Systematic Review

Manual Therapy for Hip Osteoarthritis: A Systematic Review and Meta-analysis

Qiong Wang, MD[1,2], Teng-teng Wang, MD[1,3], Xiao-feng Qi, MD[1,3], Min Yao, MD[1,2,3], Xue-jun Cui, PhD[1,2], Yong-jun Wang, PhD[1,2], and Qian-qian Liang, PhD[1,2]

From: [1]Institute of Spine Disease, Shanghai University of Traditional Chinese Medicine, China; [2]Longhua Hospital, Shanghai University of Traditional Chinese Medicine, China; [3]Longhua College of Clinical Medicine, Shanghai University of Traditional Chinese Medicine, China

Address Correspondence:
Qian-qian Liang, PhD
Institute of Spine Disease
Shanghai University of Traditional Chinese Medicine
Longhua hospital
Shanghai Univserity of Traditional Chinese Medicine
China
E-mail:
liangqianqiantcm@126.com

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Background: Hip osteoarthritis (HOA) is one of the major causes of disability in seniors and is costly to society. Manual therapy is one therapeutic approach to treating HOA.

Objectives: To assess the effect of manual therapy compared to the placebo or wait-list/no treatment or a minimal intervention control for HOA at post-treatment and short-, intermediate- and long-term follow-ups.

Study Design: A systematic review and meta-analysis of randomized controlled trials (RCTs).

Setting: Hospital outpatient clinic in China.

Methods: We searched PubMed, EMBASE, the Cochrane Library, CINAHL, ISI web of knowledge, and Chinese databases from the inception to October 2014 without language restrictions. References of systematic reviews and other related reviews, files in our department, and conference proceedings as grey literature were also screened by hand.

RCTs compared manual therapy to the placebo, wait-list/no treatment or a minimal intervention control with an appropriate and precise description of randomization. Two reviewers independently conducted the search results identification, data extraction, and methodological quality assessment. We calculated the risk difference (RD) for dichotomous data and the mean difference (MD) or standardized mean difference (SMD) for continuous data in a fixed or random effect model.

Outcome Measures: The primary outcomes were self-reported pain in the past week and physical function. The secondary outcomes were the quality of life, global perceived effect, patients' satisfaction, cost, and adverse events.

Results: Six studies involving 515 HOA patients were included. Five of the 6 studies ranked as high quality in the methodological assessment. Immediately post-treatment, there was low-quality evidence that manual therapy could not statistically significantly relieve pain (SMD: -0.07 [95%CI -0.38 to 0.24]); for physical function, a moderate quality of evidence showed that manual therapy could not improve the physical function significantly (SMD: 0.14 [95%CI -0.08 to 0.37]). We still found low-quality evidence that manual therapy did not benefit the patients in the global perceived effect (RD: 0.12 [95%CI -0.12 to 0.36]), and in terms of quality of life. In addition, the risks of patients in the manual therapy group was 0.13 times higher than that in the controls (RD: 0.13 [95%CI -0.05 to 0.31]) in the low-quality evidence studies. We could not find any evidence that manual therapy benefits the patients at short-, intermediate- or long-term follow-up. There were no studies reporting patients' satisfaction or cost.

Limitations: The limitations of this systematic review include the paucity of literature and inevitable heterogeneity between included studies.

Conclusion: This review did not suggest there was enough evidence for manual therapy for the management of HOA. However, we are not confident in making such a conclusion due to the limitations listed above.

Key words: Manual therapy, hip osteoarthritis, efficacy, systematic review, meta-analysis

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Hip osteoarthritis (HOA) is one of the major causes of disability in the elderly (1). People suffering from HOA are troubled with chronic pain and morning stiffness in and around the hip joint, which leads to additional limitations of daily activities. The estimated prevalence of HOA is approximately 3.9% for men and 5.1% for women (2). HOA increases parallel to age and obesity (2). As the life expectancy and number of overweight adults increase, the number of HOA patients is expected to grow greatly and therefore result in a major public health problem in the near future.

According to the recommendation of the American College of Rheumatology (ACR), the pharmacological treatment of HOA is primarily pain medicine, such as acetaminophen, oral non-steroidal anti-inflammatory drugs (NSAIDs), tramadol, or intra-articular corticosteroid injection. The limitations of these medications include gastrointestinal upset and dose dependency. As to non-pharmacological interventions, exercise and losing weight are strongly recommended, while participating in self-management programs and manual therapy in combination with supervised exercise were conditionally recommended (3,4). Nevertheless, there were no indications of manual therapy alone for the treatment of HOA, although it ranks as the fifth most widely used complementary and alternative medicine (5) and is widely used in the management of musculoskeletal disorders worldwide (6,7).

In the last 5 years, people have paid attention to manual therapy for HOA, and several well-designed randomized controlled trials (RCTs) were published. However, the effect of manual therapy is still unclear, which put manual therapy practitioners and HOA patients in a dilemma of whether to choose a manual therapy alone when facing HOA. Therefore, we decided to conduct a systematic review by comprehensively collecting RCTs without language restriction to estimate the efficacy of manual therapy (manipulation, mobilization, or massage) compared to controls (placebo, wait-list/no treatment, or a minimal intervention) in the management of HOA. The outcomes are pain, function, global perceived effect, quality of life, and adverse effects at the post-treatment and short-, intermediate-, and long-term follow-ups.

Methods

Types of Studies

Published or unpublished RCTs with an appropriate and precise randomization focused on the clinical effectiveness of manual therapy on HOA were included in our review, either in full text or abstract form.

Types of Participants

The participants were adults suffering from pain due to HOA diagnosed by orthopedic surgeons or rheumatologists according to the classification of the ACR. The diagnosis is often made with reasonable certainty based on a history and clinical examination. The main complaints of HOA include the following: 1) hip pain with less than 15° of internal rotation and less than 115° of flexion in the hip joint or 2) hip pain with more than 15° of internal rotation and pain on hip internal rotation, as well as morning stiffness of the hip lasting more than 60 minutes. X-rays may be used to confirm the diagnosis of HOA. Unilateral or bilateral HOA were acceptable for inclusion in this review.

Studies were excluded if they investigated acute hip pain or HOA with 1) other complaints of musculoskeletal disorders, such as low back pain, neck pain, or knee OA; 2) previous hip joint replacement or hip arthroplasty or history of congenital/adolescent hip disease; 3) hip or pelvis fracture; 4) rheumatoid arthritis, ankylosing spondylitis, or other rheumatic diseases; or 5) intra-articular hip corticosteroid injection within one month.

Types of Intervention

In our review, manual therapy is defined as contact with the soft tissues, bones, joints, or the surroundings of patients with the hands, feet, arms, or elbows of the health care practitioners to enhance health and well-being. It is one of the oldest forms of medicine known and has been practiced worldwide since ancient times; it includes manipulation, mobilization, or massage techniques.

Eligible controls included 1) sham, placebo intervention, or waiting-list; 2) no treatment control (including manual therapy + other treatment versus other treatment); and 3) minimal intervention control, such as exercise, education, and psychotherapy.

Studies only comparing different types of manual therapy, such as Chinese massage versus Swedish massage or mobilization versus manipulation, were excluded. Moreover, the comparators of different frequencies of the same technique without a third control group were excluded. For example, massages applied once weekly for 10 weeks versus twice weekly for 10 weeks were excluded. Interventions combining 2 or more physical treatments without the same physical treat-

ment comparators were also excluded. Nevertheless, home exercise or education was hypothesized to be of little therapeutic effect. Thus, the therapeutic effect of manual therapy combined with home exercise and/or education was approximately equal to that of manual therapy alone.

Types of Outcome Measures

Primary Outcomes

The primary outcomes of interest were patients' self-reported pain relief and improvement in physical function.

All scales measuring pain were eligible because it was anticipated that pain was a complex symptom that could be measured by a variety of scales. The tool measuring pain could be the Visual Analogue Scale (VAS, 0 – 10 scale or 0 – 100 scale), the Numerical Pain Rating Scale (NPRS), the pain subscale of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), or the Arthritis Impact Measurement Scale (AIMS). For physical function, we chose complex scales such as WOMAC; the Harris Hip Score (HHS); the Hip disability, Osteoarthritis Outcome Score (HOOS); and the Lower Extremity Functional Scale (LEFS) in our review. The WOMAC (5 questions for pain, 2 for stiffness, and 17 for physical function) was a self-administered complex scale that was widely used to assess patients with hip/knee osteoarthritis in the dimensions of pain, stiffness, and function (8). All forms of the WOMAC were eligible, including the 5-point Likert, 11-point numerical rating, or 100 VAS. Higher scores on the WOMAC indicate worse function, while a high score on the HHS, LEFS, and HOOS indicates better functioning.

Mean differences (MD) or standardized mean differences (SMD) at the endpoints were calculated in our review for the meta-analyses. When there were missing data or only medians available at the endpoint, we emailed or called the authors of the studies. Studies with only medians were not excluded but were analyzed descriptively. Studies that did not report any of the primary outcomes were not eligible for review.

Secondary Outcomes

The secondary outcomes were patients' satisfaction, quality of life, and global perceived effect. We also extracted data on adverse effects and cost when available. All forms were acceptable, either as categorical or continuous variables.

The duration of the follow-up period was defined as immediately post-treatment (up to one day), short-term follow-up (from one day to 3 months), intermediate-term follow-up (from 3 months to 6 months), and long-term follow-up (from 6 month to one year and beyond).

For the primary outcomes, the measurement time should include immediately post-treatment and short-, intermediate-, or long-term follow-up when available. There were no time point limitations for the secondary outcomes.

Search Strategy

A search strategy was made by 2 reviewers (XJC and QW). QW conducted the computerized bibliographic databases of literature from the inception to October 2014 without language restriction.

Electronic Searches

PubMed, EMBASE, the Cochrane Library, CINAHL (EBSCO), ISI web of knowledge, CNKI (including China Doctor/Master Dissertation Full Text Database and China Proceedings Conference Full Text Database), Vip Journal Integration Platform (VJIP), Wan Fang Data, and Chinese BioMedical (CBM) databases (Sinomed) were searched in October 2014. The search terms included "hip osteoarthritis," "manual therapy," "massage," "manipulation," and "mobilization." Details of the English search strategy in PubMed are listed in Appendix 1.

Searching Other Resources

We screened the references of systematic reviews and other related reviews to identify relative studies. We also manually searched conference proceedings (such as the International Federation of Manual Therapy, Chinese Journal of Traditional Medical Traumatology & Orthopedics, and China Journal of Orthopedics & Traumatology) and files from our department as supplemental material. The final inclusion decisions were made by closely reviewing the full studies.

Protocol and Registration

The protocol for this meta-analysis was registered online (PROSPERO2014: CRD42014014851) and is available from www.crd.york.ac.uk/PROSPERO_REBRANDING/ display_record.asp? ID=CRD42014014851.

Data Collection and Analysis

Selection of Studies

All references searched were imported into End-

note X7. After duplicate elimination, 2 reviewers (QW and TTW) independently screened for relevance according to the title and abstract. The quadratic weighted Kappa statistic (Kw) was used to assess agreement of the primary study selection studies. Disagreements were solved by moving uncertain studies to the next step of the reviewing process. Then, the other 2 reviewers (XFQ and QQL) selected the related abstracts. Next, potentially relevant articles were retrieved as full text for comprehensive assessment according to inclusion criteria independently by 2 reviewers (QQL and XFQ). Disagreements were resolved by discussion with a third author (XJC) to reach the final decision. All of the reviewers involved in the selection were trained ahead of time to fully comprehend the inclusion and exclusion criteria.

Data Extraction and Management

Two reviewers (TTW and XFQ) independently extracted data by a pre-pilot standardized form, which included the first authors' last names, publication years, countries, number of analyzed/randomized, diagnosis, intervention types, control groups, dosages, outcome measurements, treatment effects, study duration, follow-ups, and cost of care.

Assessment of Risk of Bias in Included Studies

Two reviewers (TTW and XFQ) independently assessed the risk of bias using a 12-item tool according to the recommendation of the Cochrane Back Group (9). The 12 items included randomization, allocation, patients/care provider/outcome assessor blindness, dropout, intention to treat, selective reporting, baseline, cointerventions and compliances, assessment time, which were graded as low, high, or unclear risks. A study was considered as low risk when it met more than 6 criteria and was without obvious flaws. We used the quadratic weighted Kappa (Kw) statistic to assess the disagreement. Disagreement was resolved by discussion with a third review author (MY). A study ranked as high risk would not be excluded from this review, but it might degrade our confidence of recommendation.

Assessment of Heterogeneity and Data Analysis

Data analysis was performed by Review Manager (version 5.3) (Available from http://tech.cochrane.org/. For the pooled effect measurement, clinical judgment and the Chi-squared test were used to assess heterogeneity. Heterogeneity could not be ignored when studies pooled together were not clinically reasonable or the I2 was greater than 50% in the Chi-squared test ($P > 0.05$). We calculated the MDs and 95% confidence intervals (CI) in the fixed effect model for the same scale for continuous data, as well as the absence of heterogeneity, as standardized mean differences (SMD) in a random effect model. For example, if studies were pooled together and measured by the VAS and there was no heterogeneity either clinically or statistically, we used the MD in a fixed effect model. When pain in different studies was measured by different scales, such as the VAS, NPRS, or another scale, the SMD in the random effect model was used. For dichotomous outcomes without heterogeneity, we calculated the risk difference (RD) in a fixed effect model or in a random effect model. Subgroup analysis and sensitivity analysis would also be applied when obvious heterogeneity existed for the factors of symptom duration, methodological quality, and types of manual therapy or different comparators.

Assessment of Reporting Biases

A funnel plot was used to report biases, and a sensitivity analysis was planned when necessary.

Data Synthesis

The GRADE approach was used to assess the quality of the evidence. There were 5 domains that might decrease the quality of the evidence: 1) the study design, 2) risk of bias, 3) inconsistency of the results, 4) indirectness, and 5) imprecision. The 5 quality levels of evidence were defined as 1) high-quality evidence, which indicated further research was very unlikely to change the confidence of the estimate effect; 2) moderate-quality evidence, indicating further research was likely to have an important impact on the confidence in the estimate of effect and might change the estimate; 3) low-quality evidence, indicating further research was very likely to have an important impact on the confidence in the estimate of effect and was likely to change the estimate; 4) very low-quality evidence, indicating great uncertainty about the estimate; and 5) no evidence, indicating no evidence from any RCTs included (10). Two reviewers (QW and MY) independently graded the outcomes, and disagreement was resolved by discussion with a third reviewer (XJC). GRADE analysis was performed by the GRADE profiler (Version 3.6) (by GRADE working group and available from:www.gradepro.org.).

Results

Result of Search

The search of electronic databases, conference articles, and reference materials was performed from September 31 to October 12, 2014. We obtained 2,526 records in total, of which 1,429 were duplicate records, 1,069 records were excluded after reviewing the title and abstract, and the remaining 28 potentially related records were kept for full-text review. After closely reviewing the full text, 22 studies were excluded as follows: 2 studies were excluded due to combination with other joint osteoarthritis (11,12), 2 due to comments (13,14), 5 for not being RCTs (15-19), 2 for no manual therapy intervention group (20,21), 3 due to inadequate study protocols (22-24), 6 because of duplicate reports (25-30), one due to an indefinite diagnosis (31), and one due to inappropriate randomization (32). Four studies (33-37) were identified for further review from the references of systematic reviews or related reviews, but none of them were eligible for inclusion. Ultimately, we obtained 23 related records from manually searching, but none of them fully met all of the inclusion criteria. Finally, we included 6 studies for our review (38-43) (Fig. 1).

Five studies (38-40,42,43) were parallel designed

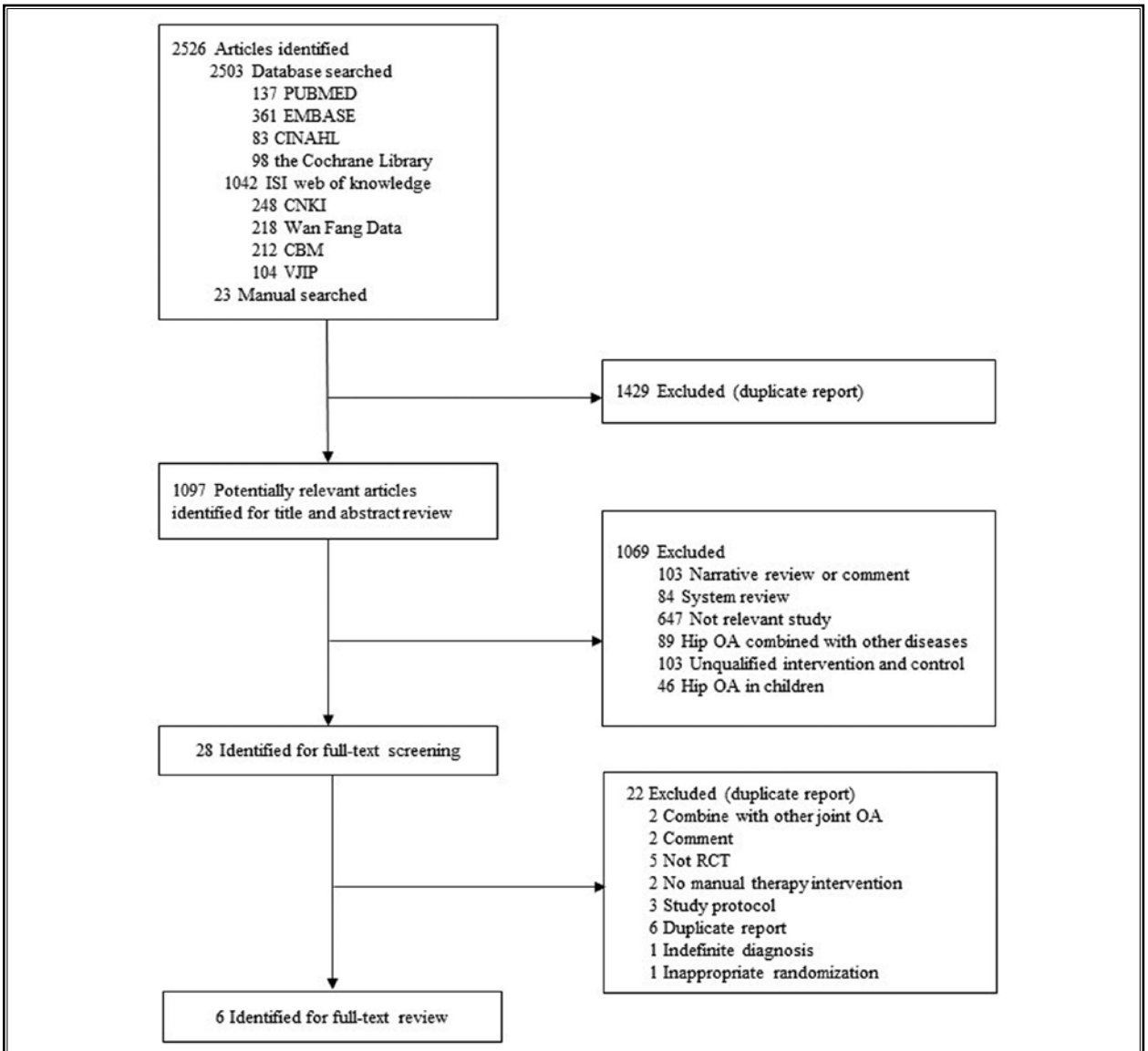

Fig. 1. *Study flow chart.*

RCTs, while one was a crossover study in which the control group received the intervention after 9 weeks of the initial intervention (41). The sample size ranged from 23 (39) to 111 (40). Five studies were single-center studies conducted in Australia (38,40), England (39), the Netherlands (42), and Denmark (43), while only one study (41) was a multicenter study and took place in Ireland. Five hundred and fifteen patients more than 63 years old and with a duration ranging from one month to 10 years were included in this review. The diagnosis was the ACR classification combined with a radiographic change, except in one study (39) that only had an ACR classification.

Manipulation, mobilization, massage, manual stretching, and traction were the main HOA techniques applied. The HOA frequency was twice weekly (40,42,43), once a week (39,41), or ranged from twice a week to once every 2 weeks depending on the protocol (38), and the treatment lasted from 5 weeks to 12 weeks. The control groups included a sham (38) or blank (39-41,43) intervention, except in one study that used an exercise comparator (42). All of the studies included described pain and function, 5 studies (38,40-43) described global perceived effect, 3 studies (38,41,42) described quality of life, and 4 studies (38,39,42,43) described adverse effects. No studies described patients' satisfaction or cost. Details of the included studies are listed in Table 1.

Table 1. *Characteristics of included studies.*

Study IDs Countries	Methods	Participants	Interventions	Outcomes	Follow-ups
Bennell [38] 2014 Australia	RCT NAR: 102(62)/102(62)	Diagnosis: ACR criteria and radiographic change Age: 64.5±8.6 years old (index group) 62.7±6.4 years old (control group) Duration: 36 (24-60) months (index group); 30(24-60) months(control group) Grading: radiographic disease severity grade: 51 participants in grade 2, 25 in grade 3, 26 in grade 4 BMI: 29.2 Unilateral or bilateral: both, 61 unilateral	Index group: manual therapy (manipulation, mobilization, massage, and stretches), home based exercise, education Control group: inactive ultrasound, inter gel without massage Dosage: twice in the first week, once weekly for 6 weeks, then once every 2 weeks. 10 times in 12 weeks totally.	Pain intensity: VAS (0-100) Function: WOMAC (Likert version) Global perceived effect: 7 point ordinal scale Quality of life: Quality of Life instrument version 2 Adverse events	9 months
Blackman 2014 [39] England	RCT NAR: 21(18)/23 (unclear)	Diagnosis: buttock or groin pain associated with weight bearing activities Age: 66.04 years old Duration: 14.91 months Grading and BMI: not report Unilateral or bilateral: unilateral	Index group: manual therapy (stretches) combined with home based exercise Control group: home based exercise Dosage: once a week, 7 times in total	Pain intensity: VAS (0-100) Function: LEFS Adverse events	no
Brantingham 2012 [40] Australia	RCT NAR: 111(62)/111(62)	Diagnosis: ACR and the Kellgren-Lawrence grade for hip OA Age: 63.04 years old Duration: 58.88 days (about 2 months) Grading: ACR criteria A: 43, criteria B: 68 BMI: 24.04 Unilateral or bilateral: not report	Index group: mobilization, manipulation, massage + targeted hip MMT + exercise Control group: targeted hip MMT plus exercise Dosage: 9 treatments in 5-week period	Pain intensity: WOMAC pain score Function: WOMAC Global perceived effect: (OTE) tool	3 months
French 2013 [41] Ireland	RCT NAR: 88(61)/88(61)	Diagnosis: ACR clinical and radiographic criteria Age: 61.76±9.72 years old(index group), 64.83±9.82 years old(control group) Duration: 35.03 months BMI: the percentage of overweight or obese is 75% Unilateral or bilateral: both, the bilateral percentage is 27.27%	Index group: mobilization, traction, stretching 15minutes +30 minutes strengthening exercise Control group: 30 minutes strengthening exercise Dosage: 6-8 times, 8 weeks	Pain intensity: VAS (0-10) Function: WOMAC Quality of life: SF-36	no

Table 1 cont. *Characteristics of included studies*.

Study IDs Countries	Methods	Participants	Interventions	Outcomes	Follow-ups
Hoeksma 2004 [42] Netherlands	RCT NAR: 109(76)/109(76)	Diagnosis: ACR and radiographic criteria Age: 71.51 years old Duration: 1 month to 1 year: 37, 1 to 2 years: 25, 2 to 5 years 24, 5 to 10 years: 18, > 10 years: 5 Grading before recruitment: 80% had a Kellgren/Lawrence score of 2 or 3 BMI: not report Unilateral or bilateral: unilateral	Index group: stretching and traction Control group: exercises Dosage: twice weekly, 5 weeks, 9 times in total	Pain intensity: VAS (0-100) Function: HHS Global perceived effect: 6-point Likert scale Quality of life: SF-36 Adverse events	4, 7 months
Poulsen 2013 [43] Denmark	RCT NAR:68 (unknown)/75(31)	Diagnosis: ACR and radiographic criteria Age: 67.2 years Duration: 28.96 months Grading before recruitment: Minimal JSW for involved joint: 1.51mm BMI: 26.84 Unilateral or bilateral: unilateral	Index group: trigger point release, stretching and manipulation + education Control group: education alone Dosage: twice a week, 6 weeks, 12 times in total	Pain intensity: NRS Function: HOOS Global perceived effect: percentage classified themselves as improved Adverse events	3,12 months

ACR, American College of Rheumatology; RCT, Randomized controlled trial; NAR, Number of Analyzed(women)/ Randomized(women); WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; LEFS, Lower Extremity Functional Scale; HOOS, Hip disability and Osteoarthritis Outcome Score; OTE, Overall Therapy Effectiveness; VS, versus; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; HHS, Harris Hip Score.

Risk of Bias in Included Studies

Inter-rater agreement by 2 independent reviewers on the methodological quality of studies was almost perfect (Cohen's Kappa = 0.93) (44). Judgments about each risk of bias item was presented as a percentage across all included studies, and each risk of bias item for each included study is listed in Fig. 2 and Fig. 3, respectively. The number of items that were low risks for each included study ranged from 5 to 9 out of a maximum score of 12. All of the studies included were rated as low risk in the selection bias, attribution bias and compliance acceptable, and similar outcome assessment time. None of the studies included described an appropriate blindness of patients or health care providers. Nevertheless, 5 of the 6 studies were ranked as low risk because they masked the outcome assessors efficiently. Two of the 6 studies (39,43) included did not analyze all of the randomized participants allocated. We could not judge the selective bias of 3 studies because they did not register or publish a protocol (39,40,42). For the baseline, half of the studies included (40-42) were similar in terms of the most important prognostic indicators; one study (38) could not be assessed due to the lack of information provided, while 2 studies (39,43) were not comparable, although one (43) had adjusted the significance level from 0.1 to 0.05. Three studies included (38,42,43) described the co-interventions avoided, while the remaining studies were unclear from the description. In summary, 5 of the 6 studies (38,40-43) were rated as low risk according to Furlan et al (9), and one study was not (39).

Effects of Interventions

Pain Intensity in the Past Week

Six studies involving 515 patients reported pain intensity. They showed a low quality of evidence that manual therapy could not statistically relieve pain with SMD: -0.07 (95%CI -0.38 to 0.24) in a random effect model (Fig. 4 and Table 2). Of the 6 studies, only the study of Poulsen et al (43) found a significant treatment effect, as the 95% CI did not cross the standard difference of "0." The funnel plot of the 6 studies was vertically asymmetrical, which indicated possible publication bias, and the studies favor of manual therapy were lost (Fig. 5).

Two studies (40,43) involving 180 patients reported a pain score in the past week at short-term follow-up

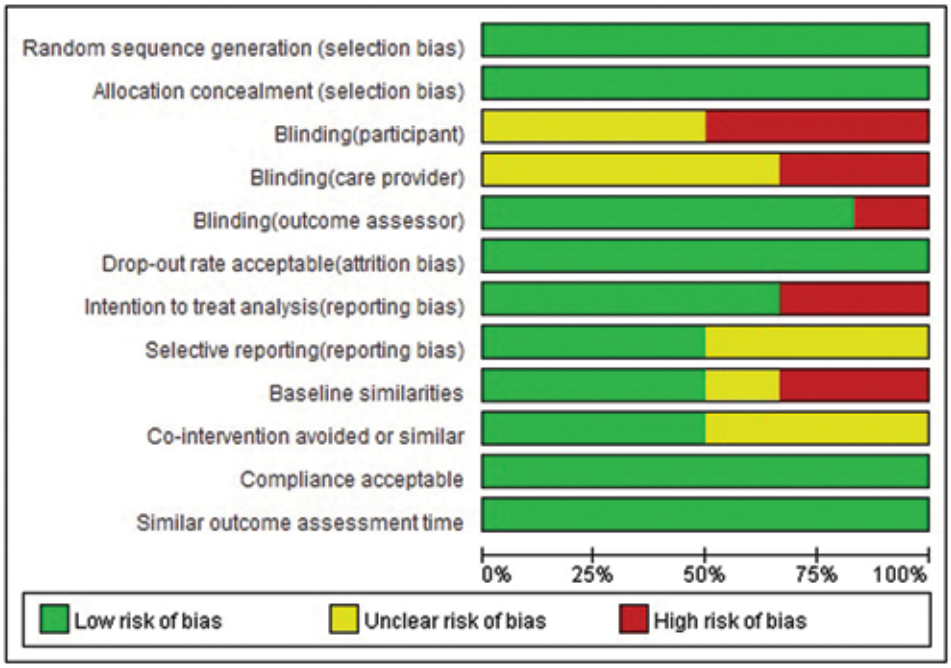

Fig. 2. *Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages accross all included studies.*

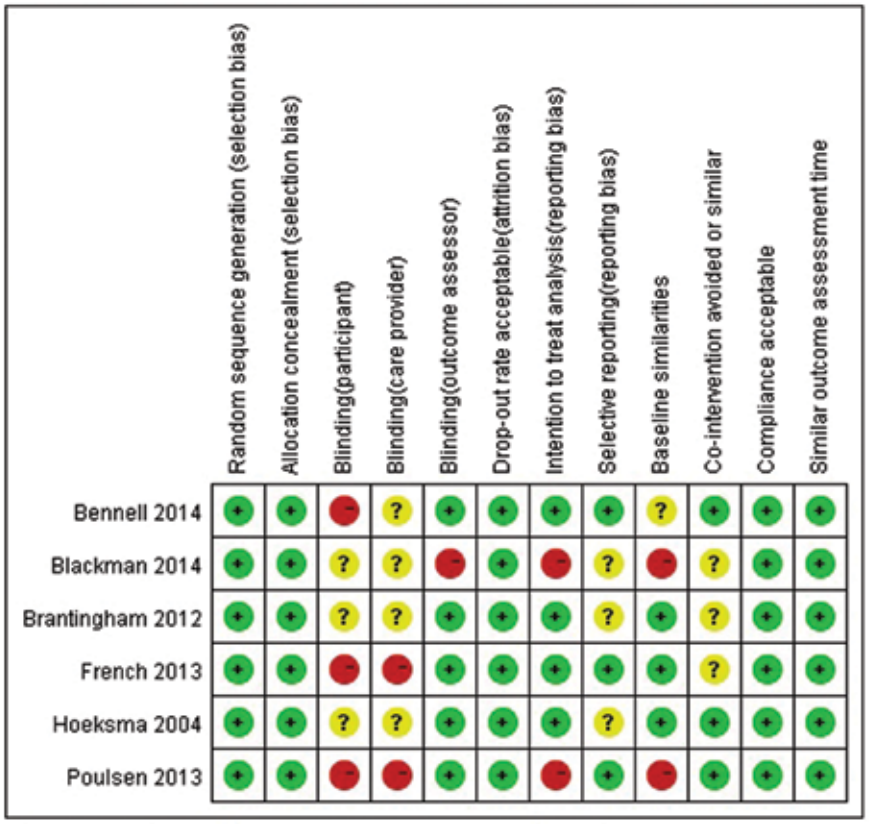

Fig. 3. Risk of bias summary: Review authors' judgements about each risk of bias item for each included study.

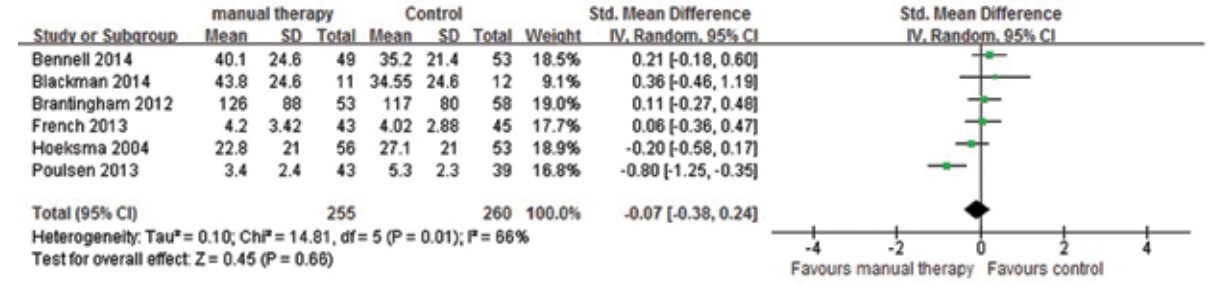

Fig. 4. Pain at immediatly post-treatment forest plot: Manual therapy compared to a placebo or control for HOA.

manual therapy for HOA

Patient or population: patients with HOA
Settings:
Intervention: manual therapy

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Manual therapy	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
pain		The mean pain in the intervention groups was **0.07 standard deviations lower** (0.38 lower to 0.24 higher)		515 (6 studies)	⊕⊕ low[1]	SMD -0.07 (-0.38 to 0.24)
womac		The mean womac in the intervention groups was **0.14 standard deviations higher** (0.08 lower to 0.37 higher)		301 (3 studies)	⊕⊕⊕ moderate[2]	SMD 0.14 (-0.08 to 0.37)
globle perceived effect	**Study population**		See comment	404 (4 studies)	⊕⊕ low[3]	Risks were calculated from pooled risk differences
	562 per 1000	**680 per 1000** (444 to 921)				
	Moderate					
	509 per 1000	**616 per 1000** (402 to 835)				
adverse event	**Study population**		See comment	309 (4 studies)	⊕⊕ low[3,4]	Risks were calculated from pooled risk differences
	77 per 1000	**207 per 1000** (27 to 387)				
	Moderate					
	28 per 1000	**75 per 1000** (10 to 140)				
pain at short-term follow-up		The mean pain at short-term follow-up in the intervention groups was **0.37 standard deviations lower** (0.83 lower to 0.09 higher)		180 (2 studies)	⊕⊕⊕ moderate[5]	SMD -0.37 (-0.83 to 0.09)
pain at long-term follow-up		The mean pain at long-term follow-up in the intervention groups was **0 standard deviations higher** (0.26 lower to 0.25 higher)		241 (3 studies)	⊕⊕⊕ moderate[5]	SMD 0 (-0.26 to 0.25)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Serious unexplained heterogeneity
[2] Wide CI
[3] Two studies suggest benefit and the other two harm indicate inconsistency
[4] The funnel plot show that there may be the equivalent number of "positive" trials that have not been included in this analysis
[5] Unexplained heterogeneity

Table 2. *GRADE evaluation of manual therapy for HOA.*

and had a moderate quality of evidence that manual therapy could not significantly relieve patients' pain (SMD: -0.37 [95%CI -0.83 to 0.09]) (Fig. 6 and Table 2). Only one study (42) (94 patients included) reported pain at intermediate-term follow-up, and it did not find any evidence that manual therapy could significantly reduce pain intensity. Three studies (38,42,43) involving 241 patients measured pain at long-term follow-up. There was a moderate quality of evidence indicating that manual therapy could not significantly relieve pain (Fig. 7 and Table 2).

Function

All of the studies measured function; only 3 studies used the same scale (the WOMAC) as the measurement (38,40,41). We pooled the data from these 3 studies together and obtained a moderate quality of evidence that manual therapy could not significantly improve

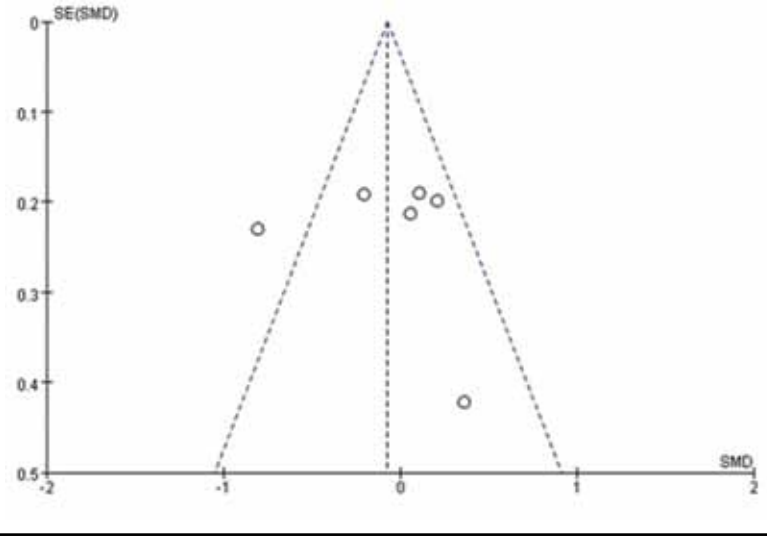

Fig. 5. Funnel plot of included studies.

function, with SMD 0.14 (95%CI -0.08 to 0.37) in a fixed effect model with a heterogeneity test I2 = 0% (Fig. 8 and Table 2). Blackman and Atkins (39) (23 patients included) found that compared with the control (home exercise), manual therapy could not improve the function in LEES, whereas Hoeksma et al (42) (involving 109 patients) and Poulsen et al (43) (involving 82 patients) found that manual therapy could improve function significantly in HHS and HOOS, respectively.

Two studies (40,43) including 180 patients reported the function at short-term follow-up. Brantingham et al (40) (111 patients involved) found that there were no differences between the 2 groups in the WOMAC, whereas

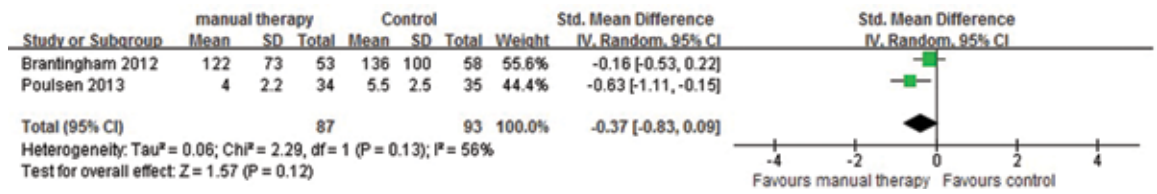

Fig. 6. Pain forest plot at short-term follow-up: Manual therapy compared to a placebo or control for HOA.

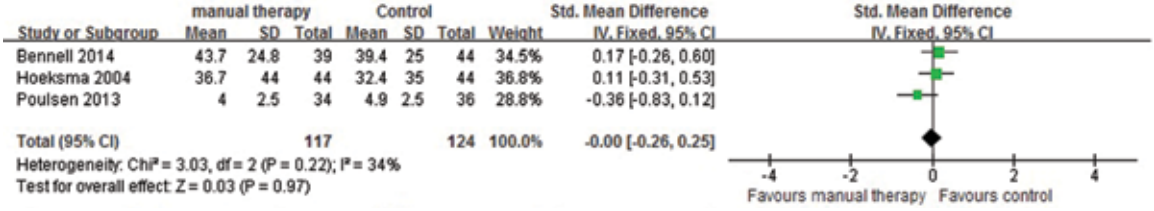

Fig. 7. Pain forest plot at long-term follow-up: Manual therapy compared to a placebo or control for HOA.

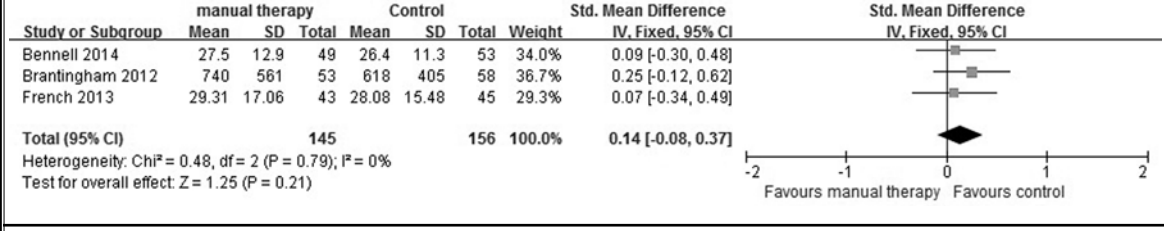

Fig. 8. WOMAC at immediately post-treatment forest plot: Manual therapy compared to a placebo or control for hip OA.

Poulsen et al (43) (69 patients involved) revealed that manual therapy was significantly better relative to the control. Hoeksma et al (42) (involving 94 patients) reported function at the intermediate-term follow-up and found that the manual therapy group could significantly improve function when compared with the exercise group. Three studies (38,42,43) including 241 patients reported the function at long-term follow-up, and all of them found that manual therapy was not significantly better relative to the control.

Global Perceived Effect

Five studies (38,40-43) reported the global perceived effect. Data from 4 of the studies (38,40,42,43) could be pooled together after being transformed into dichotomous data, while the remaining study (41) was a crossover study and only reported the global perceived effect after a crossover intervention. We did not receive the data for this latter study even though we emailed the corresponding author twice. Low-quality evidence was presented, showing that the manual therapy group was no better than the control in terms of the global perceived effect (Risk Difference (RD): 0.12 [95% CI, -0.12 to 0.36]) (Fig. 9 and Table 2). Brantingham et al (40) (111 patients involved) reported a global perceived effect at short-term follow-up and found that there were no differences between the manual therapy and control groups. No studies reported the global perceived effect at the intermediate-term follow-up. Bennell et al (38) (83 patients) reported the global perceived effect at long-term follow-up and found no difference between the manual therapy and control groups.

Quality of Life

Three studies (38,41,42) reported patients' quality of life using different scales (299 patients included). All of them were ranked as having high-quality evidence and found that compared to the control, manual therapy did not benefit patients in terms of quality of life. No studies reported the outcome at short- and intermediate-term follow-up. Two studies (38,42) including 171 patients reported the quality of life at long-term follow-up, and both of them found that there were no differences between the manual therapy group and the controls.

Adverse Effects, Patients' Satisfaction and Cost

Four studies (38,39,42,43) involving 309 patients reported adverse effects. There was a low quality of evidence showing the risk of adverse effects in the manual therapy group, which was 0.13 times greater than the control with RD and 0.13 (95%CI -0.05 to 0.31) in the random effect model due to obvious heterogeneity (I2 = 87% [$P < 0.01$]) (Fig. 10 and Table 2). Nevertheless, the adverse effects were slight and were resolved in a couple of days without any treatment. We had planned to report patients' satisfaction and cost as the protocol stated, but none of the studies included reported the satisfaction or cost.

Subgroup Analysis and Sensitivity Analysis

Because we did not obtain enough data in the categories, such as symptom duration, classification of manual therapy, dosage of manual therapy applied, methodological quality, or comparators, we did not perform subgroup analysis and sensitivity analysis as we had planned in our protocol.

Discussion

Summary of Evidence

Recently, there have been an increasing number of publications aimed at the therapeutic effect of manual

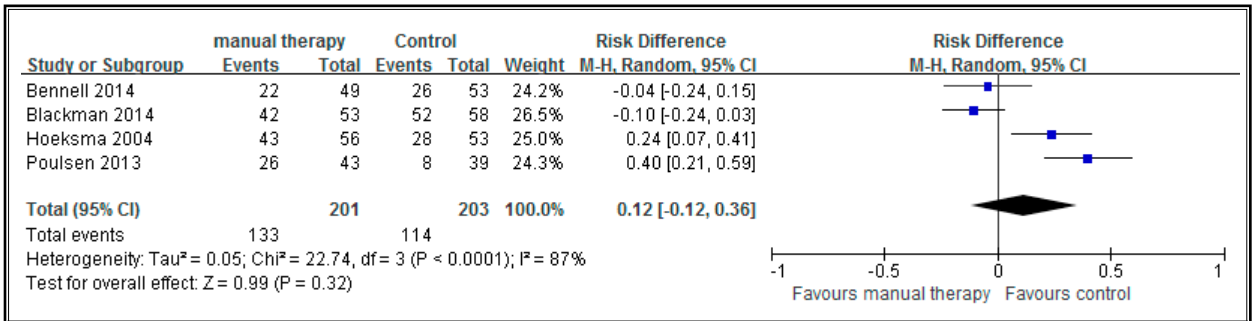

Fig. 9. Global perceived effect at immediately post-treatment forest plot: Manual therapy comparted to a placebo or control for HOA.

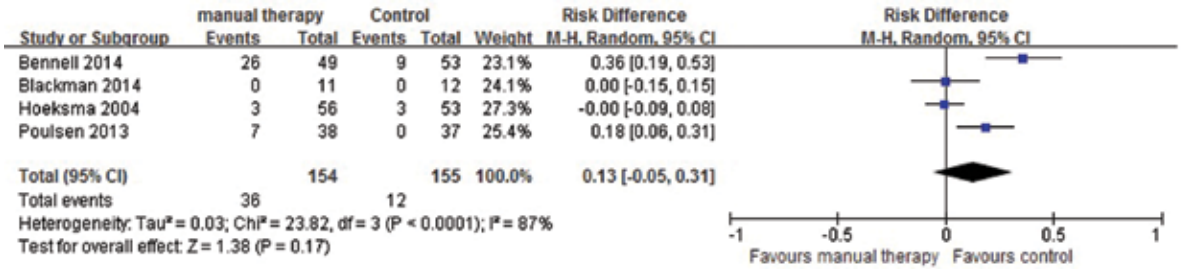

Fig. 10. Adverse event at immediately post-treatment forest plot: Manual therapy compared to a placebo or control for HOA.

therapy for HOA. However, the contribution of manual therapy to manage HOA still remains unclear. There was a systematic review on manual therapy compared to other active/inactive treatments for HOA in 2010, and the reviewers did not find any significant evidence regarding the efficacy of manual therapy due to the limited number of studies (three studies) included and the small sample size in each study (37). Another systematic review found an opposite conclusion, they found that manual therapy had a beneficial effect compared to the controls both in the short- and long-term when examining the pain reduction and physical function improvement (45). We carefully studied relevant clinical outcomes, including pain, function, global perceived effect, and quality of life, but only found a moderate to low quality of evidence that manual therapy alone could not relieve pain or improve the function of the hip relative to a control.

Most of the studies (5/6) included were high-quality studies. All of the studies included described appropriate randomization and concealment of allocation. None of the included studies met all of the criteria for patient and health care provider blinding. Although we thought these flaws could be acceptable because it was impossible to blind the health care providers and it was nearly impossible to blind the patients, these unavoidable imperfections significantly influenced the results, especially because all of the outcomes were self-reported. To reduce the bias in the future, we could tell the patients both in the intervention group and the control that the treatment they received was effective and ask them to keep the type of treatment they received a secret. Moreover, the outcome assessors could be blinded properly, and most of the studies included described an appropriate method to blind the patients. Compared to the control or exercise group, there were some risks of manual therapy, but the adverse events were minimal and transient, which was similar to manual therapy on other musculoskeletal disorders (34,46).

Limitations and Strengths of This Review

There were limitations in our review. The bias from selecting the studies for inclusion in a meta-analysis cannot be avoided. Although we tried our best to search relevant articles including different languages (English and Chinese) and hand searched relevant articles and conference proceedings, we were still uncertain that all relevant studies were indexed. Moreover, the publication bias and unexplained heterogeneity must also be taken into account.

Our review included more patients than others with regards to efficacy. We included all studies about HOA in the French et al systematic review (47), and all of the studies in Adigun's systematic review (37) except one case series (48) because only RCTs were qualified for review in our study. We intended to investigate the efficacy of manual therapy including Western and Eastern treatments for HOA and systematically searched the English and Chinese databases to ensure we had a comprehensive combination of references. We obtained 6 studies to compare manual therapy with other active or sham controls after closely reviewing all of the studies, assessing methodological quality and extracting data. However, we regrettably did not obtain studies about Eastern techniques that fully met all of the including criteria.

To our knowledge, there were few systematic reviews focused on combined osteoarthritis, such as knee osteoarthritis and/or HOA (45), or manual therapy combined with other active interventions on HOA alone (49), and we almost obtained the same conclusion but lack confidence to confirm that manual therapy alone could not relieve the pain or improve the physical function due to hip (or/and knee) osteoarthritis.

Indication of Future Research

The obvious heterogeneity in the pooling effect may be due to the clinical diversity, including the duration of patient participation and the diverse forms of

manual therapy. As a complex intervention (50), the efficacy of manual therapy was greatly influenced by the components of the techniques. According to Sherman et al (51), the types of manual therapy could be classified based on the goals of the treatment, the style, and the techniques. In addition, the level of care providers may have a strong learning curve effect, which means that the effect of the intervention can be increased by time; for example, a person who trained to do manual therapy for 10 years is certainly better than one who only trained for one month (52). Frequency (number of manual therapy session per week), duration (time used in one manual therapy session), and dosage (total sessions in a course) can also influence the efficacy of therapy. However, none of the studies included in our review explored the components of manual therapy that influenced its effects; rather, the therapy was considered as a single treatment. There were insufficient studies in a subgroup or subcategory, which made it impossible to conduct a subgroup or sensitive analysis or meta-regression analysis. The first step to develop manual therapy as a complex intervention was to identify what was already known about manual therapy and the methods that have been used to evaluate them. To do this, a high-quality systematic review of relevant evidence is a good approach (53). Therefore, we pooled the data together despite the unavoidable heterogeneity in the heterogeneity test and found a low to moderate quality of evidence that manual therapy could not statistically significantly reduce pain and improve physical function at any of the time points measured.

A future study might identify manual therapy as a complex intervention to study which components influenced its therapeutic effect most or to focus on the earlier stage of HOA with a shorter duration instead of a long duration. Future studies could also adopt duration or age stratification to analyze the effect of manual therapy alone for HOA.

Furthermore, the tools of outcome measurement are quite different, and future research might follow a certain guideline with definite outcomes to precede RCTs.

Conclusions

Most of the studies (5/6) ranked high in terms of quality, with a moderate number of participants and without obvious methodological flaws. From the pooling effect, we only established low-quality evidence that manual therapy could not manage pain due to OA and established a moderate quality of evidence that manual therapy could not improve the function of the hip. Thus, we are unable to confidently make a definitive conclusion due to the insufficient data and limitations listed previously. A future study might focus on manual therapy as a complex intervention whose efficacy is greatly influenced by the components of techniques, the skills of the health care practitioner, and the frequency and dosage of therapy.

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Appendix 1. Searching strategy

1 osteoarthritis,hip[mh]
2 (Hip Osteoarthritides or Hip Osteoarthritis or Osteoarthritides, Hip or Coxarthrosis or Coxarthroses or Osteoarthritis Of Hip or Osteoarthritis Of Hips or coxitis or osphyarthrosis) [tw]
3 1 or 2
4 osteoarthritis[mh]
5 (Osteoarthritides or Osteoarthrosis or Osteoarthroses or Arthritis, Degenerative or Arthritides, Degenerative or Degenerative Arthritides or Degenerative Arthritis or Osteoarthrosis Deformans) [tw]
6 Arthralgia[mh]

7 (Arthralgias or Joint Pain or Joint Pains or Pain, Joint or Pains, Joint or Polyarthralgia or Polyarthralgias)[tw]
8 chronic pain[mh]

9 (Chronic Pains or Pains, Chronic or Pain, Chronic or Widespread Chronic Pain or Chronic Pain, Widespread or Chronic Pains, Widespread or Pain, Widespread Chronic or Pains, Widespread Chronic or Widespread Chronic Pains)[tw]
10 4 or 5 or 6 or 7 or 8 or 9

11 hip[mh]

12 (Hips or Coxa or Coxas) [tw]
13 hip joint[mh]
14 (Hip Joints or Joint, Hip or Joints, Hip or Acetabulofemoral Joint or Acetabulofemoral Joints or Joint, Acetabulofemoral or Joints, Acetabulofemoral or articulatio coxae)[tw]
15 11 or 12 or 13 or 14

16 10 and 15
17 3 or 16
18 Musculoskeletal Manipulations[mh]
19 (Manipulations, Musculoskeletal or Manual Therapies or Manual Therapy or Therapies, Manual or Therapy, Manual or Manipulation Therapy or Manipulation Therapies or Therapies, Manipulation or Manipulative Therapies or Manipulative Therapy or Therapies, Manipulative or Therapy, Manipulative or Therapy, Manipulation)[tw]
20 Manipulation, Chiropractic[mh]
21 (Chiropractic Manipulation or Spinal Adjustment, Chiropractic or Adjustment, Chiropractic Spinal or Adjustments, Chiropractic Spinal or Chiropractic Spinal Adjustment or Chiropractic Spinal Adjustments or Spinal Adjustments, Chiropractic or Chiropractic Adjustment or Adjustment, Chiropractic)
22 Manipulation, Osteopathic[mh]
23 (Osteopathic Manipulative Treatment or Osteopathic Manipulative Treatments or Treatment, Osteopathic Manipulative or Treatments, Osteopathic Manipulative or Osteopathic Manipulation)
24 Therapy, Soft Tissue[mh]
25 (Soft Tissue Therapy)[tw]
26 Acupressure[mh]
27 (Shiatsu or Shiatzu or Zhi Ya or Chih Ya)[tw]
28 massage[mh]
29 (Craniosacral Massage or Massage, Craniosacral or Zone Therapy or Therapies, Zone or Zone Therapies or Therapy, Zone or Reflexology or Rolfing or Bodywork or Bodyworks or Massage Therapy or Massage Therapies or Therapies, Massage or Therapy, Massage
30 Manipulation, Orthopedic[mh]
31 (Orthopedic Manipulation)[tw]
32 Manipulation, Spinal[mh]
33 (Spinal Manipulation or Lumbar Manipulation or Manipulation, Lumbar or Cervical Manipulation or Manipulation, Cervical)[tw]
34 Motion Therapy, Continuous Passive[mh]
35 (Continuous Passive Movement Therapy or Passive Movement Therapy, Continuous or Movement Therapy, Continuous Passive or Passive Motion Therapy, Continuous or Continuous Passive Motion Therapy or CPM Therapy or CPM Therapies or Therapies, CPM or Therapy, CPM)[tw]
36 Vibration[mh]
37 (Vibrations)[tw]
38 (myofascial release or myofascial therapy or myofascial therapies) [tw]
39 (muscle energy technique or muscle energy techniques) [tw]
40 trigger point [tw]
41 (proprioceptive Neuromuscular Facilitation or proprioceptive Neuromuscular Facilitations)[tw]
42 cyriax friction [tw]
43 (lomilomi or lomi-lomi or trager) [tw]
44 aston patterning [tw]
45 (amma or ammo or effleurage or petrissage or hacking or tapotement) [tw]
46 Complementary Therapies[mh]
47 (Therapies, Complementary or Therapy, Complementary or Complementary Medicine or Medicine, Complementary or Alternative Medicine or Medicine, Alternative or Alternative Therapies or Therapies, Alternative or Therapy, Alternative)[tw]
48 (Tui Na or Tuina)[tw]
49 17 or 18 or 19 or 20 or…or 48
50 randomized controlled trial [pt]
51 controlled clinical trial [pt]
52 randomized [tiab]
53 placebo [tiab]
54 clinical trials as topic [mesh: noexp]
55 randomly [tiab]
56 trial [ti]
57 50 or 51 or or…56
58 animals [mh] NOT humans [mh]
59 57 not 58
60 16 and 49 and 59

PubMed search syntax
[pt] denotes a Publication Type term;
[tiab] denotes a word in the title or abstract;
[sh] denotes a subheading;
[mh] denotes a Medical Subject Heading (MeSH) term ('exploded');
[mesh: noexp] denotes a Medical Subject Heading (MeSH) term (not 'exploded');
[ti] denotes a word in the title
[tw]denotes text word

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