Bloodletting at EX-HN6 as an adjunctive therapy to eye drops for stye
A meta-analysis

Hong-wei Qiao, MDa, Na-wen Liu, MDak, Jin Wang, MBb, Shan Huang, MMa, Lei Yu, MDa, Zhong Chen, MMA

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 stye.

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 stye 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], I² = 79%), and total cure rate (RR 1.28, 95% CIs [1.20, 1.36], I² = 69%). After removing two studies, results of subgroup analysis still showed significant improvements in total effectiveness rate (RR 1.13, 95% CIs [1.08, 1.19], I² = 0%), and total cure rate (RR 1.16, 95% CIs [1.08, 1.24], I² = 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 stye.

Conclusion: BL at EX-HN6 as an adjunctive therapy to eye drops may benefit stye. 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: stye, bloodletting, ear-apex, adjunctive therapy, eye drops, effectiveness

1. Introduction

Stye, 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 stye in every age, especially in ages 30 to 50.6,7 Previous studies have reported that about 90% stye 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 stye.4,10,12

Common treatments for stye 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 stye. It is reported to get rid of “Heat” and eradicate Qi/Blood stagnation that can help recover stye.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 stye.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 stye. 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 stye.

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* Department of Traditional Chinese Medicine, a Department of Nursing Care, Tianjin First Central Hospital, Tianjin, China.
* Correspondence: Na-wen Liu, Department of Traditional Chinese Medicine, Tianjin First Central Hospital, No. 24 Fukang Road, Nankai District, Tianjin, 300192, China (e-mail: xzxxljj@yeah.net).
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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 stye 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 stye were included irrespective age, sex, race, duration, and severity of stye.

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

| Number | Search terms |
|--------|--------------|
| 1      | Hordeolum    |
| 2      | Sty          |
| 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.
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 stye were considered for inclusion. The search terms include stye, hordeolum, acute focal infection, external hordeola, sty, blood letting, blood-letting, BL, therapy, intervention, Ear-apex, EX-HN6, RCT, controlled trial, clinical trial, random, randomly, 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.

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  | 44/44               | 56/32     | E:28.4 ± 2.6; C:27.4 ± 3.3 | A + B               | B                   | 1 ①      | 3          |
| Yin 2003    | 148/148             | 67/81     | E:37.0–56.0; C:NR           | A + B               | B                   | ②        | 3          |
| Yang 2011   | 54/54               | 68/44     | A:23.2 ± 1.2                | A + B               | B                   | ②        | 1–3        |
| Yang 2011   | 200/1986            | 215/171   | NR                         | A + B               | B                   | ②        | 1–3        |
| Xu 2003     | 32/30               | 33/29     | 2.0–60.0                   | A + B               | B                   | ②        | 1–3        |
| Teng 2014   | 60/60               | 58/82     | E:25.0 ± 6.2; C:24.0 ± 7.2 | A + B               | B                   | NR       | 3          |
| Qi 2013     | 51/51               | 32/27     | E:29.0 ± 10.0; C:27.0 ± 9.0| A + B               | B                   | ①        | 3          |
| Pang 2009   | 30/30               | 32/28     | E:27.6 ± 11.0; C:26.0 ± 12.0| A + B               | B                   | ①        | NR         |
| Ou 2011     | 100/100             | 112/88    | 20.06 ± 3.97               | A + B               | B                   | ②        | 3          |
| Mi 2015     | 60/60               | 72/58     | E:32.0 ± 7.28              | A + B               | B                   | ②        | 3          |
| Chen 2000   | 111/120             | 136/95    | E:1.0–55.0; C:1.0–48.0     | A + B               | B                   | ①        | 3          |

A = bloodletting at Ear-apex, B = eye drops: including levofloxacin hydrochloride eye drops, chloramphenicol eye drops, gentamicin eye drops, erythromycin eye ointment, tobramycin 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.

Figure 2. Risk of bias summary.
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.\[27\text{–}37\]

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.\[27\text{–}37\]

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.\[28,30\text{–}32,34,36,37\] None of 11 studies reported allocation, blinding of participants and personnel, and blinding of outcome assessment,\[27\text{–}37\] except one study applied double blind to both patients and researchers.\[33\] None of 11 RCTs reported incomplete data, selective reporting, and other bias.\[27\text{–}37\]

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], \( I^2 = 79\% \))\[27\text{–}37\] (Fig. 3). After excluding two trials\[28,30\] of the remaining studies still exerted encouraging improvement in total effectiveness rate (RR 1.13, 95% CIs [1.08, 1.18], \( I^2 = 0\% \))\[28,29,31\text{–}37\] (Fig. 3).
Figure 4. Meta-analysis of total cure rate.

Figure 5. Funnel plot of total effectiveness 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.[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 management are responsible for the treatment of stye,[14–24] including BL at EX-HN6 as an adjunctive therapy to eye drops.[26–37] EX-HN6 is one of extra nerve auopoints in the ear, mostly used for BL.[24] Previous studies reported BL at EX-HN6 plus eye drops for the treatment of stye.[26–37] However, no meta-analysis has been specifically conducted to assess the effectiveness of 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 stye. 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

Conceptualization: Hong-wei Qiao, Na-wen Liu, Lei Yu.
Data curation: Hong-wei Qiao, Jin Wang, Shan Huang, Zhong Chen.
Formal analysis: Hong-wei Qiao, Na-wen Liu, Jin Wang, Lei Yu.
Investigation: Na-wen Liu.
Methodology: Hong-wei Qiao, Jin Wang, Shan Huang, Lei Yu, Zhong Chen.
Project administration: Na-wen Liu.
Resources: Hong-wei Qiao, Jin Wang, Shan Huang, Lei Yu, Zhong Chen.
Software: Hong-wei Qiao, Jin Wang, Shan Huang, Lei Yu, Zhong Chen.
Supervision: Na-wen Liu.
Validation: Hong-wei Qiao, Na-wen Liu, Jin Wang, Shan Huang, Lei Yu.
Visualization: Hong-wei Qiao, Na-wen Liu, Jin Wang, Zhong Chen.
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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