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INTRODUCTION

Review question / Objective: To evaluate the relieving pain and safety of manual therapy (MT) for the treatment of knee osteoarthritis (KOA).

Condition being studied: Knee osteoarthritis (KOA) was a chronic, degenerative disease of the knee joint of which the most common clinical manifestation was knee pain. The worldwide prevalence of radio graphically confirmed symptomatic KOA was estimated to be 3.8% and increased to more than 10% with age in people over 60 years of age. In China, the prevalence of KOA among older people was about 8.5% and the incidence of KOA had increased significantly and was trending younger. It had a serious impact on the health status of patients and overall quality of life which caused a serious economic burden to society.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 June 2023 and was last updated on 09 June 2023 (registration number INPLASY202360030).
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METHODS

Participant or population: All patients with KOA would be included in the study, regardless of age, race, gender, age limit and severity.

Intervention: The interventions in the experimental group would consist of MT only consisting of general massage, Swedish massage and other manipulative treatments.

Comparator: The control group would involve any therapy other than massage (e.g. acupuncture treatment, medication, exercise, usual care, etc.).

Study designs to be included: Case reports, empirical reports, laboratory studies and the study which unreported information of the random method wouldn’t be included.

Eligibility criteria: Patients included in the study must have a clear diagnosis of KOA and met other diagnostic criteria such as the American College of Rheumatology criteria or the Chinese Medical Association Orthopedic Branch Guidelines for the Treatment of Osteoarthritis (2018), without restrictions on the severity of the disease. The interventions in the experimental group would consist of MT only consisting of general massage, Swedish massage and other manipulative treatments and the control group would involve any therapy other than massage (e.g. acupuncture treatment, medication, exercise, usual care, etc.). In addition, if the observed differences are thought to be due to the unique contribution of MT, we have included studies that may include studies in which MT is provided as part of a package of care, that is, if the effects of MT can be isolated; for example, studies comparing MT plus usual care with usual care alone would be included, whereas investigations comparing MT plus usual care with MT alone would not be included. We also excluded studies if MT was combined with other therapies, making it difficult to distinguish the effect of MT.

Information sources: We conducted a literature search database search in the following databases for articles published from inception to December 2021 with language restricted to English or Chinese: WanFang, China Science and Technology Journal Database (VIP Database), China National Knowledge Infrastructure (CNKI), PubMed, EMBASE, Web of Science and the Cochrane Library databases. Only randomized controlled trials (RCTs) which must report the method of random on MT alone for KOA would be included. In the case of a three-arm or multi-arm RCT study, articles would also be included if two of the groups met the criteria.

Main outcome(s): The primary outcome is visual analog scale (VAS) pain assessment scale.

Quality assessment / Risk of bias analysis: The risk of bias in RCTs assessed according to the revised Cochrane Risk of Bias in Randomized Trials tool (RoB2).

Strategy of data synthesis: To synthesis the obtained data expressed as mean difference ± standard deviation (pre-treatment minus post-treatment) based on statistical methods. Heterogeneity among included studies was assessed using the Q test and presented as I² and P values. I² > 50% and/or P value < 0.1 is considered that there is significant heterogeneity among studies. If the heterogeneity test showed significant heterogeneity, a random-effects model was used; otherwise, a fixed-effects model was applied. Then, we used a random-effects model to combine the remaining data and observed if the conclusion was consistent with the one obtained previously. Meta-regression was used to evaluate the effect of treatment period and sex ratio on the results, and the threshold for statistical significance was set at P < 0.05. We used funnel plot and egger's test to evaluate the
publication bias (P < 0.1 was considered to indicate significant publication bias among enrolled studies). All analyses were carried out by Stata version 15.0 (Stata Corporation, College Station, TX).

**Subgroup analysis:** To explore the source of heterogeneity, we conducted the subgroup analysis of VAS scores based on the difference of treatment methods. The subgroup analysis of VAS scores based on course of treatment (set cut-off value as 4 weeks), although we considered the effect of the course of MT because it was not included in our previously designed protocol, we include this comparison because it represents a point for continuing discussion. We also used Galbraith plot to explore studies that may have contributed to the heterogeneity and excluded those studies.

**Sensitivity analysis:** To assess the reliability of the findings in this study, sensitivity analyses were conducted.

**Country(ies) involved:** China.

**Keywords:** Manual therapy, knee osteoarthritis, pain, safety, meta-analysis.

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