Systematic review

Analgesic effects of manual therapy in patients with musculoskeletal pain: A systematic review

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A R T I C L E   I N F O

A B S T R A C T

Background: Current evidence shows that manual therapy elicits analgesic effect in different populations (healthy, pain inflicted and patients with musculoskeletal pain) when carried out at the spinal column, although the clinical significance of these effects remains unclear. Also the analgesic effects of manual therapy on peripheral joints have not been systematically reviewed.
Methods: A systematic review was carried out following the PRISMA-guidelines. Manual therapy was defined as any manual induced articular motion with the aim of inducing analgesic effects. Outcome measure was pain threshold.
Results: A total of 13 randomized trials were included in the review. In 10 studies a significant effect was found. Pressure pain thresholds increased following spinal or peripheral manual techniques. In three studies both a local and widespread analgesic effect was found. No significant effect was found on thermal pain threshold.
Discussion: Moderate evidence indicated that manual therapy increased local pressure pain thresholds in musculoskeletal pain, immediately following the intervention. No consistent result was found on remote pressure pain threshold. No significant changes occured on thermal pain threshold values. The clinical relevance of these effects remains contradictory and therefore unclear.

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1. Introduction

Manual therapy has shown a positive effect in patients with musculoskeletal pain, although discussion exists on the strength of this effect and on the indicated patient groups (Kent et al., 2010; Miller et al., 2010; Slater et al., 2012). Insight, in the mechanical and/or physiological mechanisms on which manual therapy is based, can contribute to its use in clinical practice.

Although the effects of manual therapy are classically explained within a biomechanical paradigm, research now points to the important role of neurophysiological processes at both spinal and supraspinal levels in the modulation of nociceptive information (Bialosky et al., 2009). Pain modulation is an attribute of the nervous system and is conceptualized as the net result of complex neural interactions in which physiological and psychological information is integrated into a concrete and individual pain experience (Ossipov et al., 2010; Garland, 2012). Manual therapy techniques can play a role in these interactions as they trigger a cascade of neurophysiological events starting from some form of mechanical (manual) stimulation of the body (Bialosky et al., 2009). Evidence for these neurophysiological events comes from clinical research which show increases in pain thresholds (PTs) directly after spinal manual therapy interventions in healthy participants, in participants subjected to experimentally induced pain, and in patients with musculoskeletal pain (Coronado et al., 2012; Millan et al., 2012). In the reviews of Millan et al. (2012) and Coronado et al. (2012), it was concluded that manual therapy techniques carried out at the spinal column have significant pain modulating

effects, although the clinical relevance of these effects remain unclear. No studies on the effects of manual therapy techniques on peripheral joints were included in these studies.

To add to the ongoing debate it is important to fill this gap and to reflect on the analgesic effect of manual therapy interventions, including the clinical relevant effects on pain modulation of both spinal and peripheral joint techniques (Bialosky et al., 2009). This can provide a sound rationale for manual therapy praxis and can therefore contribute to the acceptance of manual therapy as a legitimate therapy of choice for the treatment of musculoskeletal pain.

To summarize the specific pain modulatory effects of manual therapy in this review, PTs are selected as outcome criteria. PTs are defined as the minimal amount of pressure, temperature or chemical stimulation, which participants perceive as painful (Chesterton et al., 2007). The measurement of PTs is reliable and valid, and is widely used in the clinic as well as scientific research to evaluate the effect of different therapeutic interventions (Persson et al., 2004; Prushansky et al., 2004; Chesterton et al., 2007) and to evaluate the pain modulating system (Walton et al., 2014).

The present systematic review aims to add to the current knowledge, by studying the effects of manual therapy interventions directed to both spinal and peripheral joints on pain thresholds of patients with musculoskeletal pain. In addition, this review aims to give an interpretation of the clinical significance of these effects. To date contradictory results of manual therapy on pain thresholds are reported on populations with various forms of spinal and peripheral musculoskeletal pain, and a systematic overview of the effect of manual therapy techniques on pain thresholds in patients with musculoskeletal pain is to the best of our knowledge still lacking.

2. Methods

This systematic review is reported following the PRISMA-guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (Moher et al., 2009). Methods of the analysis and inclusion criteria were specified in advance and not changed post hoc.

2.1. Eligibility criteria

Eligibility criteria were framed by the PI(C)O (Patient-Intervention-Comparison-Outcome) methodology. To be included in the present systematic review, articles had to report the results of clinical studies on pain thresholds effects (O) of manual therapy techniques (I) in patients with musculoskeletal pain (P).

2.2. Information sources and search strategy

To identify relevant articles, Embase, Medline OvidSP, Web-of-Science, Cochrane and Google scholar were searched until July 2013. Key words were derived from the PI(C)O-question and were converted to possible Mesh-terms if available. The search strategy in Embase was based on the following combination of terms:

Embase

('manipulative medicine'/exp OR kinesiotherapy/exp OR physiotherapy/exp OR physiotherapist/de OR (((manipulat* OR manual OR physical OR physio) NEAR/3 (medicine* OR therap* OR treat* OR musculoskelet*)) OR kinesiotherap* OR kinesitherap* OR physiotherap* OR ((joint* OR cervical OR lumbar OR shoulder OR musculoskelet* OR skelet* OR muscul* OR muscle* OR arm* OR forearm* OR back OR hand* OR leg* OR limb* OR neck OR pelvi* OR spinal OR spine OR wrist OR vertebra* OR

elbow) NEAR/3 (mobili* OR manipulat*))):ab,ti) AND ('pain parameters'/exp OR (((pain OR Nocicept*) NEAR/3 (modulat* OR parameter* OR threshold* OR control* OR inhibit* OR facilitat* OR toleran*)) OR (Endogen* NEAR/3 analges*)):ab,ti) AND ('musculoskeletal pain'/de OR 'arm pain'/de OR backache/exp OR 'chronic pain'/de OR 'hand pain'/de OR 'postural headache'/de OR 'leg pain'/exp OR 'limb pain'/de OR 'musculoskeletal chest pain'/de OR 'neck pain'/de OR 'nociceptive pain'/de OR 'pelvic girdle pain'/de OR 'pelvis pain syndrome'/de OR 'referred pain'/de OR 'shoulder pain'/de OR 'spinal pain'/de OR 'wrist pain'/de OR (('musculoskeletal system'/exp OR limb/exp OR back/exp OR buttock/de OR neck/exp OR trunk/de OR pelvis/exp) AND pain/exp) OR (musculoskelet* OR skelet* OR muscul* OR muscle* OR arm* OR forearm* OR back OR hand* OR leg* OR knee* OR ankle* OR hip OR thigh OR foot OR feet OR limb* OR buttock* OR Gluteal OR extremit* OR neck OR pelvi* OR shoulder* OR spinal OR wrist OR vertebra* OR elbow OR cervical OR lumbar OR Lumbosacral OR ((chronic OR nocicept* OR referred OR somatic OR tissue) NEAR/3 (pain)) OR backache OR ((postural OR othostat* OR position*) NEAR/3 headache*)):ab,ti) AND ('clinical study'/exp OR (clinical OR patient* OR trial):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Reference lists were hand-searched and relevant articles were included to make the search as complete as possible (two studies).s

2.3. Study selection

To be included in the review, articles had to meet the following criteria: 1) the study involves humans with musculoskeletal pain; 2) the topic of interest is the effect of manual therapy techniques on the function of pain thresholds; 3) written in English, German or Dutch; 4) full text reports of original research. If any of these four inclusion criteria were not met, the article was excluded. For the 2nd criterion, function of neurophysiological pain modulation mechanisms was operationalized as changes in (pressure or thermal) pain threshold. Manual therapy techniques included any manual technique used to move a spinal or peripheral joint with the aim to bring about an analgesic effect. Literature was searched and screened by the first author.

2.4. Risk of bias in individual studies

In order to determine the validity of the included studies, a quality assessment was carried out by two independent researchers (LV & JdV). LV obtained a PhD in the field of chronic pain. JdV is currently working as a PhD-researcher in the field of pain-motor interactions in patients with chronic non-specific neck pain. During the initial state of this process both researchers were unaware of each other results. After individual rating, results were compared and differences were discussed. If consensus could not be met, a definitive third opinion was provided by the last author (JN).

Quality appraising was carried out with use of checklists of the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk). The SIGN-group develops evidence based clinical practice guidelines in order to accelerate the translation of new knowledge into clinical action to improve patient-important outcomes. One aspect of the work of this group is the development of critical appraisal checklists. Articles were scored on a clearly focused research question, randomisation, concealment method, blinding of patients, therapists and/or data-analysts, differences between groups and the standardization, reliability and validity of outcome measurement. After pooling the results, the overall quality of

evidence for each outcome was rated with the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach in which study limitations, imprecision, inconsistency of results, indirectness of evidence and the likelihood of publication bias was weighed against a large amplitude of effect, dose response relationships and the likelihood that confounders minimized the effect. The overall quality of the evidence was graded on a 4 point-scale (high, moderate, low, very low) (www.gradeworkinggroup.org). Grading the evidence was done by the first author (LV).

2.5. Data items and collection

Information was extracted from each included study and presented in an evidence table (Table 2). The evidence table consisted of the following items: (1) study design; (2) sample size; (3) characteristics of study participants; (4) outcome measure; (5) intervention; (6) main results; (7) discussion and; (8) methodological quality. Data-extraction was done by LV. Changes in pain-threshold and/or pain tolerances were calculated as percentages of change.

Due to differences between the included studies with respect to pain models/type of patients enrolled (spinal and peripheral joints) and manual therapy techniques (mobilization and manipulation), pooling of data and performing a meta-analysis was considered inappropriate.

2.6. Summary measures

Principal outcome measure were changes in pain threshold. In the included studies, these measures were taken with pressure algometry and/or thermo algometry. Pre-versus post changes in algometric values were calculated in percentages.

3. Results

3.1. Study selection

A total of 6362 studies were identified (Fig. 1). After removal of duplicates and two screening rounds, 14 studies remained.

Table 1
Methodological quality of the included studies (1 = a clearly focused and appropriate question is addressed, 2 = assignment of subjects to treatment groups is randomized, 3 = an adequate concealment method is used, 4 = subject and investigators are kept blind about treatment allocation, 5 = treatment and control groups are similar at the start of the trial, 6 = groups differ only on the treatment under investigation, 7 = outcomes are measured in a standard, valid and reliable way, 8 = percentages of drop-outs are reported, 9 = subjects are analyzed in groups to which they were allocated, 10 = results are comparable for all sites at which the study is carried out. + = YES, - = No, NA = not applicable.

	1	2	3	4	5	6	7	8	9	10	Total
Collins et al. (2004)	+	+	+/−	+/−	+	+	+	+	NA	NA	+
Fernández-Camero et al. (2008)	+	+	+/−	+/−	+	+	+	+	NA	NA	+
Maduro de Camargo et al. (2011)	+	+	+/−	+/−	+	+	+	+	NA	NA	+
Mansilla-Ferragut et al. (2009)	+	+	+/−	+/−	+	+	+	+	NA	NA	+
Moss et al. (2007)	+	+	+	+	+	+	+	+	NA	NA	++
Paungmali et al. (2003)	+	+	+/−	+/−	+	+	+	+	NA	NA	+
Sterling et al. (2001)	+	+	+	+	+	+	+	+	NA	NA	++
Sterling et al. (2010)	+	+	+/−	+/−	+	+	+	+	NA	NA	+
Teys et al. (2008)	+	+	+/−	+/−	+	+	+	+	NA	NA	+
Vicenzino et al. (1996)	+	+	+/−	+/−	+	+	+	+	NA	NA	+
Vicenzino et al. (2001)	+	+	+/−	+/−	+	+	+	+	NA	NA	+
Villafañe et al. (2001)	+	+	+/−	+/−	+	+	+	+	NA	NA	+
Villafañe and Silva (2012)	+	+	+	+	+	+	+	+	NA	NA	++
Yeo & Wright (2011)	+	+	+/−	+/−	+	+	+	+	NA	NA	+

3.2. Risk of bias and level of evidence

The risk of bias and the level of evidence of the different studies are reported in Table 1. In 11 out of 14 cases (79%) the researchers agreed on methodologic quality. After a second review and a comparison of the two differences the reviewers reached complete consensus. The final score of each study is presented in Table 1. Methodological quality of the included studies ranged between moderate (+, N = 11) and good (++, N = 3). Most studies lacked an a priori power analysis and had poor blinding of participants and/or researchers.

3.3. Study characteristics

For each study, the characteristics for which data were extracted (study design, sample size, intervention, main results, discussion, methodological quality) are presented in Table 2.

A total of 450 participants were included in the fourteen studies of which 281 received some form of manual therapy intervention. Types of manual therapy techniques and patient groups differed across studies (Table 2).

In five studies a comparison was made between two groups of which one group received a manual therapy intervention and the other received some form of sham (Mansilla-Ferragut et al., 2009; Maduro de Camargo et al., 2011; Sterling et al., 2010; Villafañe et al., 2001 & Villafañe and Silva 2012). In eight studies a randomized, blinded, within subjects repeated measures design was used in which one group received both a manual therapy intervention and some form of sham (Collins et al., 2004; Fernández Carnero et al., 2008; Moss et al., 2007; Paungmali et al., 2003; Sterling et al., 2001; Teys et al., 2008; Vicenzino et al., 1996; 2001; Yeo and Wright 2011).

Pressure-pain threshold (PPT) measurement is used as *outcome measure* in all of the included studies, while thermal pain threshold (TPT) measurement in five studies (Paungmali et al., 2003; Collins et al., 2004; Fernández Carnero, 2008; Sterling et al., 2001; 2010). In the included studies, PPT's and TPT's are seen as outcome measures reflecting the effect of some form of manual therapy intervention on the modulation of pain. In all of the studies an identical measurement protocol was used. PPT's and TPT's were measured with digital devices of which reliability was established in earlier studies. Measurements were carried out three times of which the mean was taken for further analysis.

The activation in the pain modulation system not only has local effects, but potentially also generates widespread analgesia (i.e. at remote body parts). To verify this phenomenon in some of the studies, PPT's were taken from the local painful body part as well as from remote body parts (ipsilateral and/or contralateral) (Moss et al., 2007; Fernández-Carnero et al., 2008; Sterling et al., 2010; Maduro de Camargo et al., 2011). Hence, conclusions on both local and widespread pain modulation effects of manual therapy interventions can be drawn.

3.4. Local effects

In eleven of the fourteen studies (77%) a *significant increase* of PPT values was found after a manual therapy intervention. In three of these studies the percentage of change in PPT was less than 15%.

In eight studies PPT's increased 15% or more. An increase of >15% in PPT's is considered an clinically important change (Chesterton et al., 2007; Moss et al., 2007; Vicenzino et al., 1998; Sterling et al., 2001). Of these, seven studies were of moderate methodological quality (+) according to the SIGN-criteria. The clinical pain models used in these studies were: epicondylitis lateralis (3x) (Vicenzino et al., 1999; Paungmali et al., 2003;

Table 2

Evidence table (RCT = randomized clinical trial, SD = standard deviation, PPT = pressure pain threshold, TPT = thermal pain threshold, + = moderate methodological quality, ++ = good methodological quality, GRADE $\oplus$ = very low, $\oplus\oplus$ = low, $\oplus\oplus\oplus$ = moderate, $\oplus\oplus\oplus\oplus$ = high).

Author	Study design	Sample size	Characteristics of participants	Outcome measure	Intervention	Main results	Discussion	Methodological quality and grade-scoring
Collins et al. (2004)	RCT (randomized, double blind, within subjects repeated measures design)	14 (8 woman; average age: 28.28, 18–50)	Subacute grade II ankle sprain	Pressure and thermal pain threshold over the proximal third of m. tibialis anterior, Directly distal to the lateral malleolus and directly anterior to the maleolus muscle.	Mulligan's mobilization with movement technique of the ankle joint	No significant effect	No power analysis included	+ $\oplus\oplus\oplus$
Fernández-Camero et al. (2008)	RCT (randomized, single blind, within subjects repeated measures design)	10 (5 woman; average age: 42, SD 6)	Epicondylitis lateralis humeri	Pressure and thermal pain threshold over the lateral epicondyle of both elbows.	High velocity-thrust manipulation of cervical spine	Significant bilateral effect ($P = 0.01$) for PPT. PPT increased 44.2% ($\pm$19%) for the ipsilateral side and 17.7% ($\pm$15.7%) for the contralateral side. No significant changes for TPT.	No power analysis included	+ $\oplus\oplus\oplus$
Maduro de Camargo et al. (2011)	RCT (cervical spine manipulation vs no intervention)	37 (17 in intervention group; average age: 31,6, 23–45)	Mechanical neck pain	Pressure pain threshold over m. trapezius homo- and heterolateral to the side of manipulation, m. deltoideus and C5 spinous process.	High velocity-thrust manipulation on C5–C6	Significant effect ($P = 0.010$ for PPT over m. deltoideus (ipsilateral and contralateral) and C5 spinous process ($P = 0.025$). PPT increases 9.4% (ipsilateral), 6,3% (contralateral and 4,4% (C5 spinous process) No siginificant effect for PPT over m. trapezius	No power analysis included	+ $\oplus\oplus\oplus$
Mansilla-Ferragut et al. (2009)	RCT (cervical spine manipulation vs manual contact)	37 woman (18 in intervention group; average age: 36, SD 7)	Mechanical neck pain	Pressure pain threshold over sphenoid bone.	High velocity thrust manipulation of the atlanto-occipital joint	Significant effect ($P < 0.05$) for PPT over sphenoid bone. PPT increases 8%.		+ $\oplus\oplus\oplus$
Moss et al. (2007)	RCT (randomized, double blind, within subjects repeated measures design)	38 (25 woman; average age: 65, SD 11)	Knee osteoarthritis	Pressure pain threshold over the tenderest medial aspect of the affected knee and over the medial side of the ipsilateral heel.	Antero-posterior mobilization of the tibio-femoral joint	Significant effect ($P = 0.008$) for PPT over knee joint and ipsilateral heel. PPT's increases 27.3% ($\pm$3.14%) for knee joint and 15.3% ($\pm$3.08%) for heel.		++ $\oplus\oplus\oplus$
Paungmali et al. (2003)	RCT (double blind, within subjects, repeated measures design)	24 (7 woman; average age: 48.5, SD 7,2)	Epicondylitis lateralis humeri	Pressure and thermal pain threshold over the most sensitive point of the lateral epicondyle.	Mobilization with movement (Mulligan) of the elbow	Significant effect ($P = 0.017$) for PPT over elbow joint. PPT increases 15.4% No significant effect for TPT.	No power analysis included	+ $\oplus\oplus\oplus$
Sterling et al. (2001)	RCT (randomized, double blind, within subjects, repeated measures design)	30 (16 woman; average age: 35.77, SD 14.92)	Chronic cervical spine pain	Pressure and thermal pain threshold over the symptomatic segment.	Grade III antero-posterior mobilization on C5–C6	Significant effect ($P = 0.0001$) for PPT over symptomatic pain side. PPT increases 22.55%		++ $\oplus\oplus\oplus$

Table 2 (*continued*)

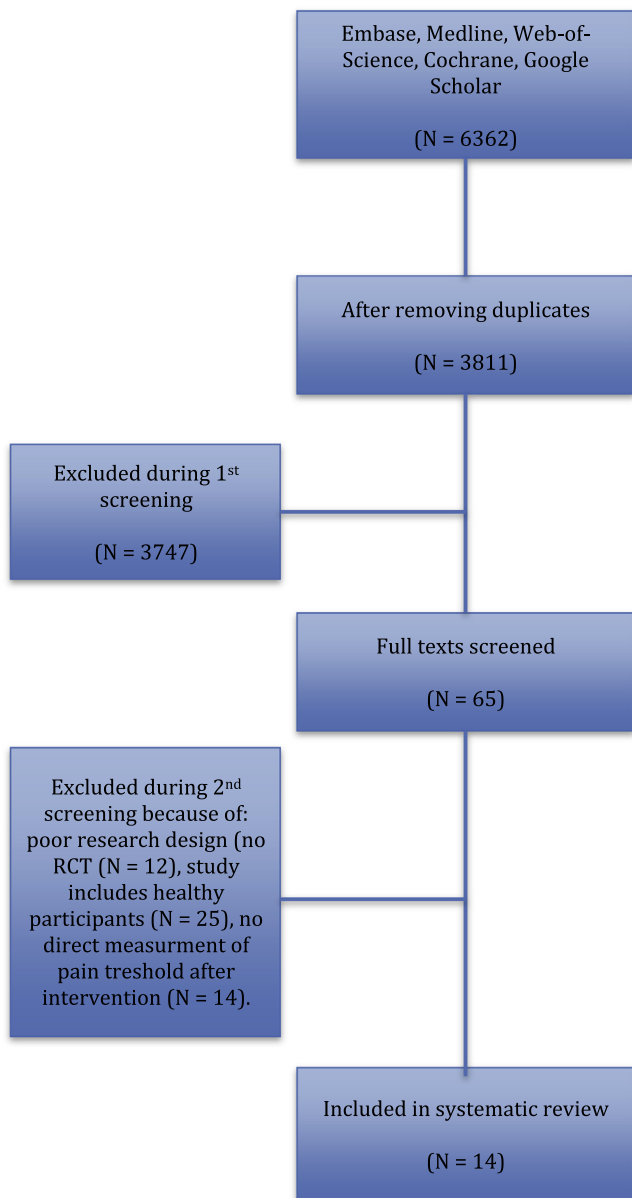| Author	Study design	Sample size	Characteristics of participants	Outcome measure	Intervention	Main results	Discussion	Methodological quality and grade-scoring
						(±2.4%) No significant effect for TPT		
Sterling et al. (2010)	RCT (Mobilisation of cervical spine vs manual contact)	39 (22 in intervention group, 14 woman; average age: 40.5, SD 13.5)	Chronic whiplash associated disorder	Pressure and thermal pain threshold over the spinous process of C6, the median nerve trunk at the elbow bilaterally and at the bilateral tibialis anterior.	Lateral glide mobilization on C5–C6	No significant difference between groups on all locations. Mean increases of PTT's are 24.1% in mobilization group and 21% in manual contact group.	Single blinding	+ ⊕⊕⊕
Teys et al. (2008)	RCT (randomized, double blind, within subjects repeated measures design)	24 (13 woman; average age: 46.1, SD 9.86)	Anterior shoulder pain	Pressure pain threshold over the most sensitive point over the anterior aspect of the shoulder.	Mobilization with movement (Mulligan) at the shoulder	Significant effect (P = 0.04) for PPT over shoulder joint. PPT increases 20,1%	No power analysis included	+ ⊕⊕⊕
Vicenzino et al. (1996)	RCT (randomized, double blind, within subjects repeated measures design)	15 (8 woman; average age: 44, 22,5–62)	Epicondylitis lateralis humeri	Pressure pain threshold over the lateral epicondyl.	Lateral glide mobilization on C5–C6	Significant effect (P < 0.05) for PPT over elbow joint. PPT increases 25%	No power analysis included	+ ⊕⊕⊕
Vicenzino et al. (2001)	RCT (repeated measures cross over design)	24 (10 woman; average age: 46.43, SD 1.68)	Epicondylitis lateralis humeri	Pressure pain threshold over the lateral epicondyl.	Mobilization with movement (Mulligan) at the elbow	Significant effect (P < 0.05) for PPT over elbow joint. PPT increases 10.26%		+ ⊕⊕⊕
Villafañe et al (2001)	RCT (mobilization vs sham)	29 woman (14 in intervention group; average age: 81.5, SD 2.24)	Carpometacarpal osteoarthritis	Pressure pain threshold over CMC joint and scaphoid bone	Posterior-anterior mobilization of carpometacarpal (CMC) joint	Significant effect (P = 0.023) for MPT over carpometacarpal joint and scaphoid bone. PPT increases 36.5% and 34.9% respectively	No power analysis included. More than 20% of participants excluded from analysis.	+ ⊕⊕⊕
Villafañe and Silva (2012)	RCT (mobilization of trapeziometacarpal joint vs sham	28 (14 in intervention group . average age: 81.43, SD 5.11)	Carpometacarpal osteoarthritis	Pressure pain threshold over the trapeziometacarpal joint, hamate bone and scaphoid bone.	Maitlands passive accesory mobilization	No significant effect of intervention directly after application.		++ ⊕⊕⊕
Yeo & Wright (2011)	RCT (randomized, double blind, within subjects, repeated measures design)	13 (3 woman; average age: 29.5, (20–49 years)	Supination sprain of the ankle. Average duration: 5 weeks (2–10 weeks)	Pressure pain threshold at the most tender point at the ankle joint line	Maitlands passive accesory mobilization of the talocrural joint	Significant effect (P = 0.000) for PPT over the ankle joint line. PPT increases 17.8%		+ ⊕⊕⊕

Fig. 1. Flow diagram of the conducted search.

3.5. Widespread effects

In three out of seven studies in which a significant increase in PPT's was found, researchers also measured PPT's on remote body parts (Moss et al., 2007; Férnandez-Carnero et al., 2008; Maduro de Camargo et al., 2011). In one study bilateral measurements were taken from the lateral aspects of the elbow in a population of patients with epicondylitis lateralis (Férnandez-Carnero et al., 2008). After a high velocity-thrust manipulation of C5/C6, PPT's on the ipsilateral side increased with 44.2%. On the contralateral side PPT's increased with 17.7%. A second study in which PPT's were performed on the m. trapezius (ipsi- and contralateral), m. deltoïdeus (ipsi- and contralateral) and C5 spinous process reveals significant, although not clinical relevant, besides for PPT's at the m. trapezius. In a third study researchers measured PPT's on the affected side and on a more remote part on the same limb (Moss et al., 2007). PPT's decreased with 27.3% on the painful side (knee), and with 15.3% on the remote body part.

3.6. Musculoskeletal pain syndrome

Different pain models were used in the included studies. All were of musculoskeletal origin and ranged from spinal (e.g. mechanical neck pain), upper extremity (e.g. epicondylitis lateralis) to lower extremity (e.g. knee osteoarthritis) pain syndromes. Consistent significant results were found in studies involving shoulder, elbow or knee related pain syndromes. In all of these significant effects were found. Inconsistent results were found in the studies involving patients with neck pain. In two out of four positive results were found, in two studies no significant results were found (although in one study substantial increases in PPT's were found in both treatment arms).

The two studies (Collins et al., 2004; Villafañe and Silva, 2012) that failed to find significant effect included peripheral joint problems (ankle sprain or carpometacarpal osteoarthritis). The study involving patients with carpometacarpal osteoarthritis in which a significant effect was found excluded 20% of the participants.

4. Discussion

The current evidence shows moderate analgesic effects of manual therapy on PPTs in patients with different forms of musculoskeletal pain. No significant changes in TPTs were found. Although the results should be interpreted with caution, as there are also studies showing no (clinical significant) effect, they support the theory that manual therapy triggers analgesic mechanisms (Bialosky et al., 2009). However, when a minimum clinical significant change of 15% in PT is chosen, a mixed picture emerges as only half (seven out of thirteen) studies show a significant result, applying this clinical criterion. This clinical interpretation of the current evidence is therefore more conservative than, that made in the reviews of Millan et al. (2012) and Coronado et al. (2012). Millan and colleagues conclude in their review that manual therapy has analgesic effects in populations in which pain is experimentally induced. This forms a major limitation regarding the extrapolation of their findings to clinical populations. The same argument applies to the review of Coronado et al. (2012), in which no distinction is made between clinical and healthy populations. In both reviews no conclusions are drawn on the clinical significance of the found results. The current review adds knowledge on these issues and underlines the inconsistent results.

The importance of this notion can however be interpreted as subordinate from a clinical point of view as in clinical practice

Fernández-Carnero et al., 2008), knee osteoarthritis (1x) (Moss et al., 2007), anterior shoulder pain (1x) (Teys et al., 2008), carpometacarpal osteoarthritis (1x) (Villafañe et al., 2001), ankle sprain (1x) (Yeo and Wright 2011) and chronic neck pain (1x) (Sterling et al., 2001). Manual therapy interventions used in these studies were: high velocity-thrust technique at the cervical spine (1x), (different forms of) articular mobilization (6x). PPT's changes were observed at the treated locations.

In three out of fourteen studies *no significant effects* were found. Only one was of good methodological quality (++). In the study of Sterling et al. (2010) no significant effect was found between a manual intervention group versus a manual contact group although in both groups PPTs changed substantially (24% and 21% respectively). Pain models used in the 'not significant group' were: subacute grade II ankle sprain (1x), chronic whiplash disorder (1x) and carpometacarpal osteoarthritis (1x). In all three studies some form of articular mobilization was used.

manual therapy articular mobilizations and/or manipulations are seldom being used as an isolated intervention. In most instances they are embedded in treatment plans which contain myofascial techniques, therapeutic exercises and/or forms of communication as well. One could assume that combining various strategies imparts a synergistic effect on the brain-orchestrated analgesic system.

From a theoretical perspective the results support the neurophysiological explanation of the positive effects of manual therapy as described by Bialosky et al. (2009), although no further insights are gained on exactly what spinal and/or central mechanisms are responsible for the results. The majority of positive results are reported at the symptomatic place. Therefore a local pain modulating effect of manual therapy must be concluded. In only three studies a regional (ipsi- and/or at the contralateral side) is reported. Therefore stimulation of central pain modulating systems is to date unclear. Further research on this point is needed.

The results show no straightforward relation between intensity of the manual technique used (manipulation versus some form of mobilization) and/or the side of application of the manual stimulus on PPT's. Therefore no conclusions can be drawn regarding the type of manual therapy techniques and/or which treatment side should be chosen. From a clinical point of view this warrants further research as some manual therapy techniques imply the risk of side effects and even complications. Also no firm conclusions on the relationship between the origin of complaints (traumatic versus insidious) or the duration of symptoms and PPTs can be drawn from the results as the results are mixed or no specific data are reported in the included studies.

The methodological quality of the included studies was moderate to good with the majority of studies lacking proper power analysis or suffering poor blinding. To expand on the current knowledge base, studies which focuses on the relation between dosage and response, the remote effects of manual therapy on PT's, the cumulative effects of manual therapy interventions and the cumulative effects of different treatment modalities (manual therapy techniques combined with exercises and/or pain physiology explanation) on pain thresholds are needed.

5. Conclusion

Moderate evidence indicated that manual therapy decreased local pressure pain thresholds in musculoskeletal pain, immediately following intervention. No significant changes occured on thermal pain threshold values. The clinical relevance of these effects remains contradictory and therefore unclear.

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