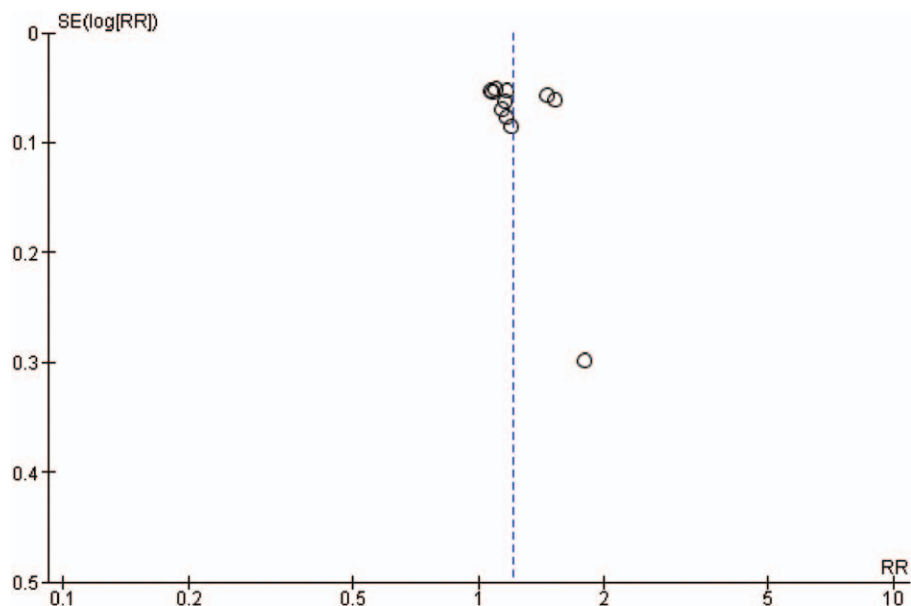


Figure 5. Funnel plot of total effectiveness rate.

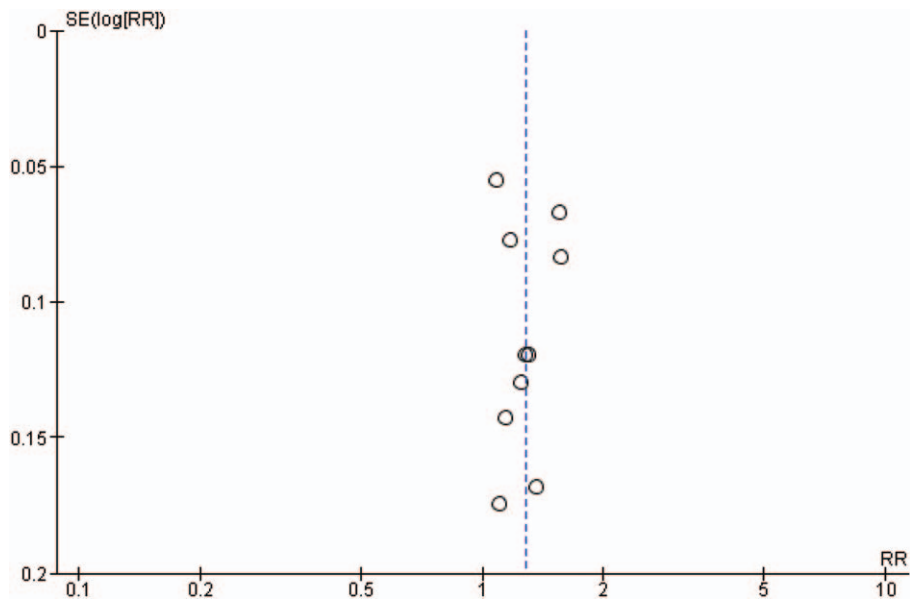


Figure 6. Funnel plot of total cure rate.

3.4.2. Total cure rate. Results of meta-analysis, consisting of 10 RCTs with 1658 patients, reported that BL at EX-HN6 as an adjunctive therapy to eye drops dramatically improved total cure rate in patients with sty (RR 1.28, 95% CIs [1.14, 1.43], $I^2 = 69\%$)^[27–33,35–37] (Fig. 4). After two studies were removed,^[28,30] the remaining results still demonstrated greater enhancement in total cure rate (RR 1.16, 95% CIs [1.08, 1.24], $I^2 = 0\%$)^[27,29,31–33,35–37] (Fig. 4).

3.4.3. Adverse reactions. None of 11 RCTs recorded and reported any adverse reactions in their primary trials. Thus, this study did not collect and analyze any data of adverse reactions.

3.4.4. Publication bias. Results of funnel plot analysis in both total effectiveness rate and total cure rate found that there was a great possibility of publication bias (Figs. 5 and 6).

4. Discussion

Stye is a common infectious eye disorder.^[1–5] Several managements are responsible for the treatment of sty,^[14–24] including BL at EX-HN6 as an adjunctive therapy to eye drops.^[26–37] EX-HN6 is one of extra nerve apoints in the ear, mostly used for BL.^[24] Previous studies reported BL at EX-HN6 plus eye drops for the treatment of sty.^[26–37] However, no meta-analysis has been specifically conducted to assess the effectiveness and safety of BL at EX-HN6 combined eye drops for sty.

This study carried out a systematic literature search to identify as comprehensive potential studies as possible. The results of this study demonstrated that BL at EX-HN6 as an adjunctive therapy to eye drops significantly enhanced total effectiveness rate and total cure rate. It indicates that BL at EX-HN6 plus eye drops is superior to the eye drops alone in this study.

There are several limitations in this study. First, the overall quality of included studies is poor, which may affect results of this study. Secondly, significant heterogeneity was identified across

included trials, possibly because of the insufficient similarity in study design, patient characteristics, time points of outcome measurement, and outcome indicators. Thirdly, this study utilized various types of eye drops with different dosage, frequency, and duration. Fourthly, all patients were from China, and no relevant studies were conducted from other countries. Fifth, this study only assessed the total effectiveness rate and total cure rate, thus, more objective outcome measurements should be applied. Finally, publication bias was identified in this study. Therefore, future studies should avoid above limitations.

5. Conclusions

The results of this study found that BL at EX-HN6 as an adjunctive therapy to eye drops may benefit sty. However, due to the poor methodological quality of included trials, more high quality RCTs is needed to warrant the findings of this study.

Author contributions

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Software: Hong-wei Qiao, Jin Wang, Shan Huang, Lei Yu, Zhong Chen.

Supervision: Na-wen Liu.

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Writing – original draft: Hong-wei Qiao, Na-wen Liu, Shan Huang, Lei Yu.

Writing – review & editing: Hong-wei Qiao, Na-wen Liu, Jin Wang, Shan Huang, Zhong Chen.

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