Acupuncture for Oculomotor Nerve Palsy: a Systematic Review Protocol

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Abstract

Background: Oculomotor nerve palsy(ONP) is a common clinical disease in neurology and ophthalmology which results in serious syndrome such as ptosis, diplopia, and limited eye movement. The major medications treating ONP usually make sense and side effects, while acupuncture is known as a safe and effective therapy for ONP. We aim to evaluate the safety and efficacy of acupuncture in the treatment of ONP.

Methods: The following database will be required from PubMed, Cochrane Library, Medline, Chinese Biomedical Literature Database, China National Knowledge Infrastructure (CNKI), Wanfang data, Chinese Scientific Journal Database, including studies and published systematic review in the reference list and grey. Three reviewers will search these databases, select data and evaluate the quality of studies separately. The methodological quality will be measured by the Cochrane risk of bias tool. The Review Manager 5.3 will be used to synthesize collected data.

Results: The systematic review will evaluate the safety and efficacy based on current evidence of acupuncture for ONP. The primary outcomes are the therapeutic efficiency, the sizes of palpebral fissure and pupil, the range of eye movement and scores of diplopia. Quality of life, and adverse effects will be assessed as secondary outcomes.

Conclusion: The study will provide high-quality recently evidence for evaluating the efficacy of acupuncture for patients with ONP. PROSPERO registration number: CRD42020162140.

1. Introduction

Oculomotor nerve palsy (ONP) is a common clinical disease in neurology and ophthalmology. ONP is a kind of disease caused by numerous etiologies, which characterized by ptosis, limited eye movement, slow or absent reaction to light and diplopia.[1] From the brain stem to any part of orbital lesion can lead to the occurrence of this disease according to direction of the oculomotor nerve. Its pathogenesis is quite complicated. It is known that the most common identifiable etiologies are ischemia, aneurysm, trauma and tumor.[2] The latest study shows that the top three are diabetes, stroke and myasthenia gravis[3] . But the specific pathogenesis is still unclear.

The manifestations of ONP are blepharoptosis, narrowing of the palpebral fissure, inferolateral inclination, double vision and loss reaction to light, dilated pupil, inability of the eyeball to move upward, inward and downward,[4] sometimes accompanied by strabismus or headaches，these symptoms seriously affect the quality of life of patients to some extent.[5] At present, mainstream treatment is to improve the neurological function of patients using nutrient nerve drugs, such as Methycobal[6-8]and Vitamin B12[9]. Hormones, vasodilators and surgery[10] are also selected. But there are some side effects and low efficacy, because of so many uncertain reasons, finding a safe and effective treatment is very necessary. In recent years, lots of researches have shown acupuncture is indeed effective to treat ONP[11-

[12]. As a traditional Chinese medicine method, acupuncture has the advantages of easy operation, no toxicity and side effect. It can relieve symptoms and patients' psychological fear, but reduce treatment costs. So acupuncture has been gradually wide used in diverse diseases.

There are many ways to treat ONP. Therefore, developing safe and effective alternative therapies for ONP are of utmost priority. Several clinical studies have shown that acupuncture could reduce symptoms[12-15] and improve quality of life. So, in this systematic review, we will evaluate the efficacy and safety of acupuncture for treating ONP.

2. Methods

The content followed preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)

2.1. Eligibility criteria

2.1.1. Types of studies. This review will include all randomized controlled trials (RCTs) in English or Chinese and without the restriction of publication type. Non-RCTs, quasi-RCTs, uncontrolled trials, case series, case reports, crossover studies, letters, and laboratory studies will be excluded.

2.1.2. Types of participants. Patients with ONP were diagnosed according to the book named *Neurology*[16]. Information relating to their age, sex, race, education, nationality, or economic status is not taken into account.

2.1.3. Types of interventions

2.1.3.1 Experimental interventions. The forms of acupuncture therapy include body acupuncture, electro-acupuncture, auricular acupuncture, intradermal needle, scalp acupuncture, ocular acupuncture, fire needling, elongated needling, and plum blossom needle. Acupoint injection, laser acupuncture, moxibustion, cupping, and acupressure will be excluded.

2.1.3.2. Control interventions. Types of control interventions include placebo control, sham acupuncture (use acupuncture needle to insert into skin without penetrating exact acupoints), western medicine compare with acupuncture, drug therapy, other therapies, no therapy and acupuncture plus 1 treatment compares with the same treatment.

2.1.4. Types of outcome measures

2.1.4.1. Primary outcomes. The primary outcome included:

(1) Scores of diplopia: visual analog scale (VAS)[11,17]

(2) Palpebral fissure size: from midpoint of upper eyelid to midpoint of lower eyelid.[13,15,18]

(3) Therapeutic efficiency: refer to the State Administration of Traditional Chinese Medicine issued *the Standard for the Diagnosis and Curative Effect of Disease and Syndromes of Traditional Chinese Medicine*[18-19].

(4) The range of eye movement: the distance from the lateral canthus to the center of the pupil was taken as the datum and the distance between the two maximal activity points was recorded[18].

(5) Measure pupil diameter: measure pupil size under light[17].

2.1.4.2. Secondary outcomes. The secondary outcome included:

(1) Measure the patients' quality of life: quality of life assessment scale SF-36(short form 36 questionnaires)[5]

(2) Adverse effects

2.2. Search strategy

To evaluate the efficacy and safety of acupuncture for ONP, the following databases will be searched: PubMed, Cochrane Library, Medline, Chinese Biomedical Literature Database, China National Knowledge Infrastructure (CNKI), Wanfang data, Chinese Scientific Journal Database. In addition, relevant references and RCTs cited in the reports will be researched as supplementary sources. We will also study the gray literature.

The search strategy for PubMed is detailed in Table 1.It will also be used for any other electronic databases.

Table 1. Search strategy used in PubMed databases

NO.	Search items
1	Randomized controlled trial ti,ab
2	Controlled clinical trial ti,ab
3	Randomized ti,ab
4	Placebo ti,ab
5	Randomly ti,ab
6	Trail ti,ab
7	Or 1-6
8	Oculomotor nerve disease mesh
9	Oculomotor nerve disease ti,ab
10	Oculomotor nerve palsy ti,ab
11	Isolate oculomotor nerve palsy ti,ab
12	Third nerve palsy ti,ab
13	Or 8-12
14	Acupuncture therapy mesh
15	Acupuncture therapy ti,ab
16	Pharmacoacupuncture therapy ti,ab
17	Pharmacoacupuncture treatment ti,ab
18	Acupuncture ti,ab
19	Acupunct ti,ab
20	Acupoints ti,ab
21	Electroacupuncture ti,ab
22	Scalp acupuncture ti,ab
23	Manual acupuncture ti,ab
24	Body acupuncture ti,ab
25	Auricular acupuncture ti,ab
26	Ocular acupuncture ti,ab
27	Warm needling ti,ab
28	Fire needling ti,ab
29	Warm needling ti,ab
30	Or 14-19
31	7 and 13 and 30

2.3. Data collection and analysis

2.3.1. Selection of studies. All reviewers will get trained to understand the aim and process of the system review and will select the trials and studies separately. Two reviewers will screen the titles, abstracts and keywords based on the inclusion criteria and the full text will be read for further assessment if necessary. Details of the research choices are shown and exclusive studies will be listed and explained. The process of study selection will be presented in PRISMA flow diagram (Fig.1)

2.3.2 .Data extraction and management. Three viewers (XHZ, SMZ and RSD) will independently extract the data from the studies and fill in the data collection form. The discrepancies and uncertainties in the process will be discussed and solved with a senior reviewer HC. We will contact the corresponding authors for more information if the details of trials were not completed. All data will be transferred into review manager software. We will extract information such as author, time of publication, participants information (age, sex), sample size, interventions, outcome indicators, and other details.

2.3.3. Risk of bias assessment. We will use Cochrane risk of bias assessment tools to evaluate 6 domains of bias(sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting ,and other sources of bias).The included studies will be divided into 3 parts: unclear , low risk, and high risk. The discrepancies will be solved with a senior reviewer called HC.

2.3.4. Assessment of heterogeneity. I square (I^2) statistic will be used to assess heterogeneity in included studies, which describes the percentage of variation between studies due to heterogeneity. If $I^2 < 50\%$, we will choose the fixed-effect model to calculate risk ratio (RR) and mean difference(MD), otherwise use a random-effect model.

2.3.5. Measures of treatment effect. We used review manager 5.3 for meta-analysis to analyze data. We will use MD or standardized mean difference with 95% confidence interval(CI) to synthesize continuous variables. For dichotomous data, we will use the RR with 95% CI.

2.3.6. Dealing with missing data. We will contact the original authors to obtain relevant information when collected data is insufficient. If the missing data are unobtainable, we will analyze the available data and describe it in the discussion. We will discuss the impact of missing data if necessary.

2.3.7. Subgroup analysis and investigation of heterogeneity. If data are available, we will perform subgroup analysis for different intervention forms. We will analyze different acupuncture therapy types, the age of patients, and other control interventions.

2.3.8. Ethics and dissemination. This review is aim to evaluate the safety and efficacy of acupuncture to treat ONP.
Formal ethical approval is not required, as the data are not individualized. The results will be disseminated through peer-reviewed publication.

2.3.9. Assessment of reporting biases. We will use a funnel plot to test reporting biases if more than 10 trials are included in the meta-analysis.

3. Discussion

ONP, a complex disease, has negative impact on patients' daily life. Especially, the optimum treatment is still controversial. Although a large of researches has been done, there is no definitive conclusion. Acupuncture can ease ONP patients' symptoms and pain. Therefore, this study will discuss the safety

and effectiveness of acupuncture for patients with ONP. Acupuncture therapy is aim to provide evidence for clinical practice and to benefit future researches.

The review may have some limitations and disadvantages. We only take English and Chinese studies into account, and other different forms of acupuncture treatments, disease selection, and disease severity may be missed.

Abbreviations

CI = confidence interval, MD = mean difference, PRISMA-P = preferred reporting items for systemic reviews and meta-analysis protocol, RCT = randomized controlled trial, RR = risk ratio, VAS = visual analog scale.

Declarations

4.1 Ethics approval and consent to participate

Not applicable

4.2 Consent for publication

Not applicable

4.3 Availability of data and materials

Not applicable

4.4 Competing interests

The authors declare that they have no competing interests

4.5 Funding

Not applicable

4.6 Authors' contributions

HC is the lead and the guarantor of this review. XHZ, SMZ , and RSD conceptualized the review and drafted the manuscript. LZ, HWY and YJL set up the research strategy included in the protocol. XHZ and HC revised the protocol critically. All authors read and provided amendment on the draft and confirmed the final manuscript.

4.7 Acknowledgements

Not applicable

References

1. L.-P. Luo,and S.-C. Zheng.Clinical observation of electroacupuncture combined with drugs in the treatment of 30 cases of oculomotor nerve palsy.Gansu University of Chinese Medicine[J].2016,33(6):72-74.

2. Taeyeon Kim , Kiyeun Nam, Bum Sun Kwon. Isolated oculomotor nerve palsy in mild traumatic brain injury: A literature review.American Journal of Physical Medicine& Rehabilitation[J].2020,99(5):430-435.

3. X.-M. Lin, J.-X. Song, F. Wang, J. Wang,Q.-L. Lu, and S.-D. Wu. Analysis of etiology and clinical features of 56 patients with oculomotor nerve palsy.Clinical Medicine Research and Practice[J].2019.10:13-17.

4. X.-L. Song, X.-P. Ma, and Z.Li. Therapeutic observation on acupuncture plus fire-needle therapy for oculomotor nerve palsy.Shanghai J Acu-mox[J].2013,32(11):931-932.

5. J.-Y. Teng, Z.-D. Wang, X.-Q.Chen, S.-Y. Hu.Assessment of the clinical efficacy and safety of acupuncture combined with conventional therapy for patients with oculomotor nerve palsy.Int Clin Exp Med 2019,12(7):9203-9209.

6. S.-J. Zhang, S.-R. Li, J.-S. Li, J.Liu, and R.-X. Song, Clinical observation on acupuncture for treatme- nt of paralytic strabismus.Zhongguo Zhen Jiu[J].2009,29(10):799-803.

7. Y.-M. Chen, and Y.-M.Ren.Observation on the curative effect of acupuncture combined with medicine on oculomotor nerve palsy. Journal of Clinical Medicial[J].2017,4(68):13346-13347.

8. C.-L. Li.The curative effect of traditional Chinese medicine combined with western medicine on oculo- motor nerve palsy. Chinese Journal of Practical Nervous Diseases[J].2015,18(10):25-27.

9. G. Akdal, G. G. Yener, E. Ada, and G.M.Halmagyi.Eye movement disorders in vitamin B12 deficien- cy:two new cases and a review of the literature. European Journal of Neurology[J].2007,14(10):1170-1172

10. Sotirios Basiakos, Michael Gräf, Markus N.Splitting of the lateral rectus muscle with medial transpo- sition to treat oculomotor palsy: a retrospective analysis of 29 consecutive cases. Grafe's Archive for Cli nical and Experimental Ophthalmology[J].2019,257(9):2001-2014.

11. Q.-X. Chen,W. Zou, D. Ju, L.-W. Zhu, and X.-W. Sun.Acupuncture treatment for oculomotor paresis: clinical observation of 20 cases. Journal of Clinical Acupuncture and Moxibustion[J].2014,30(10):31-33.

12. Moshe Frenkel,Judy Frenkel.Oculomotor nerve palsy treated with acupuncture. Alternative Therapies in Health and Medicine[J].2002,8(2):118-120.

13. C.-E. Wang, and D.-A. Zhou.Clinical efficacy of acupuncture and rehabilitation treatment on oculomotor nerve palsy patients. Int Eye Sci[J]2014(14)6:1165-1167.

14. L. Yang, X.-Y. Liu,and J.Hao. Integrated TCM treatment for oculomotor paralysis in 37 middle-eged patients.World Chinese Medicine[J].2013,8(8):912-913.

15. Jin-Qi Bi,WeiLi,Qi Yang,Bao-lin Li, Qing-Gang Meng,Yu-fu Liu,Acupuncture for the treatment of oculomotor paralysis:A pilot randomised controlled trial.Hindawi[J],2016:1-6.

16. J.-Wu.Neurology[M]Beijing:People's Medical Publishing House,2005:8-9.

17. G.-B. Sheng, and M. Dong.Clinical observation of pricking muscles along the regular meridians of eyes with acupuncture for treatment of oculomotor paralysis.TCM Information[J].2011,28(6):96-97

18. X.-J Ji, L.-Y Zhou, and et al. Efficacy observation on electroacupuncture in the treatment of oculomotor impairment caused by ophthalmic nerve injury.Chinese Acupuncture and Moxibustion[J].2013,33(11).975-979.

19. The State Administration of Traditional Chinese Medicine.the Standard for the Diagnosis and Curative Effect of Disease and Syndrome of Traditional Chinese Medicine[M].Nanjing:Nanjing University Press,1994:70-71.
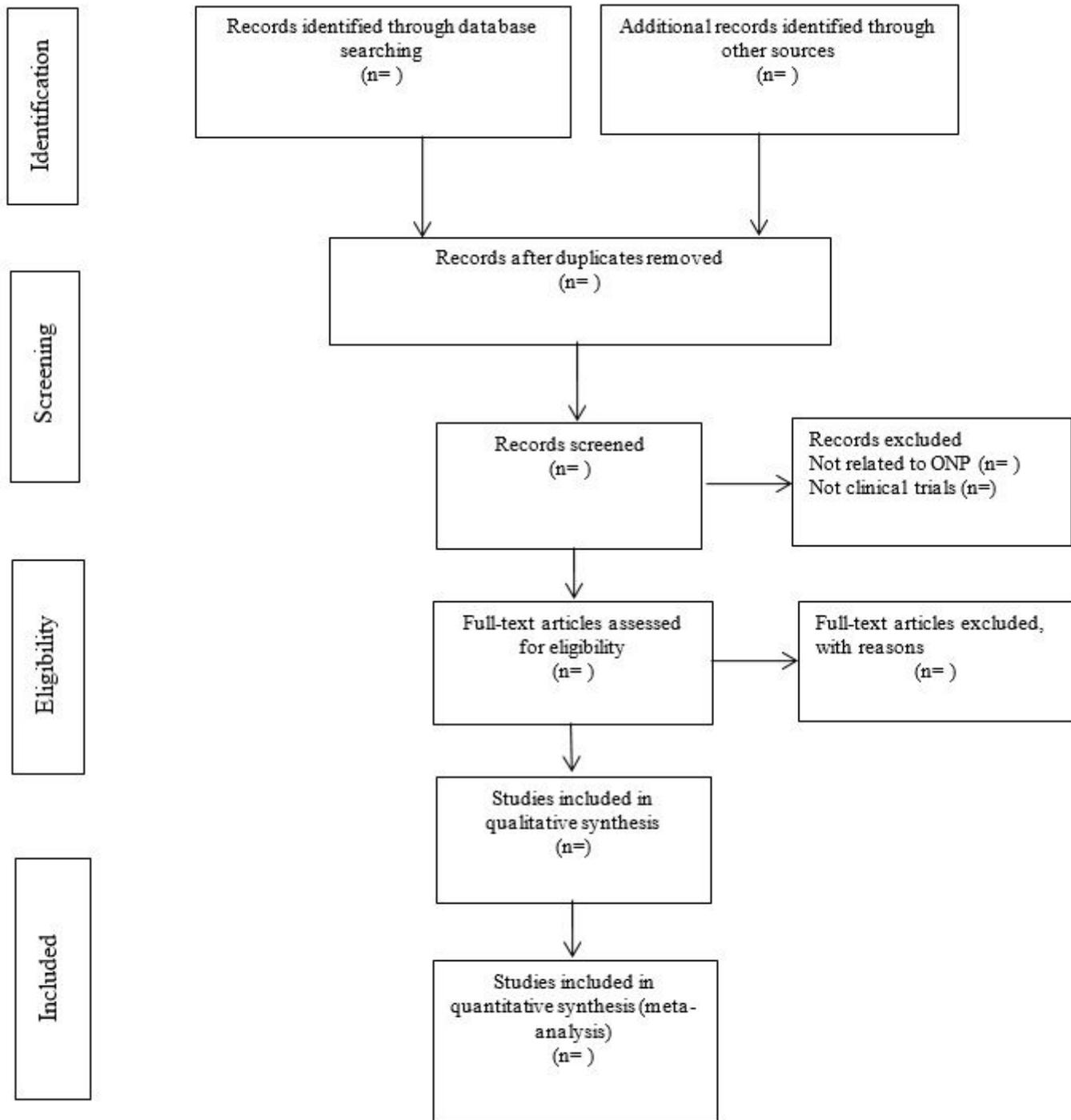
Figures

Figure 1

PRISMA flow diagram of study process. PRISMA=preferred reporting items for systematic reviews and meta-analysis