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Comparative safety and efficacy of manual therapy interventions for cervicogenic headache: a systematic review and network meta-analysis

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 8 September 2025 and was last updated on 8 September 2025.

INTRODUCTION

Review question / Objective To evaluate and compare the safety and efficacy of spinal manipulation, mobilization, and massage for the management of cervicogenic headache (CGH) using meta-analytic techniques.

Condition being studied Cervicogenic Headache (CGH) is a secondary headache disorder that originates from dysfunction or pathology of the cervical spine and its associated structures, such as the joints, discs, or soft tissues. Unlike primary headaches (e.g., migraine or tension-type), CGH arises due to referred pain from the neck, typically involving the upper cervical nerves (C1–C3). Clinically, CGH is characterized by unilateral head pain that often starts in the neck and radiates to the frontotemporal or orbital regions. The pain is usually non-throbbing, moderate to severe in intensity, and aggravated by neck movement or sustained awkward postures. Patients may also experience reduced cervical range of motion, neck stiffness, and associated symptoms such as dizziness or shoulder discomfort. Diagnosis relies on clinical features and the exclusion of primary headache disorders, while treatment often targets the underlying cervical dysfunction through physical therapies and manual interventions.

METHODS

Participant or population P (Patients): studies included had to focus on patients diagnosed with CGH according to accepted diagnostic criteria.
This ensures the studies are highly relevant to the topic of interest.

Intervention I (Intervention): the intervention must involve one or more manual therapies such as manipulation, mobilization, or massage.

Comparator Comparative Interventions
In this review, the target population consisted of patients with a confirmed diagnosis of cervicogenic headache (CGH) based on established diagnostic criteria. The interventions of interest were manual therapy techniques, specifically spinal manipulation, mobilization (including sustained natural apophyseal glides, SNAGs), and massage. These were evaluated either as stand-alone treatments or in combination with other modalities.

The comparative interventions (controls) included:

Alternative manual therapies (e.g., comparing manipulation with mobilization or massage),

Sham or placebo treatments (designed to control for nonspecific effects of manual contact or patient expectations),

Exercise-based interventions (including strengthening, stretching, or multimodal rehabilitation programs), and

No treatment or usual care (serving as baseline comparators).

This broad comparative framework allowed for meaningful evaluation of the relative effectiveness of each manual therapy approach, while ensuring that sham and exercise comparators captured both placebo and active non-manual interventions. Outcomes were consistently assessed using validated measures of pain and disability, including the Visual Analog Scale (VAS), Neck Disability Index (NDI), Headache Disability Inventory (HDI), and Flexion-Rotation Test (FRT).

Study designs to be included Randomized controlled trials (RCTs) with full text available.

Eligibility criteria Additional Inclusion and Exclusion Criteria
Beyond the PICOS framework, studies were excluded if:

The headache was diagnosed as migraine, tension-type headache, or another non-cervicogenic cause.

They were case reports or included fewer than five participants.

They were not published in peer-reviewed journals.

They were not published in English.

Impact of Control Group Variability
Considerable variability in control group design was noted across included studies. Inconsistent sham interventions (e.g., placebo mobilizations vs. minimal interventions) create challenges in isolating the true effects of manual therapy. For example, sham or "placebo" groups sometimes involved low-grade mobilizations that could still provide therapeutic benefit, thereby diluting or masking the effects of the intervention under investigation. This variability raises the possibility of bias in interpretation, as differences in control conditions may either exaggerate or underestimate the relative efficacy of spinal manipulation, mobilization, or massage. Future research should aim for more standardized control designs to minimize this source of bias.

Information sources
To ensure a comprehensive search and minimize the risk of publication bias, multiple sources of information will be systematically explored. The primary sources will include the following electronic bibliographic databases: PubMed/MEDLINE, Embase, and the Cochrane Library, which provide broad coverage of clinical trials, systematic reviews, and relevant biomedical literature. In addition, ClinicalTrials.gov will be searched to identify ongoing or recently completed trials that may not yet be published in peer-reviewed journals.

Where necessary, trial registers and reference lists of relevant systematic reviews and included studies will also be screened to capture additional eligible trials. Authors of potentially relevant studies may be contacted to clarify methodological details or to provide missing outcome data that are not available in the published articles.

To reduce publication bias, grey literature sources such as conference abstracts and dissertations will be considered, provided they meet the inclusion criteria. However, only studies published in peer-reviewed journals and in the English language will ultimately be included in the analysis, as per the predefined exclusion criteria.

This multi-source approach ensures that the review captures both published and unpublished evidence, thereby increasing the reliability and completeness of the findings.

Main outcome(s) Outcomes

The primary outcome of interest will be pain intensity, assessed using validated measures such as the Visual Analog Scale (VAS) or Numerical Pain Rating Scale (NPRS). Secondary outcomes will include functional disability measured by the Neck Disability Index (NDI) and the Headache Disability Inventory (HDI), as well as cervical range of motion evaluated through the Flexion-Rotation Test (FRT).

Outcomes will be extracted at multiple time points to assess both short-term and long-term effects. Short-term outcomes will be defined as those measured within 0–12 weeks post-intervention, medium-term outcomes as 3–6 months, and long-term outcomes as >6 months. Where studies report multiple follow-up points, the longest available follow-up within each category will be selected for meta-analysis.

Effect measures will be expressed as mean differences (MDs) or standardized mean differences (SMDs) with 95% confidence intervals (CIs), depending on the consistency of measurement tools across studies. Both absolute and relative improvements will be considered, and pooled estimates will be generated using pairwise and network meta-analytic techniques.

Quality assessment / Risk of bias analysis

The methodological quality of all included randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias (ROB) tool, which is considered the gold standard for evaluating potential sources of bias in clinical trials. Two independent reviewers evaluated each study across the following domains:

Selection bias – adequacy of random sequence generation and allocation concealment.

Performance bias – blinding of participants and study personnel to minimize treatment expectation effects.

Detection bias – blinding of outcome assessors to reduce measurement bias.

Attrition bias – completeness of outcome data and handling of withdrawals or dropouts.

Reporting bias – selective reporting of outcomes relative to study protocols or prespecified endpoints.

Other potential biases – including design-specific concerns such as baseline imbalances, funding sources, or deviations from intended interventions.

Each domain was rated as low risk, high risk, or unclear risk of bias, with supporting justifications documented. Disagreements between reviewers were resolved by consensus or through arbitration by a third reviewer. The overall quality of each trial was summarized, and graphical plots were generated to display the distribution of risk levels across studies.

This structured assessment ensured transparency in evaluating the internal validity of the evidence base and provided context for interpreting the pooled effect estimates. Sensitivity analyses were subsequently planned to determine whether excluding high-risk studies would materially alter the findings.

Strategy of data synthesis

Quality Assessment

The methodological quality of the included randomized controlled trials was evaluated using the Cochrane Risk of Bias (ROB) tool. Two reviewers independently assessed each study across six domains:

Selection bias – adequacy of random sequence generation and allocation concealment.

Performance bias – blinding of participants and study personnel.

Detection bias – blinding of outcome assessment.

Attrition bias – completeness of outcome data and handling of withdrawals.

Reporting bias – selective outcome reporting.

Other biases – including methodological or design-specific concerns.

Each domain was rated as low risk, high risk, or unclear risk. Disagreements between reviewers were resolved through discussion with a third reviewer to ensure accuracy and consistency. Results of the ROB evaluation were summarized graphically to illustrate the proportion of studies falling into each risk category.

This rigorous assessment process ensured that the findings of the review were based on high-quality evidence, with transparency regarding potential limitations in the primary studies.

Subgroup analysis To explore potential sources of heterogeneity and better understand treatment effects, planned subgroup analyses will be

conducted where data are available. Subgroups may include:

Type of manual therapy – spinal manipulation, mobilization (including SNAGs), or massage.

Comparator type – sham/placebo, exercise, usual care, or alternative manual therapy.

Follow-up duration – short-term (≤12 weeks), medium-term (3–6 months), and long-term (>6 months).

Patient characteristics – such as age group, sex distribution, or baseline headache severity, if sufficiently reported.

Study quality – stratified according to overall risk of bias ratings.

Subgroup comparisons will allow assessment of whether certain interventions are more effective under specific conditions, or whether outcomes differ according to study design and patient factors. Formal interaction tests will be applied to examine whether differences between subgroups are statistically significant.

Sensitivity analysis Sensitivity analyses will be performed to assess the robustness and stability of the pooled results. Specifically, analyses will include:

Study quality – excluding studies assessed as high risk of bias in one or more key domains.

Sample size – removing studies with small sample sizes (e.g., fewer than 30 participants per group) to examine the influence of underpowered trials.

Statistical models – comparing fixed-effect versus random-effects models to evaluate consistency of effect estimates.

Outcome reporting – excluding studies with incomplete or selectively reported outcome data.

Influence analysis – conducting leave-one-out analyses, where each study is removed sequentially to determine whether findings are disproportionately influenced by any single trial.

These steps will help ensure that the conclusions are not driven by methodological weaknesses, small studies, or statistical assumptions, thereby enhancing the validity of the overall review.

Country(ies) involved The study was conducted in China, with additional author affiliations spanning multiple countries where applicable, reflecting international collaboration in cervicogenic headache research.

Other relevant information The study is being carried out in China, with contributions from multi-national authors where applicable, including collaborations spanning additional countries reported in the included trials.

Keywords cervicogenic headache, Neck Disability Index, Flexion-Rotation Test, manual therapy, meta-analysis.

Contributions of each author
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