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The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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Effectiveness of Maitland and Mulligan mobilization methods for adults with knee osteoarthritis: A systematic review and meta-analysis

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Abstract

BACKGROUND

As a serious global problem, knee osteoarthritis (KOA) often leads to pain and disability. Manual therapy is widely used as a kind of physical treatment for KOA.

AIM

To explore further the efficacy of Maitland and Mulligan mobilization methods for adults with KOA.

METHODS

We searched PubMed, the Cochrane Library, EMBase, Web of Science and Google Scholar from inception to September 20, 2020 to collect studies comparing Maitland and Mulligan mobilization methods in adults with KOA. The quality of the studies was assessed using the Physiotherapy Evidence Database Scale for randomized controlled trials. Data analyses were performed using Review Manager 5.0 software.

RESULTS

A total of 341 articles were screened from five electronic databases (PubMed, the Cochrane Library, EMBase, Web of Science and Google Scholar) after excluding duplicates. Ultimately, eight trials involving 471 subjects were included in present systematic review and meta-analysis. The mean PEDro scale score was 6.6. Mulligan mobilization was more effective in alleviating pain [standardized mean difference (SMD) = 0.60; 95% confidence interval (CI): 0.17 to 1.03, $P = 0.007$; $I^2 = 60\%$, $P = 0.020$] and improving Western Ontario and McMaster Universities function score (SMD = 7.41; 95%CI: 2.36 to 12.47, $P = 0.004$; $I^2 = 92\%$, $P = 0.000$). There was no difference in the effect of the two kinds of mobilization on improving the range of motion (SMD = 9.63; 95%CI: -1.23 to 20.48, $P = 0.080$; $I^2 = 97\%$, $P = 0.000$).

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**CONCLUSION**

Mulligan mobilization technique is a promising intervention in alleviating pain and improving function score in KOA patients.

Key Words: Mulligan mobilization; Maitland mobilization; Manipulation; Manual therapy; Knee osteoarthritis; Meta-analysis

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Core Tip: Manual therapy is widely used as a kind of physical treatment for knee osteoarthritis. Maitland and Mulligan mobilization are two types of manual therapy used in osteoarthritis treatment. There still was no systematic reviews and meta-analyses to compare the efficacy of different mobilization techniques, such as Maitland vs Mulligan mobilization. This study aims to explore further the efficacy of Maitland and Mulligan mobilization and fill the research gaps. Mulligan mobilization was found to be a promising alternative option for knee osteoarthritis treatment. Particularly, the Mulligan mobilization has been recommended to be applied in alleviating pain and improving Western Ontario and McMaster Universities function scores.

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INTRODUCTION

Osteoarthritis (OA) is the most common type of arthritis, with 1 in 3 people over age 65 affected and a higher prevalence in women[1,2]. The knees are among the most commonly affected joints in OA[3,4]. Knee osteoarthritis (KOA) is characterized as pain, joint stiffness, functional impairment and even disability, contributing to a heavy burden on healthcare service[5,6]. Considering the severe socioeconomic burden, non-pharmacological, pharmacological and surgical approaches were applied[7]. Physical therapy has been known to play a vital role in pain relief and restoration of mobility and function in KOA patients[8]. Manual therapy is a widely used physical treatment for KOA[9]. Several studies have reported positive effects of manual physical therapy on KOA[9-11]. The American College of Rheumatology recommends the combination of manual therapy with exercise for KOA patients under the supervision of a physiotherapist[12]. Besides, for the patients with deficits in range of motion (ROM), manual therapy plays a role to restore or maximize ROM improvement before surgeries[13].

Maitland and Mulligan mobilization are two types of manual therapy used in OA treatment[14]. Mulligan mobilization allows the patients to perform the offending movements in a functional position, hence, leading to a rewarding outcome[15]. Maitland mobilization aims to reestablish the spinning, gliding and rolling motions of the two joints[14]. In clinical practice, movement quality can be increased *via* improving joint stability of weak muscles by applying Maitland mobilization combined with psychological effects (self-confidence and motivating factors) and corrected mechanical loading. Maitland and Mulligan mobilization therapies have been used to treat multiple diseases, such as primary adhesive capsulitis of the shoulder[16], hip osteoarthritis[17] and knee osteoarthritis[18]. As reported by previous studies, Maitland or Mulligan mobilizations were used by 99.8% of physical therapists to treat cervicogenic dizziness[19].

Recently, some reviews have found that the manual therapies might be effective and safe in ameliorating osteoarthritis symptoms[16,18,20]. A meta-analysis by Qinguang Xu *et al*[18] demonstrated that manual therapy effectively and safely alleviated pain, reduced stiffness and restored physical function in KOA patients, and thus it could be considered as a complementary and alternative option. In the studies on primary adhesive capsulitis of the shoulder, Noten *et al*[16] identified the efficacy of mobilization techniques. Although Maitland mobilization was recommended in these

studies[16,20], there still was no systematic review and meta-analysis to compare the efficacy of different mobilization techniques, such as Maitland *vs* Mulligan mobilization. Therefore, this study used an evidence-based method to determine the efficacy of Maitland and Mulligan mobilization methods in adults with KOA.

MATERIALS AND METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)[21] and the Cochrane Collaboration Handbook[22]. The protocol of this systematic review and meta-analysis was registered on the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020182532) on April 28, 2020.

Information sources

Two reviewers performed literature search individually in the following electronic databases: PubMed, The Cochrane Library, Web of Science, Embase and Google Scholar, from the time of inception to September 20, 2020. We also reviewed the reference lists of relevant reviews and meta-analyses[23,24].

Search strategy

The search terms included related text words and medical subject headings regarding 'Mulligan' or 'Maitland' or 'Mobilization with Movement' or 'MWM' or 'Passive joint mobilization' or 'PJM' or 'musculoskeletal manipulations' or 'mobilization' or "manual therapy" and "Knee Osteoarthritis" or "knee osteo-arthritis" or "Knee Osteoarthritis" or "Osteoarthritis of Knee" or "Osteoarthritis of the Knee". We had tailored search strategy for each database, and details of the predefined search criteria are provided in [Supplementary Table 1](#).

Eligibility criteria

Trials were considered eligible if the following items were met: (1) Adult patients with KOA at any stage according to Kellgren and Lawrence grading system; (2) Containing data about Maitland joint mobilization or mobilization with movement technique with or without other interventions; (3) Reporting pain, range of motion, functional performance/ability or other relevant outcomes; and (4) Controlled clinical trials.

Since our aim was to explore the different efficacy of these two techniques in ROM, pain and functional performance in KOA, some experiments containing the combination of joint mobilization (Maitland or Mulligan) with other common treatments were also included, as long as they mainly focused on assessing the effect of these two types of joint mobilization methods.

Study selection

Two independent reviewers (Li LL, Hu XJ) removed duplication, screened titles, abstracts and full texts and agreed on the final eligibility. Negotiation was required when there was disagreement[25]. We recorded the reasons for exclusion of full texts.

Data collection process and data items

Two independent reviewers (Li LL, Di YH) extracted the data from included articles using a pre-designed form, including the following parameters: Author's name, publication year, sample size, study design, type/frequency/duration of the intervention and outcome assessment. Any disagreements were discussed and resolved by the two authors.

Risk of bias in individual studies

The quality of the included articles was assessed by two reviewers individually using PEDro scale. The results given by the two reviewers were compared and any disagreements were resolved by all three authors. The PEDro scale is based on the Delphi list and reported to be reliable for randomized controlled trials (RCTs) of physical therapy in systematic reviews. The PEDro scale consists of 11 items, including: (1) Specified eligibility criteria of studies; (2) Random allocation of studies; (3) Concealed allocation; (4) Similarity between groups at baseline; (5) Blinding of all subjects; (6) Blinding of all therapists; (7) blinding of all assessors; (8) Less than 15% dropouts; (9) Intention-to-treat analysis; (10) statistical comparisons between groups; and (11) Point measures and variability data. PEDro score was calculated by assessing

the items 2-11. Each item was scored as either 1 or 0 according to whether the item was met or not, respectively. The total score of the scale is 10. Articles were classified into three distinct categories, including high (7-10), moderate (4-6) and low (0-3) quality.

Statistical analysis

All data were analyzed by using Cochrane Collaboration software (Review Manager Version 5.2 for Windows). Only continuous variables (range of motion, pain, function scale) were identified, therefore, the difference in means between the intervention groups with 95% confidence intervals (CI) was used as the main summary measures to determine the effect size of the results[26]. The final value and the standard deviation of the results were recorded as well as the number of patients in each treatment group at the last time of the follow-up. To evaluate the heterogeneity of the included studies, the χ^2 statistical test and I^2 statistic were performed. The extent of heterogeneity was measured by the I^2 statistical test and presented as the total percentage of variation between the studies. The I^2 value was considered low if I^2 was 0%-25%, moderate if I^2 was 25%-50% and high if I^2 was 50%-90%. A random effect model was employed if the heterogeneity was relatively high. Conversely, in case of low heterogeneity, a fixed effect model was used to analyze the data with inverse variance weighting[27]. Sensitivity analysis was conducted to identify the potential sources of high heterogeneity[28]. The statistical significance was assessed by using the Z index of overall effects[27]. Funnel plots was used to assess potential publication biases. If the included trials were < 10, we did not test for publication bias[29].

RESULTS

A total of 341 articles were screened from five electronic databases. After removing 333 articles, of which 125 were duplicates, 206 articles were screened out through title and abstract review, 10 articles were still for further consideration. After excluding two studies, eight trials involving 471 subjects were included in the present systematic review and meta-analysis (the reasons for their exclusion were given in Figure 1).

Characteristics of included studies

The characteristics regarding the study population, intervention, follow-up period and main results of the studies are presented in Table 1.

Risk of bias

All the articles included were assessed with the PEDro Scale (Table 2). The total score of methodological quality varied from 5 to 10 out of 11. The score of most studies exceeded the cut-off point 6, but only two studies scored 9. Many studies missed points on blinding of patients[14,15,30-32], therapists[14,15,30-34] and assessors[14,15,30,32]. In addition, there was often a lack of the concealment of allocation. These are shortcomings for RCTs.

Pain

Seven studies[14,15,30-34] with continuous data on pain degree were included in the meta-analysis, with a total of 354 participants. Five studies[14,15,30,31,33] reported the severity of pain using visual analogue scale, while the other two studies[32,34] adopted another Numeric Pain Rating Scale. The Numeric Pain Rating Scale is a segmented numeric version of the visual analogue scale, and both scales use a horizontal bar or line to rate the degree of pain. Thus, these two scales could be considered as the same. According to the forest plot (Figure 2), the pooled standardized mean difference (SMD) was 0.60 (SMD = 0.60; 95%CI: 0.17 to 1.03; $P = 0.007$).

ROM

Data were collected from five studies[14,30,31,33,35] with continuous data containing a total population of 204 participants. According to the forest plot (Figure 3), random effect model showed that there was no difference in the effect of the two mobilization methods on improving ROM (SMD = 9.63; 95%CI: -1.23 to 20.48; $P = 0.08$).

Western Ontario and McMaster Universities (WOMAC) function score

Six studies, with 297 participants, reported WOMAC function score[14,15,31-33,35], and one study[14] reported WOMAC function and pain score. According to the forest

Table 1 Characteristics of the included studies

Study	Comparators	Sample size	Age (yr)	Interventional type	Interval	Treatment period	Outcomes
Sambandam <i>et al</i> [31], 2011	Mulligan	20	61.0 ± 5.8 ¹	Unspecific; CT: 10 min hot pack and quad isometrics, 10 rep; HE: 10 rep isometric quadriceps	Once per day	2 wk	1, 2, 3
	Maitland	20	60.0 ± 5.1 ¹				
Kiran <i>et al</i> [14], 2018	Mulligan	31	47.5 ± 0.6 ¹	Depending on pain; CT: 10 min hot pack and quad isometrics	3 times per week	2 wk	1, 2, 3
	Maitland	31	0.6 ¹	Grade 1, 2 for pain; Grade 3 for ROM; CT: 10 min hot pack and quad isometrics			
Jeyakumar <i>et al</i> [30], 2017	Mulligan	20	51.0 ± 1.5 ¹	Medial, lateral, and rotational Mulligan without a belt; one glide per sec for 30 sec; 3 sets per treatment session; CT: hot pack, quad isometrics and SLR	Once per day	3 wk	1, 2
	Maitland	20	50.0 ± 2.7 ¹	Medial, lateral, posterior glide; one glide per seconds for 30 seconds; 3 sets per treatment session; CT: hot pack, quad isometric and SLR			
Multu <i>et al</i> [33], 2018	Mulligan	21	54.2 ± 7.3 ¹	A sustained manual glide of the tibia (medial, lateral, or rotation) during active; knee flexion and extension, 3 sets of 10 rep; EP: aerobic, active ROM, strength, stretching exercises	3 times per week	4 wk	1, 2, 3
	Maitland	21	56.3 ± 6.6 ¹	Knee distraction and dorsal glides, ventral glides and patellar glides in all direction; 2-3 oscillations per seconds for 1-2 min; 3-6 rep; EP: aerobic, active ROM, strength, stretching exercises			
Lalnunpuui <i>et al</i> [35], 2016	Mulligan	15	49.5 ± 5.5 ¹	Medial, lateral, rotation and dorsal mobilization with active knee flexion; 3 sets of 10 rep; EP: isometric strengthening (quad, hamstring, VMO), Stretch (quad, hamstring), ROM	3 sessions per week	4 wk	2, 3
	Maitland	15	48.5 ± 6.9 ¹	Tibia-femoral anterior-posterior glide, Tibia-femoral posterior-anterior glide, Patella-femoral caudal-cephaloid glide, 2-3 oscillations per sec for 1-2 min. EP: isometric strengthening (quad, hamstring, VMO), Stretch (quad, hamstring), ROM			
Giri [32], 2019	Mulligan	30	61-70 ²	A sustained manual glide of the tibia (either medial, lateral, anterior, posterior or rotation) during active knee flexion and extension; 3 sets of 10 rep. Mulligan taping: tape with brown rigid tape	3 times per week	2 wk	1, 3
	Maitland	30		Tibia-femoral anterior and posterior glided. Kinesio taping: superior "Y" technique			
Rao <i>et al</i> [34], 2017	Mulligan	30	51.2 ± 9.2 ¹	According to individual condition	-	-	1
	Maitland			AP, PA, medial, lateral, compression and distraction glides; rotation			
Lalit <i>et al</i> [15], 2012	Mulligan	30	51.7 ²	internal rotation the tibia, 3 reps for 3 sets; EP: multiple angle isometrics, terminal arc knee extension, mini-squats, partial lunges one-leg balances, cross-body leg swings, 10 rep per session, 3 sessions per day	3 sessions per day	5 d	1, 3
	Maitland	30	54.7 ³	Anterior and posterior glide for tibial-femoral joint, superior-inferior and medio-lateral glides for patellar femoral joint, 10 rep per session, 3 sessions per day; EP: multiple angle isometrics, terminal arc knee extension, mini squats, partial lunges one-leg balances, cross-body leg swings (10 rep per session, 3 sessions per day)			

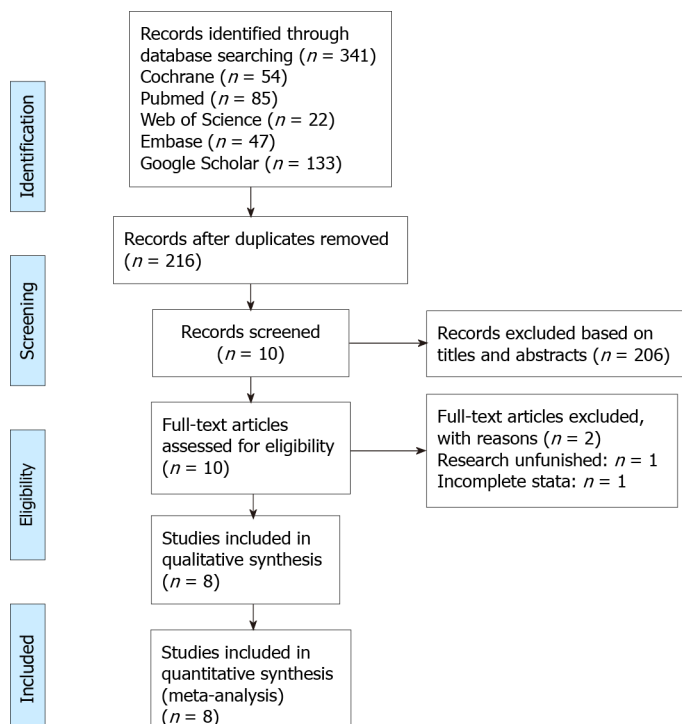
¹mean ± SD.²Range.³mean. 1: Pain; 2: ROM: Range of motion; 3: WOMAC function score: Western Ontario and McMaster Universities function score. Rep: Repetition; CT: Conventional treatment; HE: Home exercise; SLR: Straight leg raise; EP: Exercise program; VMO: Vastus medialis oblique; AP: Anterior to posterior; PA: Posterior to anterior.

plot (Figure 4), Mulligan dynamic joint mobilization was more effective in improving the WOMAC function score of patients with knee arthritis. (SMD = 7.41; 95%CI: 2.36 to 12.47; $P = 0.004$).

Table 2 Quality of included studies by PEDro Scale

Author	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	TS	Level of evidence
Lalnunpuii <i>et al</i> [31], 2016	1	1	0	1	1	1	1	1	1	1	1	10	A2
Rao <i>et al</i> [34], 2017	1	1	0	1	1	0	1	1	0	1	1	8	B
Kiran <i>et al</i> [14], 2018	1	1	0	1	0	0	0	1	1	1	1	7	B
Mutlu <i>et al</i> [33], 2018	1	1	1	1	1	0	1	1	0	1	1	9	B
Giri <i>et al</i> [32], 2019	1	1	0	1	0	0	0	1	1	1	1	7	B
Jeyakumar <i>et al</i> [30], 2017	1	1	1	1	0	0	0	1	1	1	1	8	B
Sambandam <i>et al</i> [31], 2011	0	1	0	1	0	0	1	1	1	1	1	7	B
Lalit <i>et al</i> [15], 2012	1	0	0	0	0	0	0	1	1	1	1	5	B

C1: Eligibility criteria were specified; C2: Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received); C3: Allocation was concealed; C4: The groups were similar at baseline regarding the most important prognostic indicators; C5: There was blinding of all subjects; C6: There was blinding of all therapists who administered the therapy; C7: There was blinding of all assessors who measured at least one key outcome; C8: Measurements of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; C9: All subjects for whom outcome measurements were available received the treatment or control condition as allocated, or where this was not the case, data for at least one key outcome were analyzed by "Intention to treat"; C10: The result of between-group statistical comparisons were reported for at least one key outcome; C11: The study provided both point measurements and measurements of variability for at least one key outcome; 0: Does not meet the included criteria; 1: Meets the included criteria. TS: Total score.

**Figure 1** Preferred reporting items for systematic review and meta-analyses flow diagram.**Publication bias**

The analysis of the funnel plot for publication bias suggested the absence of bias because of plot symmetry (Figure 5).

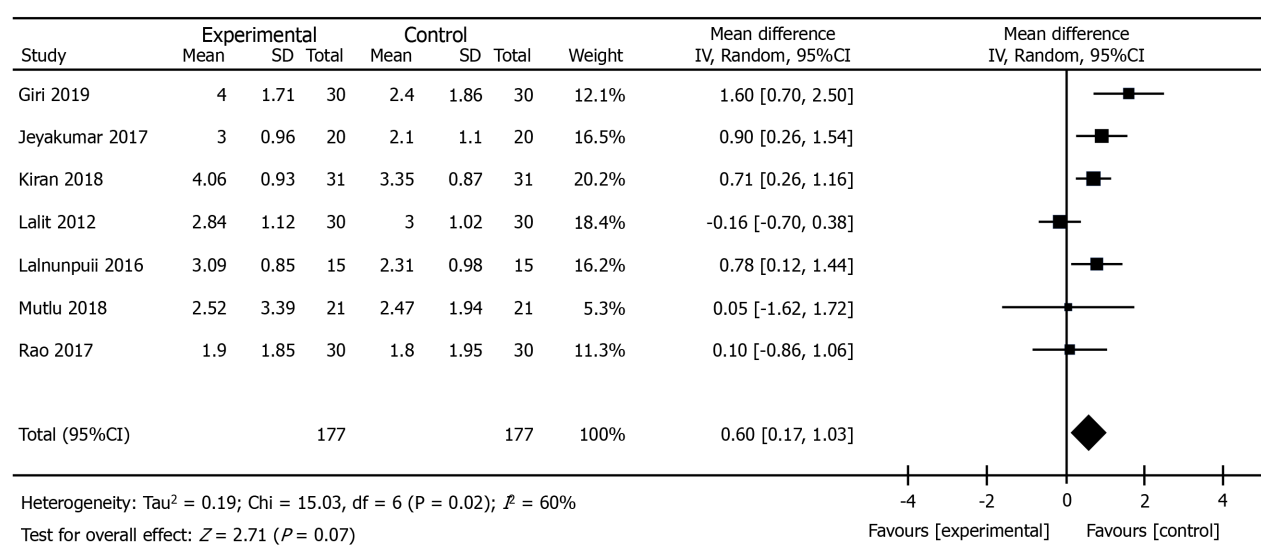


Figure 2 Forest plot of the pain. SD: Standard deviation; CI: Confidence interval.

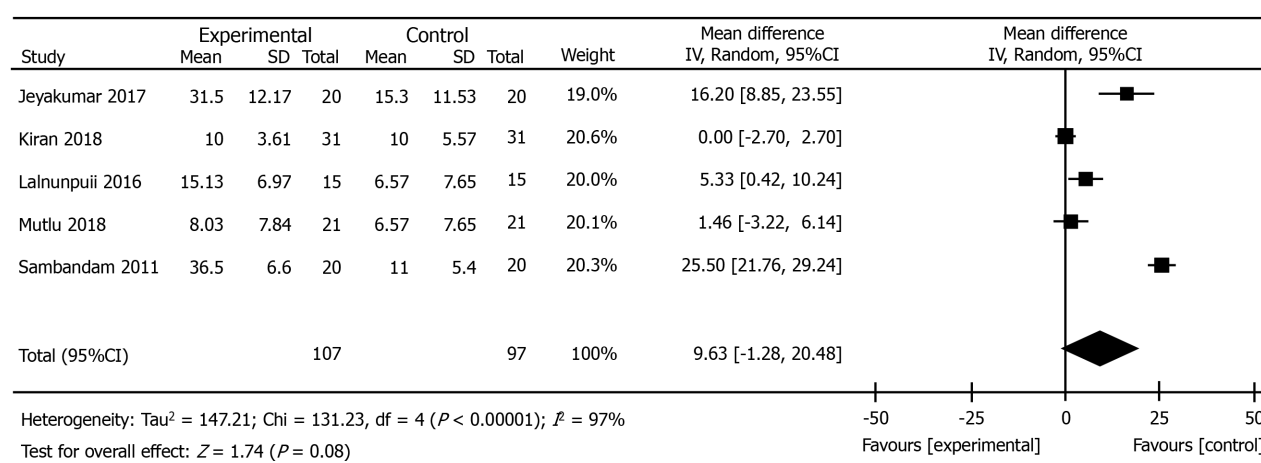


Figure 3 Forest plot of the range of motion. SD: Standard deviation; CI: Confidence interval.

DISCUSSION

Summary of evidence

In this systematic review and meta-analysis of eight randomized controlled trials including 471 KOA patients, Mulligan mobilization was found to be a promising alternative option for KOA treatment. Particularly, the Mulligan mobilization has been recommended to be applied in alleviating pain and improving WOMAC function score. Because of the poor methodological quality of included studies, more studies are needed to assess the effect of manual therapies on pain, WOMAC function score and ROM.

Limited preliminary evidence showed that Mulligan mobilization could reduce pain and improve WOMAC function compared with Maitland mobilization. This conclusion was consistent with that in previous studies. Gomes *et al*[36] found that pain was significantly improved in KOA patients who received a course of Mulligan mobilization. Besides, Bhagat *et al*[37] showed that Mulligan technique was effective in alleviating pain and improving functional mobility in KOA patients. However, in these studies[36,37], the intervention periods were not analyzed and the sample size was small. In the previous meta-analysis, Stathopoulos *et al*[17] found that the efficacy of Mulligan mobilization method on KOA was unclear due to the high heterogeneity. We speculated that shorter intervention periods or the small sample size might contribute to this heterogeneity. Therefore, further studies will be required to identify the biomechanical rationale behind the effect of mobilization in a longer treatment period.

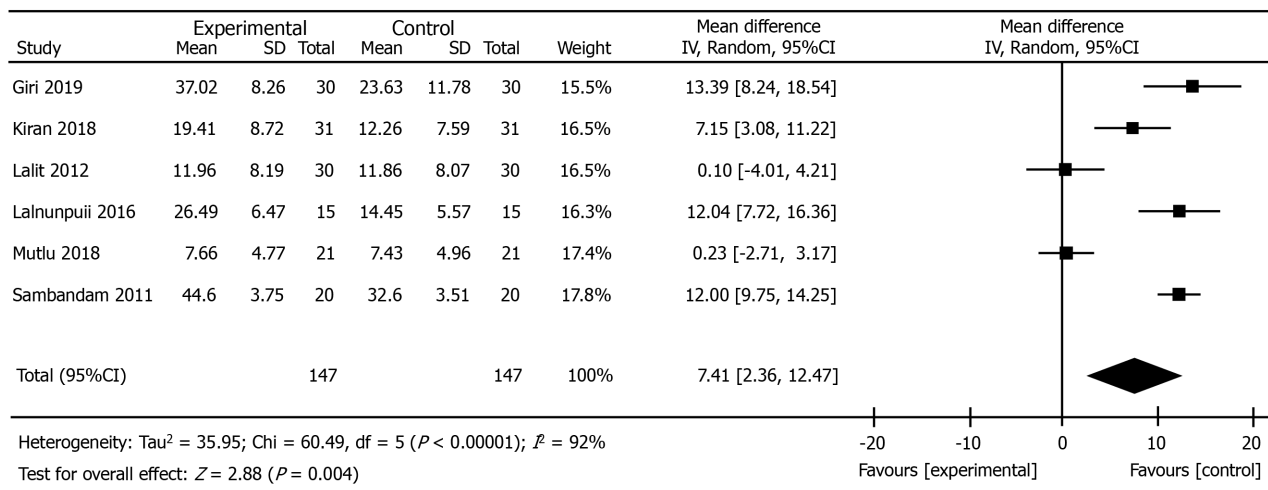


Figure 4 Forest plot of Western Ontario and McMaster Universities function score. SD: Standard deviation; CI: Confidence interval.

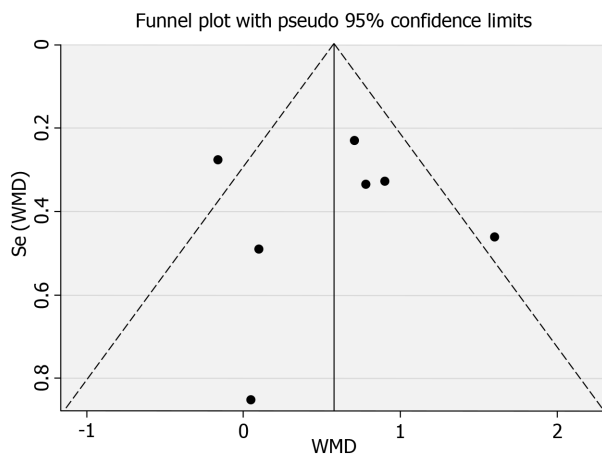


Figure 5 Publication bias.

For ROM, Mulligan mobilization might have the same efficacy as Maitland mobilization. Mulligan and Maitland mobilization, as two kinds of manual therapies, have been found to improve the mechanical loading, joint stability and strength of weak muscles through mechanical, self-confidence and motivating factors. In a cohort study, KOA patients received a manual physical therapy program focusing on passive extension mobilization of the knee, and the restoration effects in Mulligan mobilization group was not better than that in the exercise group[38]. In another study, ROM in Mulligan mobilization was improved in the long term[33]. According to the studies by Stathopoulos *et al*[17], Mulligan mobilization could only ameliorate joint dysfunctions of the upper and lower extremities and facilitated the immediate recovery of full and pain-free ROM. However, no studies have focused on the treatment period and the site of arthritis. In our study, we focused on the ROM of knees and included studies with various treatment periods. Besides, the high heterogeneity might decrease the reliabilities of the results. Further study and follow-ups will be needed to validate the conclusion.

Overall, KOA is regarded as a complex disorder with multiple risk factors, such as generalized constitutional factors (age, female sex, *etc.*)[39] and local adverse mechanical factors (trauma, malalignment, *etc.*)[40]. Confined to the current evidence, we did not limit sex, age, body weight or even history, which may influence the representativeness and application of conclusions. In addition, it was found that the heterogeneity of most included RCTs was high. Thus, the positive effects of the Mulligan mobilization should be interpreted with caution. Finally, because manual therapies require hands-on treatments, it is not possible to perform the study in a blinded way, resulting in the poor score on the PEDro Scale. In the future clinical trials, attention should be paid to all the points above in study design.

Strengths and limitations

Our research has several strengths. First, as far as we are aware, this is the first systematic review and meta-analysis aiming to determine the efficacy of Maitland *vs* Mulligan mobilization with movement in KOA patients. Secondly, this meta-analysis included as many relevant outcomes as possible and was completed according to the accepted guideline[41]. Thus, the results were relatively comprehensive.

However, similar to other meta-analyses, there were also limitations[42]. Firstly, since not all the grey literature could be searched, some studies might have been missed[43]. This may be negligible with comprehensive and reliable research strategy. Secondly, the sample size in this review might not be enough, which could affect the quality of evidence. Thirdly, due to less than 10 included studies, interpretation of publication bias assessment should be done with caution[29]. Finally, we did not report the cost due to the lack of data. Thus, more RCTs should be conducted, including novel interventions, and more data on adverse effects (AEs) safety will be of necessity.

CONCLUSION

Mulligan joint mobilization is a promising intervention with the potential to improve the pain and joint function for patients with KOA. Based on real-world and other epidemiological settings, more data and surveillance will be necessary to identify the efficacy. Also, further studies are necessary to explore the cost of KOA in other ethnicities.

ARTICLE HIGHLIGHTS

Research background

Knee osteoarthritis (KOA) is the most common type of arthritis, with heavy burden on healthcare service. Manual therapy is an effective method for the treatment of KOA, but the efficacy of Maitland *vs* Mulligan mobilization techniques is still controversial.

Research motivation

Some reviews have found that the manual therapies might be effective and safe in ameliorating osteoarthritis symptoms, and Maitland mobilization was recommended in these studies. However, there still was no systematic review and meta-analysis to compare the efficacy of different mobilization techniques, such as Maitland *vs* Mulligan mobilization. Therefore, it is necessary to conduct a meta-analysis to fill this gap in our understanding.

Research objectives

To determine the efficacy of Maitland and Mulligan mobilization methods in adults with KOA.

Research methods

We searched PubMed, Embase, Web of Science, the Cochrane Library and Google Scholar from inception to September 20, 2020 to collect studies comparing Maitland and Mulligan mobilization methods in adults with KOA. Data processing and statistical analyses were performed using Cochrane Collaboration software (Review Manager Version 5.2 for Windows). The odds ratio and 95% confidence interval (CI) were employed to analyze the dichotomous variables. Meanwhile, the standardized mean difference (SMD) with a 95%CI was used to analyze the continuous variables.

Research results

A total of 341 articles were screened from five electronic databases (PubMed, the Cochrane Library, Embase, Web of Science and Google Scholar) after excluding duplicates. Ultimately, eight trials involving 471 subjects were included in present systematic review and meta-analysis. Mulligan mobilization is more effective in alleviating pain (SMD = 0.60; 95%CI: 0.17 to 1.03, $P = 0.007$; $I^2 = 60\%$, $P = 0.020$) and improving Western Ontario and McMaster Universities function score (standardized mean difference = 7.41; 95%CI: 2.36 to 12.47, $P = 0.004$; $I^2 = 92\%$, $P = 0.000$). There was no difference in the effect of the two kinds of mobilization on improving the range of

motion (standardized mean difference = 9.63; 95%CI: -1.23 to 20.48, $P = 0.080$; $I^2 = 97\%$, $P = 0.000$).

Research conclusions

The Mulligan mobilization has been recommended to be applied in alleviating pain and improving Western Ontario and McMaster Universities function score.

Research perspectives

Our meta-analysis revealed that Mulligan mobilization will be a promising alternative option for KOA treatment. Unfortunately, because of the poor methodological quality of included studies, more data and surveillance will be necessary to identify the efficacy. Also, further studies are needed to explore the cost of KOA in other ethnicities.

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