INPLASY PROTOCOL

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None declared.

The dose-effect association between electroacupuncture sessions and its effect on chronic migraine: a protocol of a meta-regression of randomized controlled trials

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Review question / Objective: **We will use a meta-regression approach to verify the dose-effect relationship between the number of electroacupuncture sessions and its effects on migraine.**

Condition being studied: **Migraine is recurrent and chronic, requiring long-term control, but the side effects caused by long-term use limit the use of pharmacotherapy, like non-steroidal anti-inflammatory drugs (NSAIDS), ergoamines and opioids. With fewer side effects and lower cost, acupuncture is becoming a more attractive option for migraine. Relevant studies have confirmed the clinical effects of electroacupuncture on migraine and its effects on intracranial blood flow velocity, functional brain imaging and neuroinflammation. However, uncertainty exists regarding the dose-effect between electroacupuncture and migraine. In recent years, inspired by the dose-effect researches in pharmacology and epidemiology, researches focusing on the dose-effect association between acupuncture and diseases has also begun to emerge. So in this protocol, we designed to use a meta-regression approach to explore the optimal electroacupuncture dose for migraine.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 December 2022 and was last updated on 21 December 2022 (registration number INPLASY2022120085).

INTRODUCTION

Review question / Objective: **We will use a meta-regression approach to verify the dose-effect relationship between the number of electroacupuncture sessions and its effects on migraine.**

Rationale: **Migraine is a common neurological disease manifested by recurrent and pulsating headaches, which**

has been a global issue with high prevalence and heavy social burden. With fewer side effects and lower cost than pharmacotherapy, electroacupuncture is becoming a more attractive option for migraine. However, there are no studies or guidelines reporting on the minimum effective dose or optimal sessions of electroacupuncture for migraine.

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METHODS

Search strategy: The basic search strategy was TS=('migraine disorders' OR 'migraine' OR 'chronic migraine' OR 'OP' OR 'hemicrania' OR 'headache' OR 'cephalgia' OR 'cephalalgia') AND TS=('acupuncture' OR 'electroacupuncture' OR 'electro-acupuncture' OR 'warm needling' OR 'needle warming moxibustion') AND TS=('random*' OR 'clinical' OR 'trial'). Similar Chinese words are used in Chinese database searching strategies. Literatures will be searched in China National Knowledge Infrastructure (CNKI), VIP database for Chinese Technical Periodicals (VIP), WANFANG database (WF), Web of Science (WOS), Pubmed, Embase, Medline and the Cochrane Library.

Participant or population: Participants (18 years and above) who were diagnosed with "migraine" according to clear diagnostic criteria regardless of gender, race or nationality.

Intervention: The interventions in the experimental group included electroacupuncture, emergency use of pain medications was also permitted. The selection of acupoints, needle retention time, stimulation techniques, parameters of electroacupuncture, and treatment sessions were not limited.

Comparator: The control group included non-acupuncture techniques, such as placebo control or other active therapies.

Study designs to be included: All the randomized controlled trials (RCTs) of electro-acupuncture therapies for the treatment of migraine, with no limitation on language or publication types. Non-RCTs, quasi-RCTs, cluster RCTs, cohort studies, case control studies, case reports and meta-analyses will be excluded.

Eligibility criteria: Inclusion criteria(1) Participants (18 years and above) were diagnosed with "migraine" according to clear diagnostic criteria regardless of gender, race or nationality;(2) The experimental group received electroacupuncture, taken painkillers when necessary; while the control group received non-acupuncture techniques, such as placebo control or other active therapies; (3) The study was a randomized controlled clinical trial with a strict randomization protocol;(4) The outcome includes the reduction of migraine attack frequency or the migraine attack frequency from baseline to post-treatment.Exclusion criteria(1) Reviews, meta-analyses, protocols, cross-over studies, cohort studies, case control studies, case reports and animal experiments;(2) Studies without clear diagnostic criteria for migraine;(3) Studies deployed auricular acupuncture, laser acupuncture, transcutaneous

electrical acupoint stimulation or other acupuncture techniques.(4) Studies without complete data or for which quantitative data are not available.

Information sources: Literatures will be searched in the following databases from inception to December 20, 2022: China National Knowledge Infrastructure (CNKI), VIP database for Chinese Technical Periodicals (VIP), WANFANG database (WF), Web of Science (WOS), Pubmed, Embase, Medline and the Cochrane Library. Clinical trial registries, like the Cochrane Central Register of Controlled Trials, WHO International Clinical Trial Registry Platform (WHO ICTRP), Chinese clinical registry (ChiCTR) and ClinicalTrials.gov will be searched for ongoing trials with unpublished data. Moreover, reference lists of eligible studies and previous reviews will also be manually reviewed. Incomplete data will be obtained by contacting the authors.

Main outcome(s): Reduction of migraine attack frequency or the migraine attack frequency from baseline to post-treatment.

Additional outcome(s): None.

Data management: Firstly, two independent investigators (FYL and ZY) eliminated duplicate articles which were republished by different journals or downloaded from different databases. Then, according to the inclusion and exclusion criteria, YZ and YW independently screened the literature by reading the abstract and the full text, and the excluded literature will be classified and marked with reasons for exclusion. Disputes in the screening process will be discussed with LZ. After the included references were determined, the standard electronic data-extraction table in Excel 2019 will be created through a meeting by all investigators, which will include the following details: (1) basic information: publication year, journal, first author's name; (2) trial characteristics: study design, simple size, grouping methods, etc; (3) participants: age, gender, diagnosis, duration, etc; (4) intervention/control method: number of treatment, frequency, duration of a session, etc; (5) outcome measurements: primary outcome, secondary outcome, etc; (6) results: mean, standard deviation (SD), adverse event, etc. XnL and WQ will independently extract data and FRL will check the input data to ensure consistency and validity.

Quality assessment / Risk of bias analysis: The risk of bias of eligible trials was measured by the Risk of Bias (ROB2) Tool in Cochrane Handbook by XoL and GX. Each criterion was graded as "low" risk of bias, "high" risk of bias and "unclear" risk of bias. The methodology quality was assessed by FYL and ZY with the Jadad scale. Any dissent occurred in the assessment procedures was judged by LZ.

Strategy of data synthesis: We will use the robust-error meta-regression method to build the relationship between acupuncture treatment sessions and "reduction of migraine attack frequency". Based on the "one-response" framework, REMR method treated each included study as a cluster and fitted the meta-regression of treating sessions against the reduction of migraine attack frequency within a whole data set. Additionally, we weighted each dose-specific effect for the pooling by using the inverse variance method, which, at the same time, can balance heteroscedasticity in REMR model and ensure the unbiasedness of parameter estimation.
The non-linear relationship will be approximated using Restricted Cubic Spline (RCS) . We will set three knots to place splines inserting values for "reduction of migraine attack frequency" and changes of "reduction of migraine attack frequency", four knots for improvement rate, to ensure that the cubic spline was restricted to be linear at the tails of the function. Modeling of potential non-linear relationships will be tested by restricting the regression coefficient to zero and a p-value<0.1.

Subgroup analysis: The subgroup analysis will be undertook when necessary.

Sensitivity analysis: We will undertook sensitivity analyses. We will conduct

sensitivity analysis by omitting low-quality RCTs (Jadad<4) and small sample size RCTs (<30). Because for one-stage dose-response meta-analysis, there were currently no valid measurement methods for assessing heterogeneity, we used the statistic ($1-R^2$) as a rough estimation of heterogeneity. Analyses were performed using the Stata 17.0 software, with a two-side test of $\alpha=0.05$ as the significant level.

Language restriction: No restriction on languages.

Country(ies) involved: China.

Other relevant information: None.

Keywords: Acupuncture, migraine, dose-effect, meta-regression analysis.

Dissemination plans: The results will be published as a paper.

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Author 1 drafted the manuscript. Author 2 and 3 searched the current research status. Author 4, 5, 6 and 7 provided the methodology and strategy of data management, quality and bias assessment, data synthesis and sensitivity analysis. Author 8, 9 and 10 reviewed and revised the manuscript.

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