The initial effects of knee joint mobilization on osteoarthritic hyperalgesia

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Abstract
Physiotherapists often employ lower limb joint mobilization to reduce pain and increase function. However, there is little experimental data confirming its efficacy. The purpose of this study was to investigate the initial effects of accessory knee joint mobilization on measures of pain and function in individuals with knee osteoarthritis. The study employed a double-blind, controlled, within-subjects repeated-measures design. Thirty-eight subjects with mild to moderate knee pain participated. The effects of a 9-min, non-noxious, AP mobilization of the tibio-femoral joint were compared with manual contact and no-contact interventions. Pressure pain threshold (PPT) and 3-m 'up and go' time were measured immediately before and after each intervention. Results
demonstrated a significantly greater mean (95% CI) percentage increase in PPT following knee joint mobilization (27.3% (20.9-33.7)) than after manual contact (6.4% (0.4-12.4)) or no-contact (-9.6% (-20.7 to 1.6)) interventions. Knee joint mobilization also increased PPT at a distal, non-painful site and reduced 'up and go' time significantly more (-5% (-9.3 to 0.8)) than manual contact (-0.4% (-4.2 to 3.5)) or no-contact control (+7.9% (2.6-13.2)) interventions. This study therefore provides new experimental evidence that accessory mobilization of an osteoarthritic knee joint immediately produces both local and widespread hypoalgesic effects. It may therefore be an effective means of reducing pain in this population. © 2006 Elsevier Ltd. All rights reserved.

Keywords: Knee; Osteoarthritis; Mobilization; Pressure pain threshold.

1. Introduction

The application of passive accessory movements to painful joints has long underpinned manual therapy practice. Although spinal and peripheral joint mobilization continues to be applied extensively in clinical practice, there is little experimental data to substantiate its effectiveness in reducing pain or improving function. Evidence for the efficacy of lower limb mobilization is particularly scarce, with the majority of studies of peripheral joints using an upper limb model (Vicenzino et al., 1996; Paungmali et al., 2003). To date, just two studies explore the hypoalgesic effects of lower limb mobilization, both of which focus on the ankle joint (Collins et al., 2004; Yeo and Wright, 2004). There is consequently an urgent need for further lower limb studies.

Although scientific literature has begun to characterize the effects of spinal manual therapy (Koes et al., 1996; Haldeman, 1999; Wright, 2002), there are only a few studies which investigate the hypoalgesic effects of peripheral joint mobilization techniques. In subjects with sub-acute ankle injury, an antero-posterior (AP) mobilization of the talo-crural joint immediately and significantly increased pressure pain threshold (PPT) and increased dorsiflexion range of motion (Yeo and Wright, 2004). This mobilization-induced hypoalgesia was significantly more effective than either an identical procedure involving static manual contact, or a control procedure with no contact.

Using similar methodology for subjects with lateral epicondylalgia, an elbow mobilization with movement technique significantly reduced hyperalgesia more effectively than either the manual contact or no-contact control procedures (Vicenzino et al., 2001). Similarly, in an animal study, knee joint mobilization reduced capsaicin-induced hyperalgesia when compared to either manual contact or no-contact control procedures (Sluka and Wright, 2001). These results, from humans and animals, support the hypothesis that peripheral mobilization reduces hyper-algesia both locally and at a distant site.

Few studies have investigated the initial effects of mobilization on motor function. Vicenzino et al. (2001) found that elbow mobilization with movement not only reduced pain but also increased pain-free grip strength in subjects with chronic tennis elbow. A similar increase in pain-free grip strength was found following a cervical glide mobilization in a similar subject group (Vicenzino et al., 1998). In a study of subjects with chronic, nonspecific neck pain, Sterling et al.
(2001a) found that cervical mobilization decreased hyperalgesia and also reduced over-activity of the superficial neck flexors during the cranio-cervical flexion test, suggesting improved activation of deep cervical flexor muscles. There have been no studies exploring the effects on motor function of lower limb joint mobilization.

A number of mechanisms have been proposed to explain how the hypoalgesic effects of passive joint mobilization may be mediated. Local mechanical disturbance may modify the chemical environment and thereby alter concentrations of inflammatory mediators (Sambajon et al., 2003). Movement may also trigger segmental inhibitory mechanisms (Melzack and Wall, 1999). In addition, it has been hypothesized that mobilization may activate descending pain inhibitory systems, mediated supraspinally (Wright, 2002; Souvlis et al., 2004). Human studies have demonstrated that joint mobilization produces rapid hypoalgesia with concurrent sympathetic nervous system and motor system excitation, a pattern similar to that generated by direct stimulation of the periaqueductal gray matter (Vicenzino et al., 1998; Sterling et al., 2001a). Recent animal studies show that the analgesia produced by knee joint mobilization involves serotonin and noradrenaline receptors in the spinal cord, thereby supporting a role for descending pain modulatory systems (Skyba et al., 2003). There is, however, a need for further studies to analyse the respective roles of local, segmental and supraspinal mechanisms in the mediation of hypoalgesia following joint mobilization.

There is little experimental data exploring the initial effects of lower limb joint mobilization. The purpose of this study therefore was to investigate the immediate effect of passive knee joint mobilization on measures of pain and function in individuals with chronic knee osteoarthritis. In addition, the study sought to explore in humans the animal model of mobilization-induced hypoalgesia demonstrated by Sluka and Wright (2001). Consequently, methodology similar to that used in previous clinical and animal models of joint mobilization was applied, whereby the effects of 9 min of joint mobilization were compared with those of manual contact and no-contact control procedures (Vicenzino et al., 1998, 2001; Yeo and Wright, 2004; Sluka and Wright, 2001).

2. Methods
The study employed a double-blind, controlled, repeated-measures design, with all within-subject factors.

2.1. Participants
Volunteers reporting mild to moderate pain from knee osteoarthritis were sought. Forty subjects from the community in Perth, Western Australia, responded to advertisements placed with local newspapers, hospital outpatient departments and community physiotherapy groups. Following a brief telephone interview, volunteers were included if they fulfilled the American College of Rheumatology classification for knee osteoarthritis (classification-tree format) (Altman et al., 1986). This requires the regular experience of knee pain, plus either osteophytes on radiograph or a combination of morning stiffness, crepitus and age 40 years or above. This classification system has demonstrated good reliability and validity (Altman et al., 1986) and is widely used as a clinical diagnostic tool (Hochberg et al., 1995). Volunteers were requested to bring their most recent knee X-rays with them to the first session. This study also required
participants to be able to walk short distances, with or without an aid. Volunteers were excluded if they had recently undergone lower limb surgery, had co-existing inflammatory or neurological conditions, experienced altered sensation around their knee, or exhibited cognitive difficulties.

Ethical approval was obtained from Curtin University Human Research Ethics Committee & Royal Perth Hospital Human Ethics Committee. All participants provided written informed consent.

2.2. Outcome measures (dependent variables)

Three pain-related measures were employed, together with two measures of function.

2.2.1. Pain-related measures

1. Pressure pain threshold (PPT) was measured using a digital pressure algometer (Somedic AB, Farsta, Sweden), in accordance with similar clinical studies (Vicenzino et al., 2001; Collins et al., 2004; Yeo and Wright, 2004). This measure has demonstrated good reliability in a number of previous investigations, demonstrating intra-class correlation coefficients (ICCs) between 0.95 and 0.99 (Vicenzino et al., 2001; Collins et al., 2004). PPT has been defined as the lowest stimulus intensity at which a subject perceives mechanical pain (Vanderweeen et al., 1996). Hypoalgesia, or decreased response to mechanical pain stimuli, therefore exhibits as increased PPT. The most tender point on the medial aspect of the subject’s affected knee was palpated, marked and photographed to ensure standardization between sessions. With the subject in side-lying, a 1 cm² algometer probe was used to apply pressure at 90° to the skin, at a rate of 40 kPa/s (Fig. 1). Subjects were instructed to activate a button when the sensation of pressure had clearly become one of painful pressure and the resultant value was recorded. Subjects were given one practice followed by three recorded trials before, and three immediately after each experimental condition. Change in mean PPT was calculated for analysis. A series of PPT readings was taken in the same manner from the medial ipsilateral heel in order to provide control data from a distal, non-pathological site.

Nota de revisor: a seguir apresenta-se uma imagem cuja legenda é: Fig. 1. Subject positioning for pressure pain testing, showing standardized patient positioning plus the use of tape to standardize knee angle. The pressure algometer (Somedic AB, Sweden) was applied to a pre-assessed and marked point on the medial aspect of the knee.
2. A horizontal 10 cm visual analogue scale (VAS), with end-points marked 'no pain' and 'worst pain imaginable', was administered immediately after the timed 'up and go' test, before and after each experimental condition, with difference scores used for analysis.

3. The self-administered Western Ontario and McMaster Universities (WOMAC) knee osteoarthritis index pain subscale (Bellamy et al., 1988) was used to evaluate knee pain at baseline and in the 24 h before and after each test session. The pain index comprises five written questions, for which there is a choice of five categorical responses, each assigned a numerical value between 0 and 4. Possible total scores for the pain subscale therefore range between 0 and 20, with a higher score indicating greater pain. This disease-specific index has shown excellent validity, reliability and repeatability in numerous studies (Theiler et al., 1999; Angst et al., 2001; Parent and Moffet, 2002).

2.2.2. Function-related measures

1. A 3m timed 'up and go' walk test (Podsiadlo and Richardson, 1991) was applied before and after each experimental condition. The test measured time taken to stand from a standard arm-less chair, briskly walk to a 3 m mark, turn and return to sit. The test has demonstrated high inter and intra-rater reliability (ICC 0.99) with elderly arthritic populations (Podsiadlo and Richardson, 1991; McMeeken et al., 1999). In order to assess more specifically the high load sit-to-stand phase, a lap-timer stop-watch was used to record sit-to-stand time as well as total time (Wall et al., 2000). It was found that two practices were required before one reliable trial could be recorded. Percentage change was used for analysis.

2. The self-administered WOMAC function subscale (Bellamy et al., 1988) was completed at the first session in order to provide baseline functional data. The index comprises 17 written questions, presented in Likert-scale format, identical to the pain subscale. Total possible scores range from 0 to 68, with a higher score demonstrating greater disability.

2.3. Experimental conditions (independent variables)

Each subject experienced all three experimental conditions in random order over three sessions. All conditions were applied for a total of 10 min,
comprising three sets of 3 min, alternating with 30-s rests. All verbal instructions and positioning were strictly standardized using a script.

1. The treatment condition consisted of a large-amplitude, AP glide of the tibia on the femur (Maitland, 1990). The subject was positioned comfortably in supine, knees in slight flexion, supported on a pillow. The therapist stabilized the femur with one hand whilst applying pain-free, oscillatory glides of the proximal tibia with the other.

2. The manual contact condition precisely reproduced the hand positioning of the treatment condition without applying any movement. All interactions, procedures and timings were identical.

3. The no-contact control condition reproduced all interactions, procedures and timing, without applying any manual contact.

2.4. Main procedures

Subjects attended at the same time of day on three occasions, each separated by at least 48 h in order to control for carry-over effects (Vicenzino et al., 1998). Subjects were requested to continue with their normal medications for the duration of the study. At the first session, preliminary data about knee pain, chronicity, co-morbidities, medications and functional status were collected using a specially designed questionnaire together with WOMAC pain and function subscales. Knee X-ray reports were reviewed by the primary researcher when needed to fulfil ARC criteria. A brief physical examination evaluated knee joint range of movement and sensation, and ensured that all subjects could differentiate between sharp and blunt. In the case of bilateral knee pain, the subject nominated the most painful side.

At subsequent sessions, the subject was asked to complete just the WOMAC-pain subscale before testing. Following this, the assessing researcher administered the timed 'up and go' test plus VAS, followed by heel and knee PPT measurements. On completion, in order to remain blind to condition, the assessor left the room whilst an experienced manipulative physiotherapist applied one of the three experimental conditions. Condition order was pre-randomized and constrained in order to ensure application of an equal spread of conditions between days. Immediately following the procedure, the assessor returned to repeat PPT, timed ‘up and go’ and VAS measurements. Subjects were asked to complete a WOMAC-pain subscale 24 h after the session.

The assessor remained blind to condition throughout the data collection phase. In order to facilitate subject blinding and reduce potential interactions, discussion between researchers and subjects was minimized at all times, relaxing music played and subjects asked to close their eyes during procedure application. No feedback was given on performance until after the final session. The extent of subject blinding was assessed through a short, self-administered, written post-experiment questionnaire, similar to previous studies (Vicenzino et al., 1998). Subjects were asked to indicate whether they had experienced a physiotherapy treatment in any of the sessions and, if so, in which session.

2.5. Reliability
A variety of measures were employed to ensure reliability at all stages of testing, as described in methodology sections above. Since reliable PPT measurement requires skilled application (Vicenzino et al., 1998; Sterling et al., 2001a), the assessor spent considerable time refining this skill. A pilot study was performed with five subjects who fulfilled the study inclusion/exclusion criteria. Test-retest reliability was calculated using ICC (model 3,k) for mean PPT values measured before and after application of the control condition (no-contact). Both ICC (95% CI) and standard error of measurement (SEM) for pilot data \((n = 5)\) indicated reasonable levels of intra-subject reliability for both knee PPT (ICC 0.94 (0.55-0.99); mean 251.84 kPa; SEM 23.90 kPa) and heel PPT (ICC 0.94 (0.59-0.99); mean 294.61 kPa; SEM 17.78 kPa). As shown in Table 1, values for the main study \((n = 38)\) showed further improvement both in reliability and measurement error. Reliability analyses for timed 'up and go' values showed lower, although adequate, reliability (TUG total ICC 0.79 (0.67-0.88); TUG sit-to-stand ICC 0.57 (0.40-0.76)).

Nota de revisor: a seguir apresenta-se uma tabela constituída por 7 colunas e 3 linhas e cuja legenda é: Table 1 Test-retest reliability values for main study \((n = 38)\), demonstrating intra-class correlation coefficient (ICC) (model 3k), with 95% confidence interval (95% CI), and standard error of measurement values for mean pressure pain threshold (PPT) measured before and after the no-contact control condition.

<table>
<thead>
<tr>
<th></th>
<th>ICC</th>
<th>95% CI - Low</th>
<th>95% CI - High</th>
<th>Standard error of measurement (kPa)</th>
<th>Mean (kPa)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee PPT</td>
<td>0.98</td>
<td>0.96</td>
<td>0.99</td>
<td>16.69</td>
<td>247.51</td>
<td>117.99</td>
</tr>
<tr>
<td>Heel PPT</td>
<td>0.98</td>
<td>0.96</td>
<td>0.99</td>
<td>15.65</td>
<td>264.25</td>
<td>110.66</td>
</tr>
</tbody>
</table>

3. Data management and analysis

Data were analysed using SPSS statistical package (version 11.0, SPSS, Chicago, Illinois). The alpha level was set at \(P<0.05\).

3.1. Normality

PPT data showed normal distribution for each condition, with low skewness values. Timed 'up and go' data were also normally distributed and required no transformations. Since all underlying assumptions were found to be valid, parametric analysis was applied to these dependent variables. VAS data, however, were highly skewed due to the large number of subjects who experienced no pain either before or during the functional test. Non-parametric statistics were therefore applied to these data.

3.2. Main analyses

Percentage change between pre- and post-condition values was used as the primary dependent variable. Since PPT measurements can vary widely between individuals and between areas of the body, use of percentage change allowed meaningful comparison of PPT results with similar studies (Vicenzino et al., 1998, 2001; Sterling et al., 2001a).

[113]
Although there has been some questioning of percentage change analysis (CPMP, 2003), Overall and Ashby (1991) demonstrated that actual change and percentage change data are associated with equally low levels of Type 1 error in randomized experimental studies. A recent study has additionally advised that primary analyses of change from baseline should include means adjustment through use of baseline values as a covariate (CPMP, 2003).

Consequently, repeated measures analysis of covariance (ANCOVA) was used to analyse differences between percentage change in knee PPT, heel PPT, WOMAC-pain and 'up and go' times, using pre-condition mean as the covariate. Change in VAS scores were analysed using Friedman's Two-Way ANOVA by Ranks.

In similar fashion to previous algometry studies (Vicenzino et al., 1998; Sterling et al., 2001a), and in line with studies using both WOMAC and pain-VAS (Bird and Dickson, 2001; Gallagher et al., 2001; Bellamy et al., 2005) a 15% difference was considered the minimum required to demonstrate a clinically significant change in PPT.

Power analyses were performed using the Power and Precision (1.20) package. For the main study, power of 0.93 was calculated for the primary PPT measurements, using a sample of 38 subjects. Power was smaller for the secondary measure of TUG (0.69).

4. Results

Comparability between pre-condition PPT means was evaluated, with no significant difference found between treatment, manual contact control and no-contact control conditions ($F_{2,74} = 1.02, P = 0.365$). Baseline data was also analysed according to day of testing. Again, no significant difference was found ($F_{2,74} = .303, p = 0.740$), suggesting avoidance of systematic bias. In order to evaluate carry-over effects between sessions, WOMAC pain data were analysed for differences between mean values for 24 h before, 24 h after and follow-up for each experimental condition. No significant differences were found.

4.1. Subjects

Of the 40 initially recruited, two subjects were unable to complete the study. One subject suffered a knee injury before starting the study, while a second was unable to attend due to altered family commitments.

The final study comprised 13 male and 25 female subjects with a mean age of 65 years, 4 months (SD 11 years; range 40-87 years). Extent of disease chronicity in the current study was similar to that of comparable studies, with 47.4% of subjects reporting knee pain for at least 5 years. However, when baseline WOMAC scores were compared with several recent knee osteoarthritis studies, subjects in the current study reported significantly lower levels of functional disability and pain. Bennell et al. (2005) reported mean scores of 8.1 (/20) for pain and 28 (/68) for function, compared with respective means (95% CIs) of 6.3 (4.9-7.6) and 21.5 (17.1-25.9) in the current study. Bellamy et al. (2005) reported even higher mean levels both of pain (11.7) and function (39.9).

4.2. Effects on pain-related measures

As illustrated in Table 1 and Fig. 2, knee mobilization significantly increased knee PPT over and above manual contact or no-contact control conditions, when adjusting for pre-condition values ($F_{2,74} = 5.26, P = 0.008$).
Knee PPT increased by a mean of 27.3% (±3.14) following treatment, with manual contact producing a 6.4% increase (±2.97) and the no-contact intervention reducing PPT by 9.5% (±5.50). Treatment differed significantly from both manual contact ($F_{1,37} = 7.81, P = 0.008$) and no-contact ($F_{1,37} = 7.55, P = 0.010$) control conditions.

Nota de revisor: a seguir apresenta-se uma imagem cuja legenda é: Fig. 2. Mean (± standard error) changes in pressure pain threshold (PPT) for knee and heel, expressed as a percentage of pre-intervention values. *Denotes significant difference between conditions ($P<0.05$).

PPT measurements taken from the distal, non-painful, heel produced a similarly significant pattern of results (Table 2 and Fig. 2), with knee mobilization resulting in the greatest heel PPT increase (mean 15.3±3.08%). Treatment also differed significantly from both manual contact ($F_{1,37} = 10.72, P < 0.001$) and no-contact ($F_{1,37} = 6.02, P < 0.019$) control conditions.

Nota de revisor: a seguir apresenta-se uma tabela constituída por 9 colunas e 20 linhas cuja legenda é: Table 2 Main results for primary and secondary dependent variables in the main study ($n = 38$), showing mean change values plus analysis of variance and co-variance statistics. *Denotes significant difference ($P<0.05$).
<table>
<thead>
<tr>
<th>Condition</th>
<th>Actual difference pre- to post-Mean</th>
<th>Analysis of variance X² r</th>
<th>Analysis of variance df</th>
<th>Analysis of variance Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPT Knee</td>
<td>Rx</td>
<td>0.63 (8.3)</td>
<td>2.11</td>
<td>2.74</td>
</tr>
<tr>
<td></td>
<td>MCC</td>
<td>-0.74 (8.16)</td>
<td>1.94</td>
<td>[sem informação]</td>
</tr>
<tr>
<td></td>
<td>NCC</td>
<td>1.32 (4.30)</td>
<td>-0.05</td>
<td>2.73</td>
</tr>
<tr>
<td>PPT Heel</td>
<td>Rx</td>
<td>5.06 (13.02)</td>
<td>-9.33</td>
<td>-0.79</td>
</tr>
<tr>
<td></td>
<td>MCC</td>
<td>-0.35 (1131)</td>
<td>-4.23</td>
<td>3.53</td>
</tr>
<tr>
<td></td>
<td>NCC</td>
<td>7.92 (16.28)</td>
<td>2.64</td>
<td>13.19</td>
</tr>
<tr>
<td>TUG: STS time</td>
<td>Rx</td>
<td>-0.51 (10.52)</td>
<td>-3.51</td>
<td>3.41</td>
</tr>
<tr>
<td></td>
<td>MCC</td>
<td>-0.11 (9.16)</td>
<td>-2.20</td>
<td>1.98</td>
</tr>
<tr>
<td></td>
<td>NCC</td>
<td>3.87 (9.39)</td>
<td>1.74</td>
<td>6.00</td>
</tr>
<tr>
<td>TUG: total time</td>
<td>Rx</td>
<td>-0.50 (1.94)</td>
<td>-0.99</td>
<td>3.42</td>
</tr>
<tr>
<td></td>
<td>MCC</td>
<td>-0.84 (2.27)</td>
<td>-1.46</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>NCC</td>
<td>-0.42 (1.86)</td>
<td>-0.95</td>
<td>0.11</td>
</tr>
<tr>
<td>WOMAC-pain</td>
<td>Rx</td>
<td>-0.50 (1.94)</td>
<td>-0.99</td>
<td>3.42</td>
</tr>
<tr>
<td></td>
<td>MCC</td>
<td>-0.84 (2.27)</td>
<td>-1.46</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>NCC</td>
<td>-0.42 (1.86)</td>
<td>-0.95</td>
<td>0.11</td>
</tr>
</tbody>
</table>
WOMAC-pain subscale values demonstrated minimal change (less than one percent) from pre- to 24 h post-experimental condition and there was no significant difference between conditions ($F_{2,74} = 0.54$, $P = 0.590$). VAS values for pain during the timed ‘up and go’ test similarly showed little change in mean difference following any of the experimental conditions (treatment $-0.63\pm1.35$; manual contact $-0.74\pm1.32$; no contact $1.32\pm0.70$). Non-parametric tests of variance demonstrated no difference in VAS between conditions (Table 2).

### 4.3. Effects on function-related measures

Knee mobilization demonstrated a significantly greater improvement in sit-to-stand times than manual contact or no-contact conditions, as shown in Fig. 3. Treatment decreased sit-to-stand time significantly more than no-contact intervention ($F_{1,37} = 12.45$, $P>0.001$). Although significant differences between both treatment and manual contact and no contact control conditions were found ($F_{1,37} = 24.15$, $P>0.001$; $F_{1,37} = 8.79$, $P = 0.006$), the difference between treatment and manual contact control was not statistically significant ($F_{1,37} = 3.75$, $P = 0.061$). Treatment also produced the greatest improvement in total ‘up and go’ time, although this difference was not statistically significant ($F_{2,74} = 2.64$, $P = 0.078$). Power for TUG values was calculated as 0.69.

Nota de revisor: a seguir apresenta-se uma imagem cuja legend é: Fig. 3. Mean ($\pm$ standard error) percentage change in time for timed ‘up and go’ test, including sit to stand (STS) and total times. *Denotes significant difference between conditions ($P<0.05$).

![Graph showing mean change in time for 'up and go' test](image)

### 4.4. Blinding

The post-experiment questionnaire revealed that 71% of subjects were unable to identify the treatment condition correctly. Removal of data for those subjects who identified the treatment session made no difference to the results.
5. Discussion

5.1. Effects on pain-related measures

This study established that 9 min of accessory mobilization of the tibiofemoral joint immediately increased knee PPT significantly more effectively than either manual contact or no-contact control procedures, in subjects with mild to moderate knee osteoarthritis. Mobilization increased knee PPT by 27.3%, compared with 6.4% resulting from manual contact, indicating appreciably reduced sensitivity to mechanical pain. This corresponds with evidence from spinal mobilization studies (Vicenzino et al., 1998; Sterling et al., 2001a) which demonstrated improvements in PPT of approximately 25% and 30% following treatment. It also supports a similar pattern found following peripheral joint mobilization. Yeo and Wright (2004) showed that mobilising sub-acute ankle injuries increased PPT 23% more than the manual contact procedure. Paungmali et al. (2003) found that an elbow mobilization with movement technique produced an improvement in PPT of 15.4%. Thus, both peripheral and spinal mobilizations immediately reduce mechanical hyperalgesia more than control procedures. In accordance with investigations of other measures (Bird and Dickson, 2001; Gallagher et al., 2001; Bellamy et al., 2005), an improvement of more than 15% may be considered to reflect a clinically significant effect.

It may be that a particular type of stimulus is required to produce an optimal response. In a similarly designed study, which produced apparently contradictory results, Collins et al. (2004) reported that a sustained glide procedure (mobilization with movement) had no effect on mechanical pain thresholds in subjects with a sub-acute ankle injury, whereas the manual contact control procedure produced significant increases in PPT. On closer examination, this ankle study, in direct contrast to comparable studies (Vicenzino et al., 2001; Yeo and Wright, 2004; the current study), in fact used gentle repetitive movements of the joint as the manual contact control for the sustained treatment procedure. All of this evidence suggests that it is the repetitive movement, rather than sustained pressure to the limb, which provides the hypoalgesic stimulus. Further studies are needed to confirm this.

The enhanced hypoalgesic effect of repetitive mobilization may reflect changes in the local cellular environment. A recent in vitro study of healthy animal fibroblasts by Sambajon et al. (2003) suggested that movement may alter concentrations of inflammatory mediators, known to sensitize peripheral nociceptors. Levels of the prostaglandin PGE$_2$, an inflammatory mediator strongly implicated in arthritic hyperalgesia, were assessed before and after fibroblast cells were subjected to cycles of mechanical deformation, designed to mimic mobilization effects. After 24 h, these 'mobilized' cells were found to contain nearly 70% less PGE$_2$ than undisturbed control cells. Future studies in vivo, comparing levels of inflammatory mediators in human osteoarthritic joints before and after joint mobilization would be instructive.

Pain relief, however, is multifactorial and complex. Although mobilization may initiate local physiological mechanisms, additional central mechanisms may also be involved. These central mechanisms could include activation of local segmental inhibitory pathways in the spinal cord, or descending inhibitory pathways from the brainstem.
It can be hypothesized that joint mobilization might activate segmental pain inhibitory mechanisms. However, we previously demonstrated in rats that pharmacological blockade of GABA or opioid receptors in the spinal cord, which are involved in segmental inhibition, has no effect on the analgesia produced by knee joint mobilization (Skyba et al., 2003). It does not appear therefore that segmental inhibitory mechanisms make a significant contribution to manual therapy hypoalgesia, but further studies using other animal models would be valuable.

We previously hypothesized that supraspinal pain inhibitory mechanisms are activated by manual therapy (Wright, 1995; Vicenzino et al., 1996; Wright, 2002; Souvlis et al., 2004). Activation of supraspinal inhibitory pathways would be expected to produce a widespread analgesic response that would include areas outside the site of injury. Our studies of spinal mobilization techniques (Vicenzino et al., 1996, 1998) have shown that cervical spine mobilization reduces hyperalgesia in the upper limb. The current study demonstrates for the first time in humans that the hypoalgesic response provoked by a peripheral mobilization is widespread and not just limited to the treated joint. A 9-min mobilization of the knee joint resulted in significant hypoalgesia distally in the foot, similar to the pattern of response seen in the animal model, where mobilising a rat knee joint for 9 min significantly reversed experimentally induced hyperalgesia at the ankle (Sluka and Wright, 2001). In the current study, the hypoalgesic response produced at the ipsilateral foot was in proportions similar to that at the treated knee (Fig. 2). This suggests that similar mechanisms may be responsible.

A number of recent human spinal studies by other groups also suggest that manipulation or mobilization of the spine may produce a more generalized hypoalgesic response. Haas et al. (2003) found that subjects with neck pain experienced as much relief with a randomly selected cervical manipulation as with a specific segmentally targeted technique. Similarly, Chiradejnant et al. (2003) found that a randomly selected lumbar mobilization technique was equally effective in reducing nonspecific low back pain as one specifically selected to treat an involved segment. Further human studies are needed to clarify the hypoalgesic response elicited by joint mobilization, through either pharmacological studies, or studies which further develop our understanding of the spatial scope and duration of the hypoalgesic response.

In addition, using behavioural pharmacology Skyba et al. (2003) show that serotonergic (5-HT1A) and noradrenergic (alpha-2) receptors in the spinal cord mediate the analgesia produced by knee joint mobilization. Since serotonin and noradrenaline releasing neurons in the spinal cord originate in supraspinal sites in the brainstem, these data support a role for descending inhibitory pathways in the hypoalgesia produced by joint mobilization.

5.2. Effects on function-related measures

This study also considered the immediate effect of knee joint mobilization on motor activity and found that there was a clear trend towards the greatest improvement in sit-to-stand and total 'up and go' time following the treatment condition (Fig. 3). This improvement may reflect reversal of reflex pain inhibition
(Hurley and Newham, 1993). Additionally, changes in motor activity may be a further indication of a centrally mediated response. It has been demonstrated that mobilization can enhance motor activity alongside hypoalgesic and sympatho-excitatory responses. Sterling et al. (2001a) found that cervical mobilization improved deep neck flexor function in subjects with neck pain. Vicenzino et al. (1998) similarly found that cervical mobilization increased pain-free grip in subjects with lateral epicondylalgia, a result which was replicated with a local elbow mobilization with movement intervention (Vicenzino et al., 2001).

Although the difference in STS times between treatment and manual contact control conditions were not significant, there was a trend towards significance ($P = 0.061$). This may reflect the lower power of the secondary measures in the study, but may also signify the larger measurement error and lower reliability (ICC 0.57) associated with using a manual stopwatch to measure fractions of seconds. The significant increase in STS time following the no-contact control condition is an interesting result. Whilst this may be a reflection of methodological limitations, increased stiffness and resulting movement limitations following prolonged immobility is also a clinical feature of lower limb osteoarthritis. The 10 min of complete immobility necessitated by the no-contact control procedure may have been sufficient to increase TUG time. Further investigation, however, is needed in order to clarify whether mobilization of a painful arthritic knee can improve motor function. Future studies will need to employ more precise tools to measure motor improvement, perhaps using electronic timing gates, EMG, or motion analysis.

5.3. Further study limitations

Both the VAS data for pain during the functional test and WOMAC pain subscale data were inconclusive, demonstrating minimal change following any of the experimental conditions. However, baseline values for both of these tools were low, thereby reducing the likelihood of significant change following any of the experimental conditions. This reverse ceiling effect may reflect the relatively mild OA effects demonstrated by subjects. It has been noted above that subjects in this study reported significantly less pain and fewer functional limitations than those in equivalent studies (Bellamy et al., 2005; Bennell et al., 2005). This, in turn, may reflect differing recruitment methods, since subjects in the current study were recruited directly from the general population rather than from established disease management programmes (Bellamy et al., 2005; Bennell et al., 2005). Although outside the aims of the current investigation, it would be useful to investigate further the possible relationship between clinical pain measures, such as the VAS and WOMAC, and experimental measures such as algometry, amongst subjects with varying degrees of disease severity.

5.4. Clinical relevance

This study provides strong evidence that non-noxious accessory mobilization of an osteoarthritic peripheral joint can immediately reduce hyperalgesia. We have shown that subjects with mild to moderate knee pain experience immediate improvement in PPT of an average 27.3% after a 9-min
treatment. Although estimates of clinically significant change in PPT are difficult, since pressure algometry is not used clinically, a number of studies have concluded that a 15-20% change in pain reflects significant change (Bird and Dickson, 2001; Gallagher et al., 2001; Bellamy et al., 2005). This study only sought to explore the immediate effects of a single mobilization treatment. However, joint mobilization tends to be used clinically for its assumed longer-term cumulative effect, over the course of several treatment sessions. Further work is therefore needed to explore hypoalgesic effects over a longer time period in order to clarify the optimal treatment dose.

Reduction in pain sensitivity may also immediately improve motor patterning (Sterling et al., 2001b). Although there were limitations in this study with regard to measurement of functional change, results suggest that mobilization of a painful osteoarthritic joint may immediately facilitate motor function. If this is so, it may be that joint mobilization could be used for its immediate effects, as a precursor to motor activation strategies, although, again, this hypothesis needs further investigation.

6. Conclusion

The purpose of this study was to investigate the initial effects on pain and function of lower limb joint mobilization. The study has provided new experimental evidence that accessory mobilization of a human osteoarthritic knee joint has both an immediate local and a more widespread hypoalgesic effect. This supports the response seen in animal studies (Sluka and Wright, 2001). Clinically therefore, joint mobilization may be an effective means of reducing osteoarthritic pain and may potentially improve motor function.

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