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Systematic Review

Does treatment duration of manual therapy influence functional outcomes for individuals with chronic ankle instability: A systematic review with meta-analysis?

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ABSTRACT

Question: Can manual therapy improve functional outcomes for individuals with chronic ankle instability?
Design: Systematic review with meta-analysis of randomized controlled trials.
Participants: Individuals with chronic ankle instability.
Intervention: Manual therapy is defined as an intervention that involves joint mobilization, and mobilization with movement.
Outcome measure: The primary outcome is patient reported function (PRF) questionnaires scores, the secondary outcomes are ankle dorsiflexion range of motion (DFROM) and balance control.
Results: Four studies were included (n = 208, mean age = 24.4) in the meta-analysis, with moderate to high quality on the PEDro scale (range 6–8). For patient reported function (PRF) questionnaires, two studies reported significant improvement after six-session manual therapy measured by foot and ankle ability measures sport subscale (FAAMS) and Cumberland ankle instability tool (CAIT), respectively. For DFROM, one session manual therapy had no significant effect on the weight-bearing lunge test (WBLT) (3 studies, n = 147, SMD = 1.24 (95%CI -0.87 to 3.36), I^2 = 96%) or non-weight-bearing inclinometer test (2 studies, n = 47, MD = 3.41° (95%CI -0.26 to 7.09),I^2 = 43%), while six-sessions manual therapy showed, a significantly positive effect on WBLT(2 studies, n = 80, SMD = 2.39, (95% CI 0.55, to 4.23), I^2 = 93%). For the SEBT, one-session manual therapy had no significant effect on overall star excursion balance test (SEBT) score (3 studies, n = 137,MD = 2.05,95%CI (−0.96,5.05), I^2 = 75%), while qualitative analysis of 2 included studies showed significant improvement both on the SEBT score and single limb balance test (SLBT).
Conclusions: Six sessions rather than one session of manual therapy improves ankle functional performance for individuals with CAI.
Trial registration number: PROSPERO CRD42017054715.

1. Introduction

Ankle sprain is the most common injury in sport. A summary of 16 years of National Collegiate Athletic Association injury surveillance data across 15 sports suggests that almost 54% of all injuries were to the lower limbs, with ankle sprain the most common injury (Hootman et al., 2007). The ankle has the highest proportion of serious injuries by sport and body part (Emery et al., 2006) and, in particular, players in basketball, football and volleyball have a high percentage of ankle injuries (Hootman et al., 2007; Buffet et al., 2015; Dvorak et al., 2011).

Chronic ankle instability (CAI) is a well-documented residual problem after ankle sprains (Yeung et al., 1994). Approximately 40% of ankle sprains result in CAI (Fong et al., 2007; Hershkovich et al., 2015). Hertel (2002)classified CAI into two parts: mechanical instability and functional instability. Due to the independent existence of recurrent ankle sprain without mechanic instability or functional instability, Hiller et al. (Hiller et al., 2011) argued that recurrent ankle sprain should be classified as the third independent component in the CAI model. Mechanical ankle instability is usually present in the form of hypermobility or hypomobility. Repetitive minor ankle injuries contributing to the laxity of ligament and joint capsule have been proposed as the major reason for mechanical instability (Hubbard et al., 2007;

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Hubbard and Hertel, 2006). Mechanical instability can progress to functional instability, which is usually revealed through dysfunction of the ankle joint. (Lin et al., 2015) Individuals with functional instability frequently get the feeling of "giving way" or experience recurrent ankle sprain (Hertel, 2002). Individuals with other aspects of CAI may also present with decreased dorsiflexion and poor functional performance. Poor motor control and balance performance may be associated with the deficits of proprioception that are generally found in individuals with CAI, and are suggested to be related to deficits in the mechanoreceptors in the injured soft tissues in the ankle region (Brown and Mynark, 2007; Hertel, 2008a; Munn et al., 2010). For athletes with CAI, there is a greater risk of ankle re-injury when playing sports (Brown and Mynark, 2007; Anandacoomarasamy and Barnsley, 2005), which impacts on their daily training and motor learning, and affects their performance in competition (Witchalls et al., 2014).

Clinically, the weight-bearing lunge test (WBLT) and the inclinometer are the most common methods used for measurement of ankle range of motion. (Powden et al., 2015) The star excursion balance test (SEBT) is usually employed to detect functional performance deficits associated with lower extremity pathology in otherwise healthy individuals, as it can challenge participants' lower limb strength, joint ROM, postural control, and proprioceptive ability (Olmsted et al., 2002). High validity and reliability has been reported for different versions of the SEBT. (Gribble, 2003) In addition, patient-report instruments are frequently involved in the study of CAI, such as visual analog scales (VAS), the foot and ankle ability measure (FAAM), and the Cumberland ankle instability tool (CAIT).

The VAS is a psychometric response scale widely applied in clinical practice to indirectly measure certain subject characteristic (or feelings) with a good reliability and validity (Bijur et al., 2001). The FAAM is a reliable, responsive and valid measure of physical function for individuals with a broad range of musculoskeletal disorders of the lower extremity, and consists of a 21-item questionnaire about activities of daily living plus an 8-item sports subscale (FAAMS).[22]The FAAM has been successfully translated into other languages and has high validity and reliability for the different versions (Mazaheri et al., 2010; Moreira et al., 2016). and a CAIT also works as a self-diagnosis and assessment tool that has been widely applied in recent studies and in clinical practice (Hiller et al., 2006).

Both surgical and non-surgical interventions have been used to manage CAI. The efficacy of surgery is controversial and there is no current consensus regarding the optimum surgical treatment for CAI (Doherty et al., 2017). However, non-surgical treatment techniques such as taping, brace, functional training and manual therapy have been considered in managing CAI and reducing the occurrence of recurrent ankle sprain (de Vries et al., 2011; Rodriguez-Merchan, 2012).

Manual therapy has been widely used in the clinic to treat CAI, especially via joint mobilization, or its variety mobilization with movement, developed by manual therapists Maitland (1977) and Mulligan (Hing et al., 2015). It is a type of passive movement of a "target" synovial joint with the aim of achieving a therapeutic effect and is widely recognized and applied in current musculoskeletal practice, but to date there is no clear consensus regarding the evidence to support this modality. Some studies have shown that manual therapy could provide a positive effect on dynamic balance and postural control for CAI (Cruz-Diaz et al., 2015; Hoch et al., 2012), but the mechanisms for this outcome have not been clearly explained. Within a relatively small body of research, controversy still exists as to whether joint mobilization can improve functional outcomes in CAI when using measurement outcomes such as balance or postural control. In clinical practice, patients usually expect an immediate and significant improvement in function after just one treatment, which requires that therapists provide evidence-based intervention in order to optimize patient-centered care. To date, however, there is no clear evidence that one session of manual therapy improves ankle ROM and balance in patients with CAI, and there is also a lack of clarity whether repeated intervention sessions would be needed to get improvement. Therefore, the present review aims to determine whether manual therapy can improve functional outcomes, as well as determine its optimal duration for individuals with CAI.

2. Materials and methods

This systematic review with meta-analysis was registered in an international database of systematic reviews in health and social care (registration number CRD42017054715; http://www.crd.york.ac.uk/PROSPERO/). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used as guidance to conduct and write the report for this review (Liberati et al., 2009).

2.1. Literature search

A systematic search of four electronic databases (PubMed, Embase, EBSCO (including MEDLINE and CINAHL) and Web of Science) was completed on 17th May 2018. Search strategies were developed according to Cochrane handbook guidelines, following the rules for "participants (P), Intervention (I), Comparison (C), Outcomes (O)" for the different electronic databases, in order to identify randomized controlled trials that used manual therapy as a non-operative treatment for chronic ankle instability (Lefebvre Carol et al., 2011). Major keywords employed covered "chronic ankle instability", "manual therapy", "joint mobilization", "balance", "postural control" (for more details see appendix 1). Reference lists of included studies were also searched for potential additional papers for the review.

2.2. Selection criteria

In order to investigate the effect of manual therapy on the treatment of chronic ankle instability, individuals meeting the minimum reporting standards for CAI recommended by Wikstrom (Wikstrom and Brown, 2014) were included regardless of age and gender; Only RCT study were included, where joint mobilization or its variant, mobilization with movement (also described as Mulligan's) were applied in individuals with CAI as the major manual therapy intervention, and where the control group in studies is defined as "wait and see" or sham treatment. However, studies in which individuals were treated by a combined protocol (e.g. *joint mobilization plus strength training*), or a crossover intervention without any functional evaluation before the wash-out period were excluded. Outcome measures have to include patient-reported function (PRF) questionnaire, or ankle dorsiflexion range of motion, or balance test. All included studies must be written in English with no restriction on publication date.

2.3. Study selection

Two researchers (XS and JH) independently completed the selection of studies. When any disagreements arose, a third researcher (JW) provided an additional opinion, to reach a consensus. At the first stage of screening, titles and abstracts of identified articles were checked for relevance. In the second stage, full-text articles were accessed and assessed against the inclusion and exclusion criteria, as well as for suitable data presentation in their results section.

2.4. Risk of bias assessment

The quality of studies was independently evaluated by two researchers based on the Physiotherapy Evidence Database (PEDro) scale. (Macedo et al., 2010; Maher et al., 2003) The PEDro scale, consisting of 11 items, is an effective tool for assessing the quality of physical therapy and rehabilitation trials. If trials were already listed on the PEDro database (http://www.pedro.org.au/), these scores were adopted. Item 1 on the PEDro scale (eligibility) is related to external validity and was

not used to calculate the method score generally. The total score range of 0–10 was calculated for each study.

2.5. Data extraction

Data for CAI were extracted from before and after manual therapy. Outcomes included ROM, SEBT score, and patient-reported functional (PRF) questionnaire (i.e. FAAM or VAS) after one session of treatment and after 6 sessions of treatment. All data were continuous variables, so means, standard deviations (SD) and sample sizes were collected to analyze for this review. As SD values were not always reported, the provided p value or 95% confidence interval (CI) in the studies was used to impute the standard deviation value (Higgins, 2011). Where possible, authors of studies were contacted to acquire information needed for this review.

2.6. Statistical assessment

Review Manager 5.3 (http://community.cochrane.org/tools/review-production-tools) was used to do the meta-analysis for this review, to calculate pooled mean effect size of standardized mean differences (SMD) or mean difference (MD) for all group comparisons and 95% confidence interval (CI). Parallel multi-groups in the studies were combined as intervention group or control group. In the meta-analysis, inverse variance and random-effect model was used to calculate a pooled effect size for included studies (Higgins, 2011). In the absence of a well-established clinically meaningful difference value for change, we used the minimum detectable change (MDC) as the threshold for deciding if an effect was clinically worthwhile.

In addition, the GRADE approach was applied to determine the quality of evidence (Wallis and Taylor, 2011). This approach entailed downgrading the evidence from high to moderate to low and to very low quality based on a set of criteria. Downgrading the evidence one place (e.g., high to moderate quality) would occur if: (1) the PEDro score was < 6 for the majority of trials in the meta-analysis (2) there were greater than low levels of statistical heterogeneity between the trials (I greater than 2 in 25% of studies) and (3) if there were large confidence intervals due to a small number of participants or high score variance. If there were serious issues with methodological quality, such as all trials in the meta-analysis were < 6 PEDro score without allocation concealment and blind assessors, then a double downgrade would occur (e.g., from high to low quality). Additionally, the highest level of evidence from qualitative analysis is defined as low. A footnote was used to explain the reasons for grade applied to each analysis.

3. Results

3.1. Description of included studies

Details of the selection process are presented in Fig. 1. Forty studies were screened to exclude those not relevant to joint mobilization, or duplicated studies and non-RCT studies. Finally, 4 studies (Cruz-Diaz et al., 2015; Harkey et al., 2014; McKeon and Wikstrom, 2016; Wells, 2012) were included in the meta-analysis. All included studies reported the effects of one-session manual therapy, and 2 included studies reported the effects of six-session manual therapy on CAI.

As functional improvements are the issue of greatest concern for individuals with CAI, the primary measures in this systematic review with meta-analysis were PRF questionnaires, and they are VAS, FAAMS and CAIT. VAS was widely employed to measure certain subjective characteristics, such as pain or stiffness, and represented by a tape measure from 0 to 10 cm 0 cm represents painless (or no stiffness), 10 cm represent unbearable pain (or maximal stiffness) perceived by individuals. In terms of FAAMS, scores less than 80% have been considered as representing impairment in sport function (Martin et al., 2005). Furthermore, low scores in CAIT usually suggest poor ankle functional performance, and individuals with CAIT score less than 27 was highly likely to suffer CAI. (Hiller et al., 2006).

The secondary outcome measures were balance performance and ankle dorsiflexion ROM (DFROM). Three of the 4 studies (Cruz-Diaz et al., 2015; Harkey et al., 2014; Wells, 2012) reported SEBT as balance performance, which has anterior (A), posterior-medial (PM) and posterior-lateral (PL) sub-scores. Given that the SEBT performance is related to the participant's leg length, the ratio of reach distance (cm) over leg length (cm) multiplied by 100% was used as a normalized score for this test (Olmsted et al., 2002). The normal scores for the three sub-directions (A, PM, and PL) in healthy athletes are 62%–69%, 84%–97%, 99%–113%, respectively. (Stiffler et al., 2015) Alternatively, one study reported the result of the single limb balance test (SLBT), using the recorded time of single limb standing as a measure of static balance performance. For DFROM, 3 of the four studies (Cruz-Diaz et al., 2015; McKeon and Wikstrom, 2016; Wells, 2012) reported weight-bearing lunge test (WBLT) scores and non-weight-bearing inclinometer (NWBI) results as ankle dorsiflexion range of motion measures. Normal ankle dorsiflexion ranges from 40 to 50° in adults, which is approximately equal to 11–14 cm measured in the WBLT (Bennell et al., 1998). Further details of the 4 studies are presented in Table 1.

3.2. Quality of studies and evidence grade

All 4 studies were considered moderate to high quality, with all PEDro scores ≥ 6 (range *6 to 8*). (Sherrington et al., 2010) All trials had random allocation for between-group comparisons. Blind allocation was used by three studies (Cruz-Diaz et al., 2015; Wells, 2012; McKeon and Mattacola, 2008), but no details were provided to explain how this was achieved during the trials. It is impossible to blind the therapists and patients to receiving “treatment” (although some treatments may be shams), owing to the nature of the interventions. However, as assessor blinding can never be achieved when patients who were not treated (i.e. “wait and see”) complete a questionnaire for PRF assessment, the term of “assessor blinding” in PEDro scale was marked as “*No*” for one included studies with primary PRF outcomes (Wells, 2012), although assessor blinding was stated in text by authors. One study included an intention-to-treat analysis (Cruz-Diaz et al., 2015). Complete details are provided in Table 2.

3.3. Synthesis of results

Meta-analysis of 2 included studies with 130 participants provide moderate evidence suggested that six sessions of manual therapy compared with wait and see or sham intervention were effective for improving ankle DFROM for CAI. Meta-analysis showed no improvements regarding ankle DFROM, SEBT after a single session of manual therapy, with high to moderate evidence. When outcomes from individual studies could not be included in meta-analysis due to the variety of selected assessment tools, a qualitative analysis was carried out. This showed that six-session rather than one-session manual therapy has significantly positive effects on PRF (FAAMS, CAIT) and balance control (SEBT, SLBT). (Table 3).

3.4. Patient report function questionnaires

Three included studies separately reported the results of patient report function questionnaires (PRF) by various questionnaires. Wells (2012) reported that manual therapy was significantly superior to control on pain and stability assessed by VAS, but no significant improvement was found in function as measured by VAS after one session of treatment. However, two studies both reported significant improvement on self-reported function after 6 sessions of manual therapy. McKeon with his colleagues (McKeon and Wikstrom, 2016) reported that significant improvements existed in FAAMS after 2-weeks of manual therapy compared with the control group, and a large effect

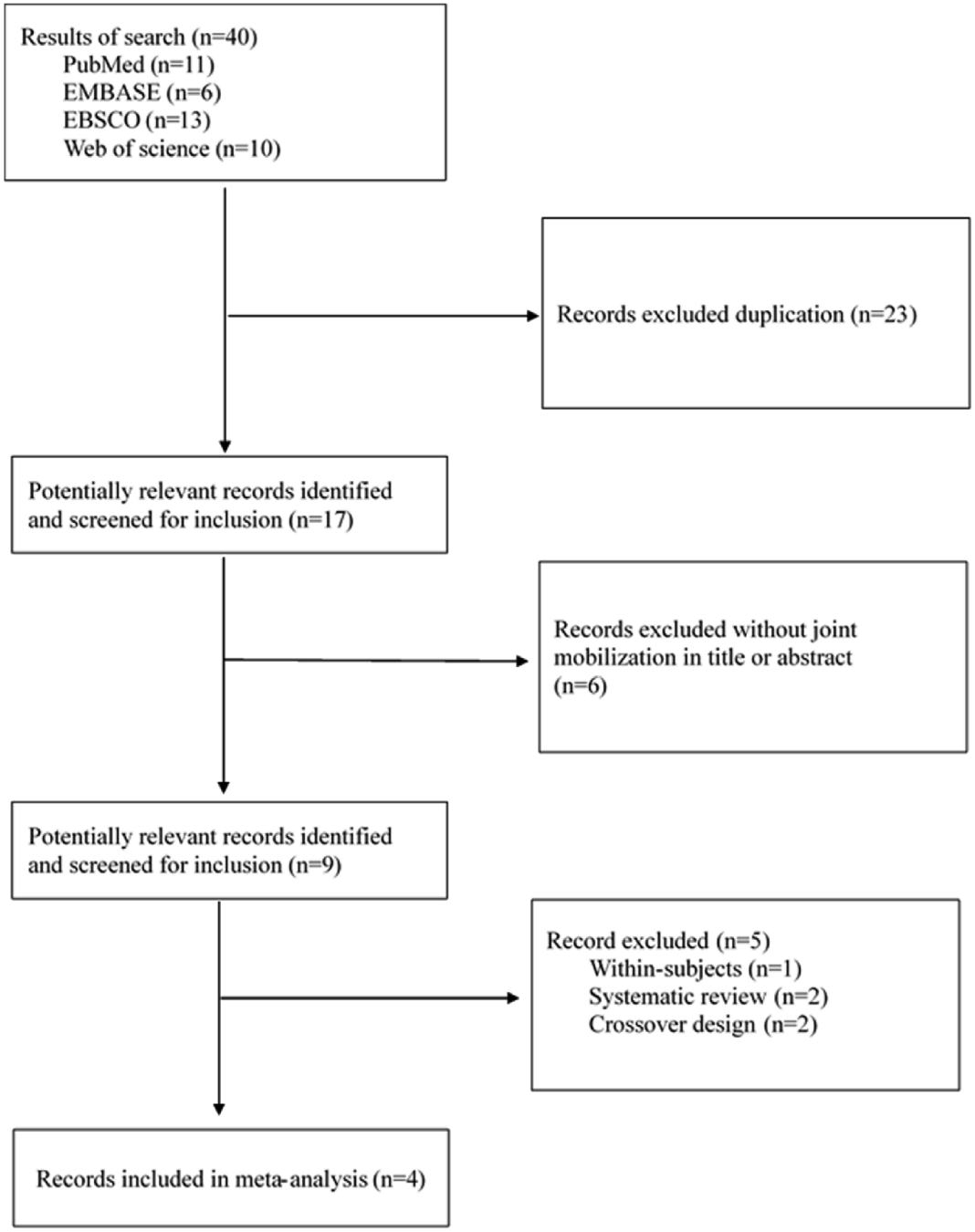

Fig. 1. Flowchart for article selection.

size exceeding the MDC was found in their research. Similarly, David et al.'s study (Cruz-Diaz et al., 2015) also found that a group treated by joint mobilization showed greater improvement in CAIT score than control group (wait and see, or sham group) when undergoing one month of treatments.

3.5. Dorsiflexion range of motion

The results of data pooling show that a single session of manual therapy is not superior to control intervention ("wait and see" or sham treatment) in improving DFROM for CAI (2 studies, n = 47, MD = 3.41 (95%CI -0.26 to 7.09),I^2 = 0%) using measurement by inclinometer (Harkey et al., 2014; Wells, 2012). The I (Emery et al., 2006) value indicates low heterogeneity in the studies suggesting good generalizability of the result (Fig. 2.1). The results of the meta-analysis comparing the immediate effects of one-session manual therapy with a control group showed that there was no significantly superior outcome for the treatment group when compared to the control group in WBLT (3 studies, n = 147, SMD = 1.24 (95% CI -0.87 to 3.36),I^2 = 96%) (Cruz-Diaz et al., 2015; Wells, 2012; McKeon and Mattacola, 2008). However, the I (Emery et al., 2006) value indicates that there is considerable heterogeneity in the studies included in the meta-analysis reducing the generalizability of this result (Fig. 2.2).

Furthermore, ankle dorsiflexion range of motion was assessed by

Table 1
Summaries of included 4 studies. C: "wait and see" control; C sham: sham treatment; WBLT: Weight-bearing lunge test; NWBI: non-weight-bearing inclinometer; MWM: mobilization with movement; JM: joint mobilization; DFROM: dorsiflexion range of motion; SEBT: star excursion balance test; CAIT: Cumberland ankle instability tool; SLBT: single limber balance test; FAAMS: foot and ankle ability measure sports subscale; VAS: visual analog scale.

Study	Study Type	Participants Entered/ Completed	Characteristics (gender M/F), age (years), height (cm), mass (kg))	Entry Criteria	Study Time	Intensity/Dose	Intervention	Outcome Measures
1. Cruz-Diaz et al., 2015	RCT	81/78	Age:27.7(6.8) MWM:13F,17M Sham: 14F,17M C:12F,17M	CAI	Immediate/ 3weeks	10 repetitions/ set, 2-min rest between sets Six sessions	MWM vs C Sham	DFROM:WBLT SEBT CAIT
2. Harkey et al., 2014	RCT	30/30	Age:21.2 (2.76) Height:168.9(8.8) Mass:70.6 (20.9) JM: 6F,9M C: 10F,5M	CAI	Immediate	60 s/set, 3 sets, 1-min rest between sets One session	JM vs C	DFROM:NWBI SEBT
3. Wells, 2012	RCT	17/17	Age (JM): 22.33 ± 4.03 Age (C): 20.63 ± 1.77 JM:4F,5M C:6F,2M	CAI	Immediate	60 s/set, 3 sets 1-min rest between sets One session	JM vs C	DFROM:WBLT and NBWI SEBT VAS
4. McKeon and Wikstrom, 2016	Multi-RCT	80/75	Age:22.7(4.4) Height:171.2(9.5) Mass: 74.4 (16.0) JM:11F,9M C:12F,8M	CAI	Immediate/1 month	2 min/set, 2 sets, 1-min rest between sets Six sessions	JM vs massage vs stretching vs C	DFROM:WBLT FAAMS SLBT

Table 2
Study quality assessment against PEDro scale.

Study	PEDro scale											
	1	2	3	4	5	6	7	8	9	10	11	Score
[a]Cruz-Diaz et al., 2015	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10
Harkey et al., 2014	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6/10
Wells, 2012	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7/10
[a]McKeon and Wikstrom, 2016	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6/10

PEDro: Physiotherapy Evidence Database.
Notes on administration of the PEDro scale.
1. Eligibility criteria were specified; 2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received); 3. Allocation was concealed; 4. The groups were similar at baseline regarding the most important prognostic indicators; 5. There was blinding of all subjects; 6. There was blinding of all therapists who administered the therapy; 7. There was blinding of all assessors who measured at least one key outcome; 8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; 9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat"; 10. The results of between-group statistical comparisons are reported for at least one key outcome; 11. The study provides both point measures and measures of variability for at least one key outcome.
[a] Scores had marked in PEDro (https://www.pedro.org.au).

WBLT after six sessions of joint mobilization in 2 included studies (Cruz-Diaz et al., 2015; McKeon and Wikstrom, 2016), which both show a positive effect. Meta-analysis shows that the effect of joint mobilization is significantly superior to control ("wait and see", or sham intervention) (2 studies, n = 80, SMD = 2.39[0.55, 4.23], I^2 = 93%), The I (Emery et al., 2006) value in the studies suggesting indicates that there is considerable heterogeneity in the studies included in the meta-analysis reducing the generalizability of this result (Fig. 2.3).

3.6. Balance performance

SEBT was used as the outcome indicator of dynamic balance following manual therapy for CAI, including three directional scores: anterior (SEBT-A), posterior-medial (SEBT-PM) and posterior-lateral (SEBT-PL). Meta-analysis of studies reporting the overall score of SEBT suggest that a single session of manual therapy is not significantly different to control (3 studies, n = 137, MD = 2.05%, (95% CI -0.96 to 5.05), I^2 = 76%). In single directions, in the SEBT-A (3 studies, n = 137, MD = 2.84%, (95% CI -1.66 to7.35), I^2 = 83%) and SEBT-PM (3 studies, n = 137, MD = 2.53%, (95% CI -0.25 to 5.30), I^2 = 27%), both meta-analysis results show that manual therapy is not significantly different to the controls (Cruz-Diaz et al., 2015; Harkey et al., 2014; Wells, 2012). The high I (Emery et al., 2006) value, especially for SEBT-A indicates that there is considerable heterogeneity in the studies included in the meta-analysis, reducing the generalizability of this result. However, In the SEBT-PL, the meta-analysis results show that manual therapy is significantly superior to no treatment or sham treatment (3 studies, n = 137, MD = 2.54% (95% CI 1.14 to 3.94), I^2 = 0%) (Cruz-Diaz et al., 2015; Harkey et al., 2014; Wells, 2012). Here, the I (Emery et al., 2006) value indicates low heterogeneity in the studies suggesting good generalizability of the result (Fig. 3).

The effect of six-sessions of manual therapy on balance control was assessed in 2 studies by SEBT, and SLBT respectively. Due to the measurement methods differ, results cannot be pooled for meta-analysis. Cruz Diaz et al.'s (Cruz-Diaz et al., 2015) study showed significant improvement in all three directions of SEBT after six sessions of manual therapy. McKeon et al. (McKeon and Wikstrom, 2016) suggested that static balance control is improved after six-sessions of joint mobilization assessed by SLBT, although the effect didn't exceed the MDC.

4. Discussion

4.1. Effects on manual therapy on patient reported function

In the current systematic review, three studies separately examined the PRF by various questionnaires (Cruz-Diaz et al., 2015; McKeon and Wikstrom, 2016; Wells, 2012). but the meta-analysis was not possible because varied questionnaires were used. Generally, this systematic review suggests that the effect of one-session manual therapy is far from enough, A recent systematic review conducted by Kosik et al., (Kosik et al., 2017) argued that it is unclear whether a single application of manual therapy could bring about improvement in PRF. (Kosik et al., 2017) However, the effect of six sessions of manual therapy were also evaluated in the current study, which suggest that six sessions can

Table 3
Synthesis of results for Manual therapy vs Control for chronic ankle instability.

Measurements	No. of studies	No. of participants	Sessions of Treatment	SMD,95%CI, I^2	MD,95%CI, I^2	Quality of the evidence (GRADE)
PRF						Low[a]
VAS	1[42]		One			*Low*[a]
CAIT&FAAMs	2[31,41]	*161*	Six			*Low*[a]
ADFROM						Moderate
WBLT(cm)	*3[31,41,42]*	*147*	*One*	*0.94 [-0.71,2.58],95%*		*Moderate*[b]
	2[31,] (McKeon, Wikstrom)	*130*	*Six*	***2.39 [0.55, 4.23],93%***		*Moderate*[b]
NWB-I(degree)	*2[40,42]*	*47*	*One*		*1.24[-0.87,3.36] °, 0%*	*High*
Balance						
SEBT (%)	3[31,40,42]	83	One		2.05[-0.96,5.05]%,76%	Moderate[b]
SEBT_A					*2.84[-1.66,7.35]%,83%*	*Moderate*[b]
SEBT_PM					*2.53[-0.25,3,4.97]%, 27%*	*Moderate*[b]
SEBT_PL					***2.54[1.14,3,94]%, 0%***	*High*
SEBT&SLBT	*2[31,41]*		*Six*			*Low*[a]

PRF: patient reported function; ADFROM: ankle dorsiflexion range of motion; WBLT: Weight-bearing lunge test; NWBI: non-weight-bearing inclinometer; SEBT: star excursion balance test, A: anterior; PM: posteromedial, PL: posterolateral; SLBT: single limber balance test.
Reasons for downgrade.
[a] Qualitative analysis.
[b] Statistical heterogeneity (I (Emery, Meeuwisse, McAllister) ≥ 25%.

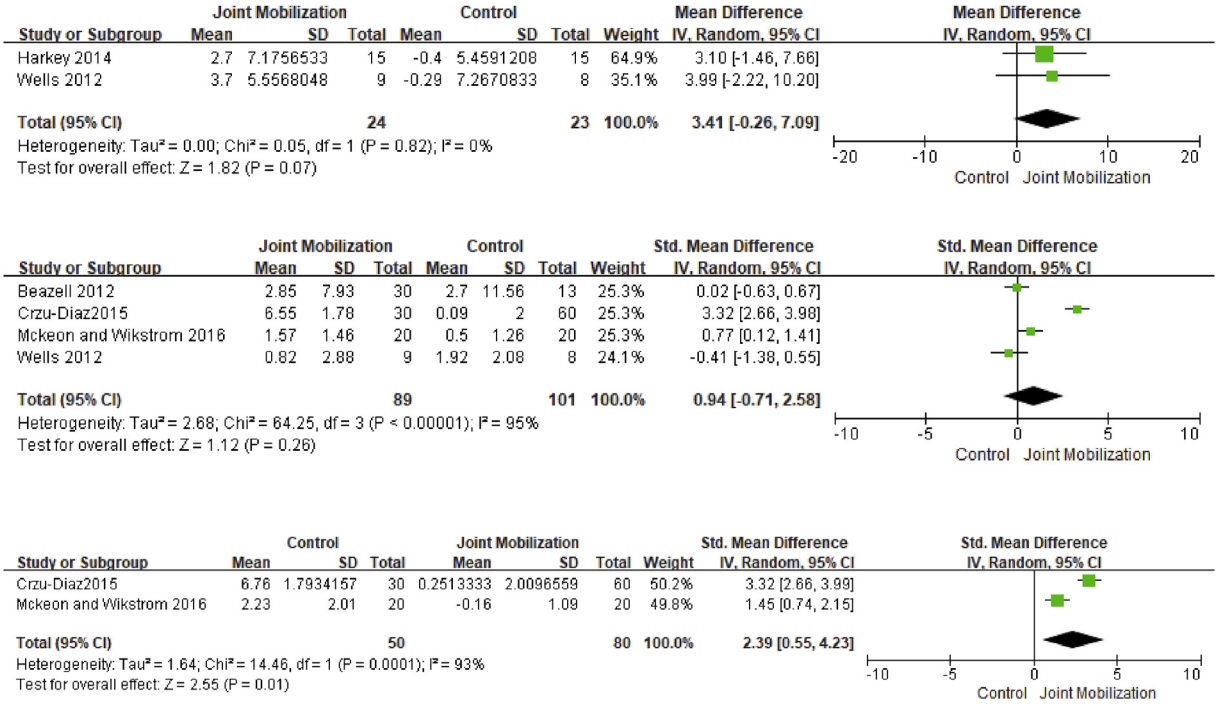

Fig. 2. 1. Effects of one session of manual therapy on ankle dorsiflexion range of motion DFROM by non-weight-bearing inclinometer (NWBI) (degree). **2**. Effects of one session of manual therapy on ankle dorsiflexion range of motion (DFROM) by weight-bearing lunge test (WBLT). **3**. Effects of six session of manual therapy on ankle dorsiflexion range of motion (DFROM) by weight-bearing lunge test (WBLT).

produce positive effect in terms of patient-reported functions for individuals with CAI. Improvement on functional outcomes is of most concern in clinical practice, the present review results indicate that to achieve this, more sessions of manual therapy combined with functional training are required in the rehabilitation process for individuals with CAI (McKeon and Mattacola, 2008; Plaza-Manzano et al., 2016).

4.2. Effects of manual therapy on range of motion

After one session of manual therapy, ankle DFROM measured in either WBLT or NWBI did not improve significantly. The SMD value of 0.94 in WBLT and the MD value of 3.41° in NWBI were both positive, but both 95% CIs crossed zero, which suggested the effect of one session of manual therapy on DFROM was trivial. However, when the WBLT results were pooled from two included studies by meta-analysis, results suggested that the effect of six-session manual therapy can significantly improve DFROM. Dorsiflexion range is important in normal gait and sport performance (Oberg et al., 1993). Some researchers have argued that individuals with CAI have altered gait patterns. (Hamacher et al., 2016) Sufficient clearance is required in the gait cycle to avoid tripping and a strong association between gait quality and DFROM during walking, especially in young people, has been reported (McIntosh et al., 2006; Mills et al., 2008). Furthermore, CAI can alter the kinematics of the lower extremity. During a cross-cutting action, loss of dorsiflexion means that individuals with CAI have significantly greater hip flexion and knee flexion in stance phase than those without CAI (Koshino et al.,

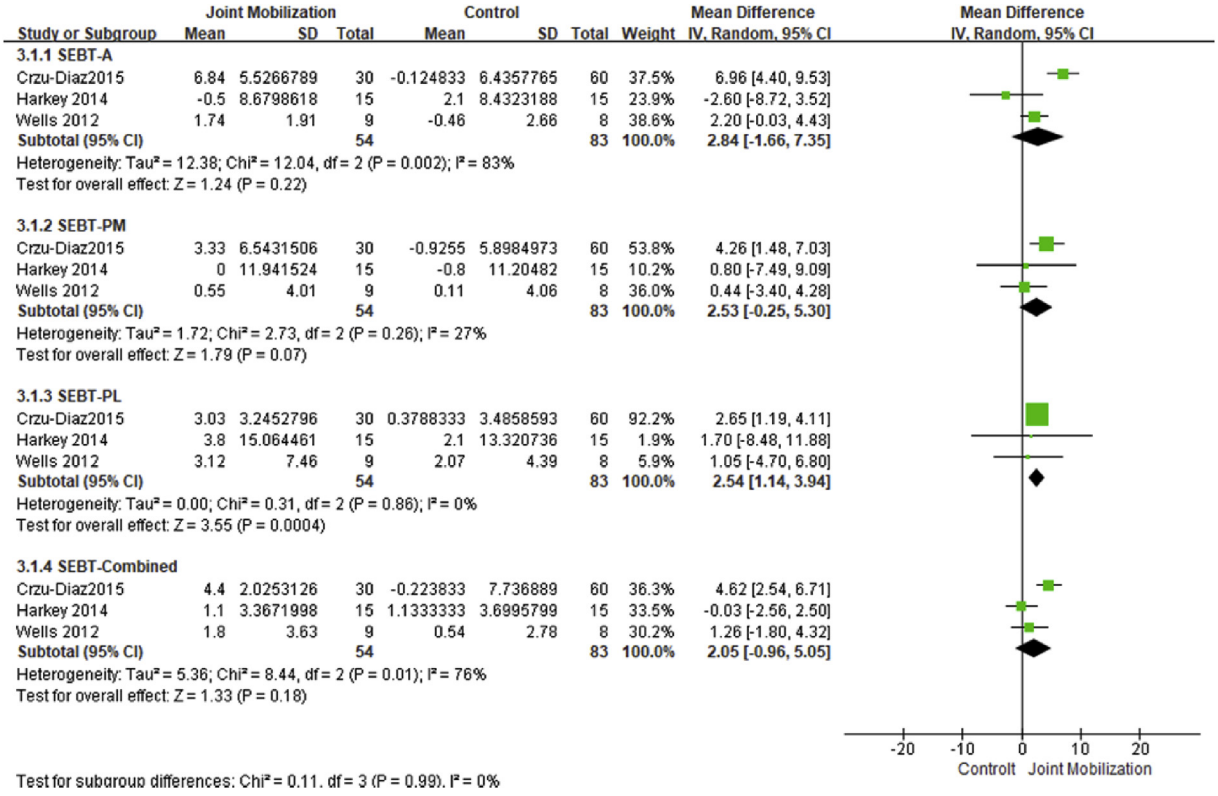

Fig. 3. Effects of one session of manual therapy on dynamic balance measured with SEBT(%)(A: Anterior direction; PM: Posteromedial direction; PL: Posterolateral direction).

2014), and reduced DFROM is associated with increased hip adduction during the step-down test (Bell-Jenje et al., 2016). Loss of dorsiflexion prevents the ankle from reaching a safe positioning for the foot during landing, which causes a high risk of tripping and recurrent ankle sprain during sport. (Drewes et al., 2009).

The findings here suggest that the effect of six sessions rather than one session of manual therapy are positive for a significant increase in DFROM for CAI, indicating that although individuals with CAI may not benefit immediately from this intervention, the treatment effect from more sessions of manual therapy has a positive outcome in order to restore function and gait. However, due to the heterogeneity of measurement units (*centimeter vs degree*) on the WBLT in the current meta-analysis, it is not possible to establish whether the improvement from six sessions exceed the MDC. Furthermore, the effects of manual therapy were time-limited. It has been reported that any increased dorsiflexion by stretching would decline after 30 min, due to the viscoelasticity of soft tissues (Mizuno et al., 2013). Therefore, further research is needed to determine the minimum sessions of manual therapy that can produce any significant improvement in DFROM and how long the effect may last. It is also necessary to evaluate the value of a combined programme, with other interventions to maintain the DFROM that is gained through manual therapy.

4.3. Effect of manual therapy on balance performance

A qualitative analysis showed that six-session manual therapy can significantly improve balance ability for individuals with CAI, both dynamic (SEBT) and static (SLBT). SEBT has previously been associated with neuromuscular control ability, (Kinzey and Armstrong, 1998) and SEBT-PM particularly has the strongest correlation with proprioception performance, measured by threshold of movement error detection, such that participants with high SEBT-PM usually have a lower threshold for movement detection, indicating better proprioception (Fournier Belley et al., 2016). In the current systematic review, improved SEBT and SLBT performance suggest that manual therapy can bring benefits for balance and proprioception at the ankle. This may be due to an effect of manual therapy on local joint and nerve structures enhancing afferent proprioceptive information for CAI (Plaza-Manzano et al., 2016). Repeated proprioception testing suggested that individuals with CAI have the potential to attain an adaptive improvement in proprioceptive acuity (Witchalls et al., 2014). It has been suggested that joint mobilization causes a fluctuation of motor evoked potentials in the tibialis anterior muscle and gastrocnemius, and could increase corticospinal excitability, which assists in muscle activation (Fisher et al., 2016). In some studies, manual therapy is reported to augment somatosensory information flow, and inferred to involve plastic changes in sensory integration within the CNS. (Clark et al., 2015; Haavik and Murphy, 2012).

However, the effect of one session manual therapy on total SEBT scores was trivial, especially on the SEBT-A and SEBT-PM, with both their 95% CI crossing zero in meta-analysis. Given that ankle dorsiflexion was found to be significantly correlated with SEBT-A particularly (Hoch et al., 2011), it is not surprising that SEBT-A did not change after one session of manual therapy when the current meta-analysis found no significant improvement in dorsiflexion after one-session of treatment. Although the meta-analysis in SEBT-PL suggested significant improvement, the score (2.54%) did exceed the reported MDC (4.28%) in the SEBT test (Cruz-Diaz et al., 2015). Therefore, the effects brought by one-session manual therapy seems too little to activate proprioceptive receptors surrounding ankle and foot complex according to previous theories (Fournier Belley et al., 2016).

Due to the limited qualitative evidence available in the current systematic review, it is still difficult to determine if six-sessions of manual therapy is sufficient to improve functional performance, especially issues related to daily or sports activities for CAI patients. Recent biomechanical studies have reported that CAI could induce strength deficits at the knee and hip, as well as alteration of lower extremity joint kinetics in a mechanism of neural drive (Kim et al., 2018; McCann

et al., 2017, Kosik et al., 2017), and balance impairments on the contralateral low limb also were found on individuals with unilateral CAI (Doherty et al., 2016). It is likely that a single therapeutic intervention of manual therapy is insufficient to reverse these changes, and combinative treatment strategies, including functional training targeting both lower limbs are necessary to reverse some of the deficits associated with CAI.

4.4. Comparison with other reviews

Doherty and colleagues (Doherty et al., 2017) recently conducted a systematic review on the prevention and treatment of acute and recurrent ankle sprains. In their review, no quantitative meta-analysis of RCTs was used to determine to what extent manual therapy can improve ankle ROM and function relevant to daily activities and sports performance. In addition, two reviews have suggested that one session of manual therapy could increase range of motion for CAI immediately, (Rodriguez-Merchan, 2012; Loudon et al., 2014) findings which are inconsistent with those of the current study. However, both studies evaluated the effect of manual therapy for individuals with acute ankle sprain, and their inclusion criteria were not identical to those employed for the current study. For patient with acute ankle sprain, edema and pain might be the main factors that affect their ankle function, while joint degeneration and proprioception impairments from long-term recurrent injury may be the main issues contributing to the ankle dysfunction for patients with CAI (Hertel, 2008b). Meanwhile neither of these reviews used meta-analysis, so the effect of manual therapy for individuals with CAI remained unquantified. Accordingly, findings from the current review extend knowledge and strengthen the evidence supporting manual therapy on patients with CAI.

In this current systematic review and meta-analysis, high heterogeneity existing between included studies might contribute to these conflicting results that would not have been apparent without the process of meta-analysis. Thus more high-quality studies need to be integrated into a subsequent meta-analysis to further determine the immediate effect of manual therapy on ankle range of motion for CAI. No previous studies have evaluated whether balance or postural control would be improved after treatment.

The outcome of the present meta-analysis provides moderate quality evidence that the effect of one session of joint mobilization is not sufficient, but low quality evidence suggests that six-sessions of joint mobilization can enhance dorsiflexion ROM and neuromuscular control for individuals with CAI. Since the intrinsic factors that contribute to balance control performance are known to be multifactorial (Gribble et al., 2004; Gabriner et al., 2015), studies incorporating other methods of assessment of neuromuscular control and proprioception after manual therapy need to be included in future research. Similarly, additional research investigating the minimum number of sessions of manual therapy in clinical application and its effect on neuromuscular control, and other performance measures, could provide guidance for physical therapists when manual therapy is employed for CAI.

4.5. Limitations

A limitation of this review is that publication bias was not assessed with a funnel plot, as a result of the low number of eligible studies (at least 10 studies required) in the meta-analysis (Lefebvre Carol et al., 2011). Another limitation is the relatively small number of total participants incorporated into this meta-analysis. This indicates that despite the fact that the application of manual therapy is a common therapeutic option among therapists in recent years, the supporting body of research literature is still not large. In addition, since there was a limited number of qualified studies included, and data was only extracted up to six sessions of treatment, so the long-term cumulative effects of treatment are not evaluated within this study. Participants in all eligible studies were almost always young adults (mean aged = 24.4), which may limit generalizability to other age groups within relevant the population.

5. Conclusion

In summary, six session rather than one session of manual therapy can improve functional performance in individuals with CAI. Moderate to low evidence suggests that six-session manual therapy can improve ankle dorsiflexion range of motion and motor control. The improvements of balance indicate a potential benefit on ankle neuromuscular control for those with CAI. This may have implications for recurrent injury prevention and sports performance maintenance and improvement. Future studies are needed to examine the potential neurological and biomechanical mechanisms that underpin the efficacy of manual therapy in CAI.

Conflicts of interest

No conflict interests.

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Appendix A. Supplementary data

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