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Brief report

Patient education with or without manual therapy compared to a control group in patients with osteoarthritis of the hip. A proof-of-principle three-arm parallel group randomized clinical trial

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SUMMARY

Objective: To investigate the effectiveness of a patient education (PE) program with or without the added effect of manual therapy (MT) compared to a minimal control intervention (MCI).
Methods: In a single-center university hospital setting, a total of 118 patients with clinical and radiographic unilateral hip osteoarthritis (OA) from primary care were randomized into one of three groups: PE, PE plus MT or MCI. The PE was taught by a physiotherapist involving five sessions. The MT was delivered by a chiropractor involving 12 sessions and the MCI included a home stretching program. Primary outcome was self-reported pain severity on an 11-box numeric rating scale (NRS) immediately following a 6-week intervention period. Patients were followed for 1 year.
Results: Primary analysis included 111 patients (94%). In the combined group (PE + MT), a clinically relevant reduction in pain severity compared to the MCI of 1.90 points (95% confidence interval (CI) 0.9–2.9) was achieved. Effect size (Cohen's d) for the PE + MT minus the MCI was 0.92 (95% CI 0.41–1.42). Number needed to treat for PE + MT was 3 (95% CI 2–7). No difference was found between the PE and MCI groups, with mean difference 0.0 (95% CI −1.0 to 1.0). At 12 months, not including patients receiving hip surgery the statistically significant difference favoring PE + MT was maintained.
Conclusions: For primary care patients with OA of the hip, a combined intervention of MT and PE was more effective than a MCI. PE alone was not superior to the MCI.
Trial registration: clinicaltrials.gov NCT01039337.

Introduction

Hip osteoarthritis (OA) is a common joint disease and when symptomatic can have significant impact on regular daily activities[1]. Recently, hip OA has been linked to higher mortality rates[2]. In end stage hip OA, joint replacement surgery is an appropriate and cost-effective treatment[3,4] but a long-term cohort study has documented that only 20% of patients with radiographic hip OA have had surgery 11–28 years after the initial diagnosis[5]. Therefore, non-surgical interventions with documented effectiveness become essential for patients who do not need, or choose not to have, surgery.

In Denmark, there is no consensus around standardized minimal care for hip OA patients in primary care and standardized patient education (PE) programs are not available to the public. In other countries, PE programs have been developed for OA patients to improve self-management through understanding of the disease and change of health behavior[6]. Although guidelines recommend PE programs as a core intervention[7], systematic reviews are contradictory in conclusions regarding their effectiveness on pain and function[8,9].

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Manual therapy (MT) has been proposed as an adjunct intervention to exercise for patients with hip OA[7,10] but evidence is based on a single randomized clinical trial (RCT)[11].

MT is offered infrequently in Denmark for hip OA patients and is likely to be dependent on clinician or therapist preference and skill. Given the limited number of trials dealing with PE and MT for hip OA to date, this study aimed to examine the feasibility of a trial set-up and investigate if the chosen outcome measures were responsive in patients with hip OA from primary care in Denmark. Therefore, the current trial was designed as a proof-of-principle trial to inform the design of future RCTs involving PE and MT by investigating the effectiveness, in terms of pain reduction, of a PE program with or without the added effect of MT compared to a minimal control intervention (MCI) involving home stretching. The secondary aim was to explore the effect of adding MT to PE.

Methods

Study design and participants

The design was a single-center proof-of-principle three-arm parallel group RCT. Patient characteristics, recruitment procedures, exclusion criteria, follow-up time points and blinding procedures have been described in the published protocol[12]. Inclusion criteria were[1] Unilateral hip pain >3 months' duration[2], Age 40–80 years[3], Radiographic hip OA defined as minimal joint space width (JSW) measurement <2.00 mm[13] or a side difference in minimal JSW >10%, and[4] Ability to speak and read Danish. Recruitment, clinical examinations and treatment all took place at the Department of Orthopaedic Surgery and Traumatology, Odense University Hospital, Denmark. The study was carried out according to the Helsinki Declaration and approved by the Regional Ethics Committee of Southern Denmark (approval number S-20080027) and the Danish Data Protection Agency (J.nr.2008-41-1910). Patients received written and oral information and signed an informed consent form.

During the first 2 months of recruitment, three exclusion criteria were added to the original criteria[1]: patients who had had MT within the previous twelve months[2]; patients who rated their pain severity as 1 or 2 on the primary outcome 11-box numerical rating scale (NRS), since improvement would not be measurable[3]; patients with polyarthritis, defined as having OA-like symptoms from more than three anatomic areas.

Randomization

Patients were randomized to one of three groups: a PE program; the PE program plus MT; or the MCI. The randomization sequence with block sizes of three, six or nine was computer generated by a person not otherwise involved in the study and envelopes were generated by yet another person not otherwise involved in the trial. To allow for patient interaction in the PE groups, a minimum of 10 patients had to be eligible to enter the study ensuring a minimum of three patients for each of the two groups involving PE. Therefore, patients would wait from the time of eligibility until the day scheduled for the allocation procedure. On the day of allocation, a number of sealed opaque envelopes matching the number of patients scheduled were generated and each patient selected an envelope following completion of patient-reported outcome measures. The envelope was opened in front of the project nurse and allocation was made to the appropriate group. If allocation was to the MCI group, the nurse provided written advice on a home stretching program derived from the PE program together with a 5–10-min instruction. The project nurse was not involved in the assessment of patients.

Interventions

Protocols for the PE program, MT and MCI are attached in Appendix 1. The PE program, originally termed 'Hip School'[14] was taught by a physiotherapist with 11 years' experience in orthopedic hospital departments involving aspects of PE and rehabilitation. The therapist received special training teaching the program prior to the study. The PE program included two individual sessions and three group sessions. The MT was administered by the first author (EP), a chiropractor with 20 years of clinical experience and 10 years of specific clinical and research interest in patients with hip OA. MT was scheduled twice a week for the 6-week intervention period and treatment was individualized to each patient depending on examination findings (Appendix 1). Instructions for the home stretching program were given by the project nurse who had 10 years of experience with orthopedic patients.

Outcome measures

The primary outcome was pain severity rated on an 11-box NRS, measured after 6 weeks of intervention. Patients were asked to rate the worst pain experienced during the previous week. The scale is recommended and documented as reliable, valid and responsive in chronic pain patients[15,16].

The original protocol registered with clinicaltrials.gov (NCT01039337) listed two primary outcomes: pain severity and physical function. Due to CONSORT recommendations and to avoid multiplicity of analysis, pain severity was selected as the sole primary outcome *a priori* before completing the trial and before accessing the data, as published in the study protocol[12].

Secondary outcome measures were the Hip disability and Osteoarthritis Outcome Score (HOOS) range 0–100, worst to best; patients' perceived global effect of interventions, percentage in each group having classified themselves as improved; passive hip range of motion (ROM); use of pain medication at 12 months and hip replacement surgery within the 12 month follow-up period. Both HOOS and patients' perceived global effect of interventions are considered valid and responsive in patients with musculoskeletal conditions[17,18]. Hip ROM was measured following a standardized protocol. The outcome assessor was a physiotherapist not otherwise involved in the assessment or treatment of patients. A reproducibility study of the ROM measurements was conducted involving 51 patients. The intraclass correlation coefficient ($ICC_{1,0}$)[19] ranged from 0.73 to 0.93 with narrow 95% confidence intervals (CIs) and standard error of the measurements ($SEM_{agreement}$)[20] ranging between 1.1 and 6.1. The variables 'use of pain medication' and 'hip surgery' at 12-month follow-up were dichotomized into yes/no. 'Pain medication was dichotomized into yes/no as less than 50% of patients at baseline listed usage of pain medication. At baseline patients in all three groups were instructed not to change their pain medication if at all possible making dose calculation highly unreliable. Further, reporting was hampered because patients could not remember name or dosage of medication. The protocol paper lists EuroQoL-5D and a patient specific functional scale (PSFS) as secondary outcome measures. They are planned to be reported separately.

Follow-up time points and blinding

Baseline questionnaires including primary and secondary outcomes were completed at the university hospital on the day of randomization and were repeated after 6 weeks and 3 and 12 months. They were mailed to patients prior to the appointment for the physical examination and were returned in a sealed envelope to the examination assessor, who performed all examinations at all

time points. Patients were instructed not to reveal group allocation to the assessor, but blinding was not confirmed for all patients.

Adverse events

A standardized questionnaire was used to assess adverse reactions in all groups including questions on location, severity, onset, duration, and influence on activities of daily living (ADL). Patients were asked at the last sessions in the PE and PE + MT groups whereas the MCI group was interviewed by a secretary by phone immediately after the 6 weeks intervention period. Adverse events were only collected for the last 50% of patients completing the trial since the benefit of assessing adverse events information was recognized half way into the trial.

Sample size

In patients with hip OA, the minimal clinically important improvement for pain is estimated to be 15 points on a 0–100 scale[21]. Using a conservative estimate, we aimed at demonstrating a statistically significant difference of 17 points on the primary outcome after treatment with a 5% significance level and 80% power between the group of PE vs MCI or PE + MT vs MCI. Thus, 30 patients were to be included in each group assuming a joint normal distribution for baseline and 6-week follow-up with a correlation of 0.3 and equal variances. Allowing for a 15% drop out, it was decided to include a minimum of 106 patients.

Statistical analyses

Double data entry was done by a research assistant not otherwise participating in the study. The study population were all patients randomized, excluding those where violations of the inclusion criteria was detected after randomization. Patients withdrawn prior to the 6 weeks follow-up were described and compared to the other patients, but excluded in the main analyses. Otherwise, the main analyses followed the intention-to-treat principle analyzing all patients "as randomized" including those who received hip surgery between 6 weeks and 12 months[12]. In addition, a per-protocol analysis was performed for the 12 month data excluding patients having had hip replacement. The primary statistical analysis was performed with respect to the change over the 6-week intervention period where the largest treatment effect was expected. In the planning of the study only the comparisons PE vs MCI and PE + MT vs MCI with respect to the main outcome were considered as confirmative, and the comparison PE vs PE + MT was considered as explorative. The overall group differences in pain severity were analyzed using analysis of covariance (ANCOVA) with adjustment for baseline values with a significance level of 0.05. The pre-specified pair-wise comparisons between the two active treatments and the MCI were analyzed using Dunnett's procedure ensuring a global significance level of 0.05, which does not require the ANCOVA omnibus test to be significant[22]. Effect sizes were computed by dividing the effect estimates from the ANCOVA by the pooled standard deviation (SD) of the baseline values. The number needed to treat (NNT) was calculated for each of the active treatment groups in comparison to the MCI including 95% CIs (if statistically significant). The NNT estimates the number of patients who need to undergo treatment in order for one patient to experience a pain reduction of at least 25% from baseline to 6 weeks. A secondary exploratory analysis of the difference between the PE group and PE + MT was performed using Bonferroni corrected ANCOVA. The secondary statistical analysis included the same approach as described above for all the secondary outcomes involving continuous data.

A longitudinal analysis of the primary and secondary outcomes, incorporating data from baseline, 6 weeks, 3 months and 12 months, was conducted using a linear mixed model approach. The *P*-values of the two comparisons with the MCI group were again based on Dunnett's procedure. Binary outcomes, use of pain medication and hip surgery at 12 months, were analyzed by pairwise application of Fisher's exact test. Effect sizes reporting Cohen's d including 95% CIs are displayed for the comparisons: PE and MCI, PE + MT and MCI, PE and PE + MT. Due to the low number of drop outs, a decision was made not to use the multiple imputation model for missing data as described in the protocol.

Patients' perceived global effect of interventions was categorized into (1) improved (patients responding with 'better' or 'much better') and (2) no change (other response options). Statistical software used for analyses was Stata 12 (StataCorp, Texas, USA).

Results

From December 2008 to May 2010, 331 patients were screened and recruitment ended when 118 eligible patients had been randomized. Patient flow through the study is illustrated in Fig. 1. Two hundred and eighty-eight were referred from general practitioners, 22 from chiropractors, 15 by orthopedic surgeons and six patients contacted the project directly. Two hundred and thirteen were not eligible to enter the trial; the reasons being listed in Appendix 2. After randomization but on the same day, four patients previously found eligible were excluded: three presented with bilateral hip pain and one with lower leg neuropathy. At the first appointment for MT, three previously randomized patients were excluded: one did not have clinical signs of hip OA and two presented with polyarthritis. In order not to disrupt the sequence of randomization, each letter for the seven who had been excluded was re-entered into the sequence and thus, a total of 111 patients were included in the analyses at the primary end point at 6 weeks. Patient characteristics at baseline are presented in Table I. Of the 71 patients from the two groups receiving PE, 10 missed one group session, one missed two sessions and four missed the second personal interview. Thirty-five patients participated in the MT intervention: 33 participated in all 12 sessions, one participated in 11 sessions and one withdrew after seven sessions.

At 6 weeks follow-up, nine patients (8.1%) had withdrawn. In the PE group, one withdrew due to lack of commitment. In the PE + MT group, four withdrew: one felt the treatment was too time-consuming, one wanted hip surgery, one had surgery for another unrelated health reason and one became worse from the MT. The mean age of patients withdrawing was 71.8 years (SD 3.3) and pain severity at baseline on the NRS score was 5.8 (SD 2.2). In the MCI group, three were discontented with the group allocation and one wanted hip surgery. The mean age of patients withdrawing was 63.2 years (SD 11.0) and pain severity on the NRS score was 6.5 (SD 1.7). At 3 months, one patient from the PE group (0.9%) had received hip surgery (3 months data missing) and between 3 and 12 months, 20 (18%) had received hip surgery. Mean scores of NRS, HOOS and ROM at baseline, 6 weeks, 3 and 12 months for the three groups are listed in Appendix 3.

Primary outcome

Mean change scores including SDs from baseline to 6-week follow-up are presented in Table II and group differences with 95% CIs and effect sizes including 95% CIs are listed in Table III.

At the primary end point (6 weeks), no overall statistically significant differences were found between all three groups for mean pain severity (PE: 5.3 [SD 2.3], PE + MT: 3.4 [2.4], MCI: 5.3 [1.7] $P = 0.058$). For the pair-wise comparison, the PE + MT group

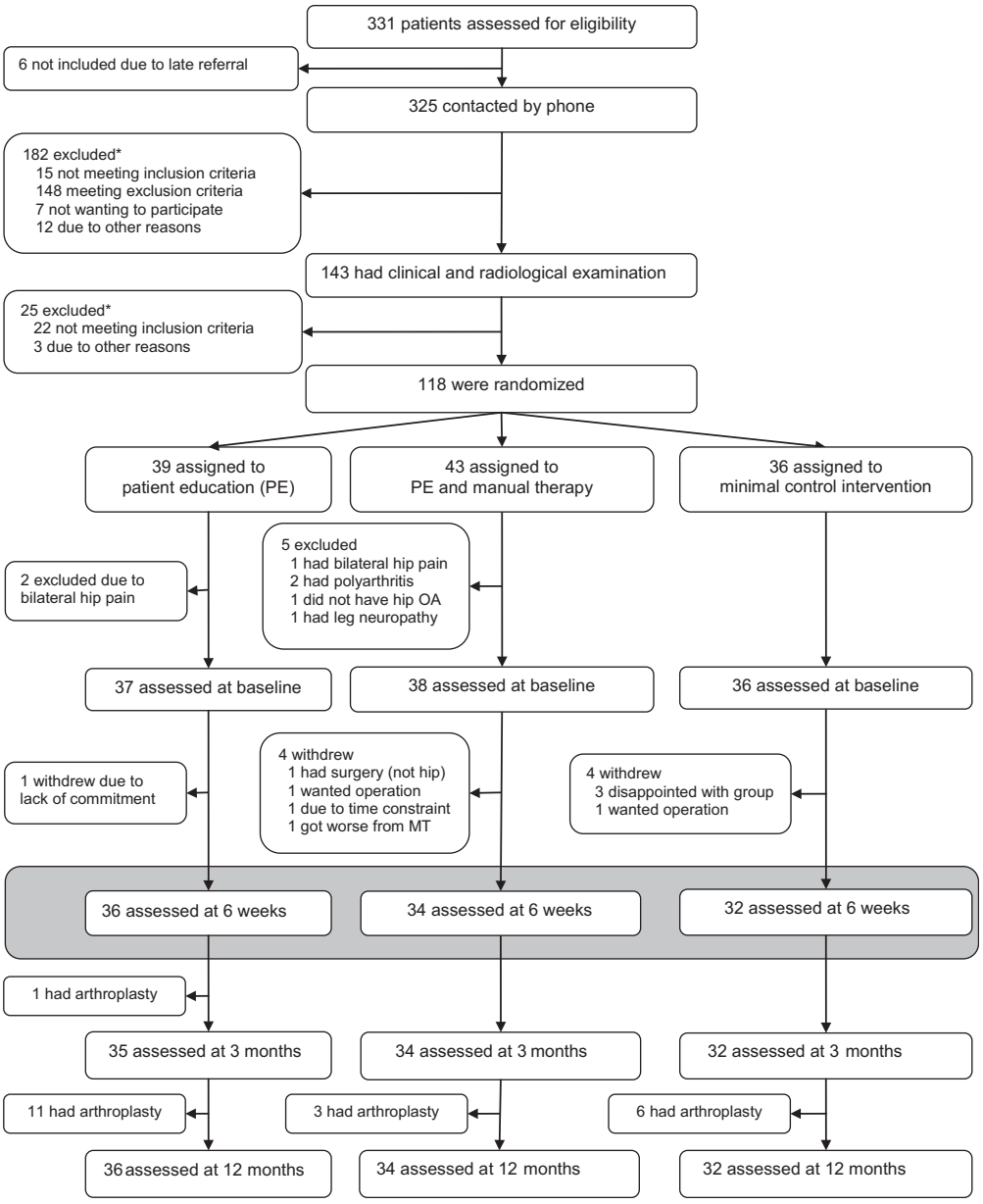

Fig. 1. Chart of patient recruitment and randomization. Primary end point indicated at 6 weeks. *Excluded patients are specified in Appendix 2. Shaded area indicates primary end point for primary outcome.

achieved a 1.9 points greater pain reduction compared to the MCI (95% CI 0.9–2.9). No difference was found between the PE and MCI groups (95% CI −1.0 to 1.0). Effect size for the PE + MT minus the MCI group was 0.92 (95% CI 0.41–1.42) and for the PE minus the MCI group, 0.02 (−0.49 to 0.46). The number of patients in each group experiencing pain reduction of at least 25% from baseline to 6 weeks was PE = 8, PE + MT = 21 and MCI = 7. The NNT for PE + MT vs MCI was 3 (95% CI 2–7).

Secondary outcomes at 6 weeks

Differences between all three groups were significant for the HOOS subscales Pain ($P = 0.021$), Function in sport and recreation (Sport/Rec.) ($P = 0.022$) and Hip-related quality of life (QoL) ($P = 0.040$) but not for the subscales of Symptoms ($P = 0.095$) and Function in daily living (ADL) ($P = 0.060$). All HOOS subscales demonstrated clinically relevant and statistically significant superiority, $P < 0.05$ for the PE + MT group when compared to the MCI group: 17 points (95% CI 11–23) for Pain; 13 points (5–20) for Symptoms; 14 points (7–22) for ADL; 17 points (8–25) for Sport/Rec.; and 13 points (6–20) for QoL. Mean differences between PE and MCI were small (range −4 to 1) and not statistically significant, $P > 0.05$. Effect sizes for HOOS subscales for PE + MT minus MCI ranged between 0.75 and 1.08. For ROM measurements, neither overall nor pair-wise comparisons were statistically significant. Mean change scores including SDs from baseline to 6-week follow-up are presented in Table II. Group differences with 95% CIs and effect sizes including 95% CIs are listed in Table III.

Exploratory analysis of difference between PE and PE + MT groups at 6 weeks

The PE + MT group was able to reduce pain severity with a clinically relevant difference of 1.9 points compared to PE alone, 95% CI (0.8–2.9). The same pattern was demonstrated for all HOOS subscales. No difference between groups was found for ROM

Table I
Characteristics at baseline for patients with unilateral hip OA

Variable	PE	PE + MT	MCI
Number of patients per group	37	38	36
Age in years, mean (SD)	65.5 (7.3)	65.8 (8.5)	62.5 (9.4)
Female gender, *n* (% within group)	14 (38)	17 (45)	17 (47)
Body mass index (BMI) (kg/m^2), mean (SD)	27.4 (3.4)	26.3 (3.6)	26.7 (4.2)
Involved side right/left (*n*)	17/20	26/12	24/12
Duration of symptoms in months, mean (SD)	32 (25)	26 (26)	37 (50)
Range (months)	6–96	4–120	4–300
Minimal JSW for involved joint (mm) mean (SD)	1.46 (1.11)	1.56 (1.05)	1.61 (1.11)
Minimal JSW <2.00 (*n*)	26	27	23
Minimal JSW side difference > 25% (n)	9	10	9
Minimal JSW side difference <25% and > 10% (*n*)	2	1	4
Worst pain experience, 11-box NRS (0–10), mean (SD)	5.1 (2.0)	5.4 (2.4)	5.8 (1.6)
HOOS pain, mean (SD)	64 (14)	62 (17)	58 (14)
HOOS symptom, mean (SD)	62 (17)	61 (18)	59 (15)
HOOS function of daily living, mean (SD)	68 (15)	68 (20)	64 (15)
HOOS sport and recreation, mean (SD)	53 (22)	55 (21)	49 (21)
HOOS hip-related QoL, mean (SD)	53 (18)	52 (17)	46 (12)
Flexion ROM (°), mean (SD)	106 (14.8)	105 (13.8)	109 (12.6)
Abduction–adduction ROM (°), mean (SD)	41 (8.2)	41 (8.2)	42 (8.8)
Internal–external rotation ROM (°), mean (SD)	64 (15.2)	65 (13.8)	65 (11.8)
Pain medication, *n* (% within group)	20 (54)	16 (42)	15 (42)
Employed (*n*)	12	14	18
Unemployed (*n*)	0	0	1
Retired (*n*)	24	24	17
Health-related pension (*n*)	1	0	0
Current sick leave due to the hip (*n*)	0	0	1
Source of recruitment			
General practitioner, *n* (% within group)	33 (89.2)	31 (81.6)	30 (83.3)
Chiropractor, *n* (% within group)	3 (8.1)	5 (13.2)	4 (11.1)
Orthopedic surgeon, *n* (% within group)	0	0	1 (2.8)
Self-referral, *n* (% within group)	1 (2.7)	2 (5.3)	1 (2.8)

measurements. Group differences including 95% CIs and effect sizes including 95% CIs are listed in Table IV.

Pair-wise comparison between PE and MCI and PE + MT and MCI including all time points

When applying Dunnett's procedure to the linear mixed model, none of the outcome measures demonstrated statistically significant or clinically relevant differences between any of the two active interventions and the MCI. Applying the same analyses and excluding patients having received hip replacement surgery (per-protocol analysis), the combined PE + MT group had reduced pain severity on the NRS with 1.1 points (0.1–2.1), $P = 0.026$, compared to the MCI group and all HOOS subscales improved in the PE + MT group in comparison to the MCI group demonstrating statistically significant changes (Table III). Mean change scores and SDs from baseline to 12 months for both as randomized and per-protocol analyses are presented in Table II. Group differences with 95% CIs incorporating all time points are presented in Table III. Mean scores and SDs for NRS pain severity for the three groups at all time-points incorporating the as randomized and per-protocol analyses are presented in Fig. 2(A and B).

Patients' perceived global effect of intervention

At 6 weeks, 76.5% of patients in the PE + MT group had classified themselves as improved compared to 22.2% in the PE group and 12.5% in the MCI group, $P < 0.001$.

Table II
Change scores from baseline to 6 weeks and 12 months. As randomized (ar) and per-protocol (pp) analyses are presented for the change scores at 12 months. Means (SD)

Variable	PE	PE + MT	MCI
NRS pain			
6 Weeks	0.3 (1.9)	−1.9 (2.3)	−0.3 (1.5)
12 Months (ar)	−1.5 (3.6)	−1.8 (3.1)	−1.5 (2.6)
12 Months (pp)	0.5 (2.3)	−1.2 (2.7)	−1.0 (2.0)
HOOS pain			
6 Weeks	−1 (11)	18 (13)	3 (13)
12 Months (ar)	11 (23)	16 (20)	13 (18)
12 Months (pp)	−3 (13)	13 (19)	8 (11)
HOOS symptoms			
6 Weeks	−1 (15)	15 (15)	4 (11)
12 Months (ar)	10 (23)	12 (19)	10 (18)
12 Months (pp)	−2 (17)	9 (16)	8 (13)
HOOS function in daily living			
6 Weeks	1 (10)	15 (16)	5 (13)
12 Months (ar)	9 (21)	13 (20)	10 (18)
12 Months (pp)	−3 (13)	10 (19)	7 (13)
HOOS sport and recreation			
6 Weeks	2 (14)	21 (18)	11 (18)
12 Months (ar)	10 (21)	13 (22)	11 (22)
12 Months (pp)	−1 (16)	11 (22)	7 (19)
HOOS hip-related QoL			
6 Weeks	−2 (11)	12 (18)	4 (10)
12 Months (ar)	10 (27)	10 (20)	12 (21)
12 Months (pp)	−4 (18)	6 (17)	6 (13)
ROM − flexion			
6 Weeks	−1 (11)	−6 (15)	−3 (7)
12 Months (pp)	−1 (12)	−5 (16)	−2 (10)
ROM − abduction–adduction			
6 Weeks	1 (6)	−3 (7)	1 (8)
12 Months (pp)	−4 (5)	−3 (8)	1 (8)
ROM − internal–external rotation			
6 Weeks	−3 (9)	−2 (13)	−4 (12)
12 Months (pp)	0 (9)	−4 (11)	0 (11)

HOOS = hip osteoarthritis disability and osteoarthritis outcome score; ROM = range of motion.

Use of pain medication at 12 months was not statistically significantly different for the pair-wise comparisons (PE = 23, PE + MT = 10, MCI = 14) and there was no difference between the three groups with respect to hip surgery (PE = 12, PE + MT = 4, MCI = 7), $P = 0.071$. Patients having received hip surgery were significantly worse at baseline for pain severity ($P = 0.003$), duration of symptoms ($P = 0.029$) and use of medication ($P = 0.002$) when compared to patients not having had surgery.

Adverse reactions or unintended effects

Data on adverse reactions were collected for the last 63 consecutive patients included. The PE group reported no adverse events. In the PE + MT group, seven patients reported discomfort, muscle soreness or mild pain appearing up to 24 h after MT, lasting for no more than 24 h and not affecting ADL. One patient reported moderate pain appearing after 4 weeks of therapy, lasting for 2 weeks, and having some effect on ADL. In the MCI group, two patients reported worsening of hip pain following home stretches. The pain lasted for more than 2 days and had a moderate effect on ADL. Both patients stopped the specific home stretches.

Discussion

This RCT successfully demonstrated differences in short-term outcomes when comparing a combined PE and MT intervention to a MCI in patients with hip OA referred from primary care. Even with small group sizes, the combined PE and MT intervention demonstrated a clinically relevant pain reduction and

Table III
Group differences of mean change scores incl. 95% CIs at 6 week and 12 months for PE vs MCI and PE + MT vs MCI. Group differences at 12 months list as randomized and per-protocol analyses. Effect sizes (Cohen's d) based on ANCOVA analysis incl. 95% CIs at 6 weeks

Variable	Difference, PE vs MCI (95% CIs)	Effect size (95% CIs)	Difference, PE + MT vs MCI (95% CIs)	Effect size (95% CIs)
NRS pain				
6 Weeks	−0.0 (−1.0 to 0.9)	−0.02 (−0.49 to 0.46)	−1.9 (−2.9 to −0.9)	−0.92 (−1.42 to −0.41)
12 Months (ar)	−0.5 (−2.0 to 0.9)		−0.5 (−1.9 to 0.9)	
12 Months (pp)	−0.1 (−1.1 to 0.9)		−1.1 (−2.1 to −0.1)	
HOOS pain				
6 Weeks	0.7 (−6 to 7)	0.01 (−0.47 to 0.49)	17 (11–23)	1.08 (0.56–1.59)
12 Months (ar)	3 (−7 to 13)		6 (−4 to 16)	
12 Months (pp)	2 (−6 to 9)		10 (3–18)	
HOOS symptoms				
6 Weeks	−2 (−10 to 5)	−0.13 (−0.61 to 0.34)	13 (5–20)	0.75 (0.25–1.25)
12 Months (ar)	2 (−8 to 12)		3 (−7 to 13)	
12 Months (pp)	−1 (−9 to 8)		8 (0–16)	
HOOS function in daily living				
6 Weeks	0 (−7 to 6)	−0.05 (−0.53 to 0.42)	14 (7–20)	0.85 (0.34–1.36)
12 Months (ar)	3 (−7 to 13)		6 (−4 to 16)	
12 Months (pp)	1 (−8 to 9)		9 (1–17)	
HOOS sport and recreation				
6 Weeks	−4 (−12 to 4)	−0.20 (−0.67 to 0.28)	17 (8–25)	0.87 (0.36–1.37)
12 Months (ar)	4 (−7 to 15)		8 (−2 to 19)	
12 Months (pp)	−1 (−11 to 9)		12 (2–22)	
HOOS hip-related QoL				
6 Weeks	1 (−6 to 7)	0.04 (−0.44 to 0.52)	13 (6–20)	0.88 (0.37–1.38)
12 Months (ar)	4 (−7 to 14)		6 (−5 to 18)	
12 Months (pp)	3 (−5 to 11)		10 (2–17)	
ROM − flexion				
6 Weeks	−7 (−12 to −1)	−0.54 (−1.03 to 0.04)	−3 (−9 to 2)	−0.26 (−0.75 to 0.23)
12 Months (pp)	−5 (−11 to 2)		−3 (−8 to 3)	
ROM − abduction–adduction				
6 Weeks	−2 (−6 to 1)	−0.29 (−0.77 to 0.20)	2 (−1 to 5)	0.25 (−0.25 to 0.74)
12 Months (pp)	−1 (−5 to 3)		1 (−3 to 5)	
ROM − internal–external rotation				
6 Weeks	−4 (−10 to 2)	−0.29 (−0.78 to 0.20)	−4 (−11 to 2)	−0.28 (−0.78 to 0.22)
12 Months (pp)	−3 (−10 to 4)		0 (−7 to 7)	

improvement in self-reported ADL and QoL with a large effect size when compared to the control group receiving a minimal intervention of home stretching. No difference was found when comparing PE alone to the minimal intervention.

The finding of pain reduction and improvement in all of the HOOS subscales in the group receiving PE + MT may have several explanations. First, the physical components of the MT are a possible contributor to the effect[23]. In trials including MT with documented effectiveness, the consistent component is joint manipulation (forceful traction). Hoeksma *et al.* demonstrated MT including manipulation to be superior to exercise therapy in patients with hip OA[24], Vaarbakken and Ljunggren reported results similar to ours when comparing forceful traction to standard traction mobilization in patients with hip disability[25] and Abbott *et al.* has recently demonstrated MT including thrust techniques (forceful traction) being superior to usual care[26]. Among practitioners of MT, manipulation is by definition different to mobilization[27,28]. The difference between the two is the force generated and studies on patients with hip OA using standard mobilization techniques have not demonstrated effectiveness when compared to forceful traction/manipulation[24,25]. Second, the combined intervention group received 12 more sessions than the PE alone group and 17 more sessions than the MCI group, introducing the risk of attention bias[29] but the studies by Hoeksma *et al.*[24] and Vaarbakken & Ljunggren[25] both controlled for attention and demonstrated significant improvement when forceful traction/manipulation was applied in comparison to non-forceful traction/mobilization. Third, the placebo effect is a possible explanation. In a meta-analysis of drug trials, Zhang *et al.* have reported an effect size of 0.37 (95% CI 0.21–0.53) for pain reduction in hip OA patients receiving placebo treatment[30]. The lack of statistical significance for the difference observed at 12 months is probably due to the positive outcome after hip replacement surgery. Indeed, the per-protocol analyses demonstrate clinically relevant and statistically significant differences for all patient-reported outcomes in favor of the PE + MT group at 12 months.

No differences were found between the PE and MCI groups at any follow-up. This is in accordance with conclusions from a meta-analysis from 2005 on the effectiveness of PE programs for hip and knee OA patients and subsequent studies demonstrating little or no effect on pain and function of self-management or PE programs for patients with arthritis[8,31–34]. Inclusion of a MCI was based on no minimal intervention is currently standard for hip OA patients in Denmark and a home program in the form of a leaflet is common at time of first diagnosis. Further, this particular PE program has not been compared to a minimal non-pharmacological intervention.

Table IV
Differences of mean change scores incl. 95% CIs and effect sizes (Cohen's d) incl. 95% CIs at 6 weeks between PE and PE + MT

Variable	Difference, PE vs PE + MT (95% CIs)*	Effect size (95% CIs)
NRS pain	−1.9 (−2.9 to −0.8)	0.79 (0.30–1.27)
HOOS pain	16 (10–23)	0.97 (0.47–1.46)
HOOS symptoms	15 (7–23)	0.82 (0.33–1.30)
HOOS function in daily living	14 (7–21)	0.84 (0.34–1.32)
HOOS sport and recreation	21 (12–30)	0.94 (0.45–1.44)
HOOS hip-related QoL	12 (5–20)	0.72 (0.23–1.20)
ROM − flexion	4 (−2 to 9)	0.28 (−0.20 to 0.75)
ROM − abduction–adduction	4 (0–8)	0.53 (0.04–1.00)
ROM − internal–external rotation	0 (−6 to 7)	0.01 (−0.49 to 0.46)

* Bonferroni corrected ANCOVA.

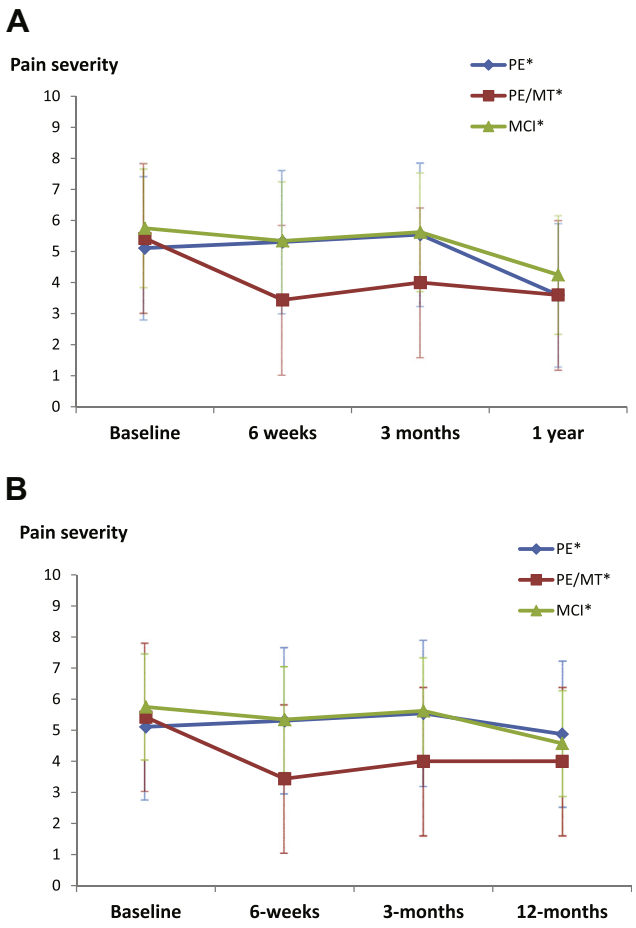

Fig. 2. Pain severity on an 11-box NRS at baseline, 6 weeks, 3 and 12 months including SDs. A. as randomized. B. per-protocol. *PE = patient education, MT = manual therapy, MCI = minimal control intervention.

These results should be interpreted in the light of several potential limitations. First, we included patients with minimal JSW difference, defined as >10% and <25%, which is within the limits of measurement error. But due to randomization and equal distribution of the seven patients with minimal JSW difference between the three treatment groups, we consider the influence minimal. Second, performance-based measures of physical function are recommended as secondary outcomes in hip and knee OA research but were not incorporated in this study due to practical and logistical issues[35,36]. Third, the recruitment process was not optimal resulting in seven patients being excluded post-randomization but before initiation of treatment, however this is unlikely to have caused bias[37]. Fourth, because our study was not powered to compare the PE and PE + MT interventions, our main results could formally not be tested in a confirmative manner. Lastly, the PE and MT were administered by only one therapist/chiropractor, limiting the external validity.

Overall, our study was able to demonstrate that also in Denmark with little experience in using PE and MT for OA patients, it is possible to conduct RCTs able to demonstrate relevant differences between non-surgical non-pharmacological interventions. Therefore, we consider our current framework a useful tool in planning future studies including larger cohorts allowing investigations of more subtle differences between relevant treatment options. Future trials should consider the following: (1) MT should be compared to PE alone and the optimal frequency and dose of MT should be determined; (2) inclusion of patients with co-morbidities and multiple sites of symptomatic OA to improve generalizability; (3) more than one therapist should deliver the MT and PE.

We suggest that patients currently receiving MT for hip OA in primary care should be informed about possible short-term discomfort, muscle soreness or mild pain lasting up to 48 h following MT.

In conclusion, this proof-of-principle trial was able to demonstrate clinical and statistically significant differences between a combined intervention consisting of MT and PE when compared to a MCI including home stretching for both primary (pain) and secondary outcomes in patients with unilateral hip OA. PE alone was no different to a MCI in reducing pain.

Author contributions

EP, HWC, ER, JH and SO participated in the conception and design of the study. None of the authors participated in data collection except EP who interviewed patients receiving MT for adverse events. EP drafted the manuscript. All authors participated in interpretation of the data, in critical revision of the manuscript and made important contributions to the content. All authors read and approved the final manuscript. EP, JH, HWC and SO take responsibility for the integrity of the work as a whole, from inception to finished article.

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Conflict of interest

All authors declare that they have no competing interests.

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Appendix 1. Protocols for PE, MT and MCI

Patients in all three groups receive instruction not to initiate or alter use of pain medication or use of glucosamine products during the 6-week intervention period.

PE

The PE program was taught by a physiotherapist, who had received specific training for teaching this program. It is designed by Maria Klässbo and the original text and illustrations are translated into Danish with permission[14].

The program includes a total of five sessions: one initial personal interview, three group sessions and one follow-up interview. Power point presentations and anatomic models are used as teaching aids. Each patient receives a sheet of paper with recommendations for activities of daily living (ADL) and home stretching exercises related to balance and hip mobility.

Initial interview (45 min)

The aim of the interview is to assist the therapist to understand the condition from the patient's viewpoint including pain experience, influence on ADL and levels of self-motivation. Ranges of reduced hip mobility and levels of coordination and balance are assessed for targeting specific exercises.

Group sessions

The purpose of group sessions is to create interaction between patients and have them share their individual experiences.

Group session 1 (1½ h)

Hip anatomy is taught including the purpose of cartilage, bone, joint capsule, ligaments, muscles and blood supply. Basic epidemiology includes age and gender distribution, risk factors and natural course of the disease. Diagnosis of hip OA clinically and radiographically is explained.

Group session 2 (1½ h)

The session is initiated by a short review. Hip muscle action, influence of locomotion and hip mobility on maintaining a healthy joint as well as how OA affects muscle function, ROM and movement are explained. Advice is given on keeping an active lifestyle and activities like swimming, cycling and walking are recommended.

Group session 3 (1½ h)

The session is initiated by a short review. The main lecture theme is pain including which tissue is pain sensitive and what signifies pain. Discussions are initiated on self-management of pain and pros and cons of pharmacological pain management. Different non-pharmacological treatment options are covered including acupuncture, physiotherapy and surgery.

Follow-up interview (½ h)

The purpose of this interview is to uncover unanswered questions and to sustain patients in exercise regimes.

Home stretches in the program are to be performed daily.

MT

The protocol is developed by the principal investigator (EP). It includes three different manual therapies: trigger point release therapy (TPPR), muscular stretching by muscle energy technique (MET) and joint manipulation.

Therapy is individualized according to examination findings of pain producing trigger points, reduced ROMs and end range assessment at each ROM. The duration of treatment sessions is 15–25 min twice a week for 6 weeks. Patients receive the three MT techniques in the sequence of TPPR, MET and joint manipulation.

TPPR

The aim of TPPR is to obtain desensitization and muscular relaxation of trigger points through digital mechanical pressure. The posterior and lateral hip muscles are palpated and trigger points are identified by locating taught and tender muscle fibers. Digital pressure is applied to trigger points until the patient senses a numbing effect of the pressure. This is normally accomplished in 1–3 min. The technique is described by Travell and Simons[38].

MET

The aim of the MET is to obtain muscle relaxation and improve ROM through stretching. The technique initiates with the therapist taking the joint to one of its active end ranges followed by asking the patient to push the leg in the opposite direction to the restriction using the antagonist muscle group. The contraction is held for 10 s with 20–30% of full contraction. The therapist resists this movement to achieve an isometric contraction. This is immediately followed by an agonist contraction in the direction of the resistance with the therapist assisting this movement to a "new" end range. This procedure is repeated three times and ended by keeping the final position for 10 s. MET is applied in the directions of ROM affected and can be applied to a specific ROM or coupled movements (e.g., combined flexion, abduction and external rotation). The technique is described by Chaitow[39].

Joint manipulation

The aim of joint manipulation is to affect hip musculature and joint capsule through forceful distraction also known as high volume low amplitude (HVLA) thrusts. The therapist places the joint in individual or combined ROMs, which have been evaluated to be affected by reduced ROM or altered end-play feel. At end range of joint movement, the joint is distracted and an HVLA thrust is applied using manual force. The force and speed applied should be of a sufficient magnitude aimed at cavitation of the joint[27,28]. Combined movements are flexion with internal rotation, flexion with external rotation or flexion with translatory abduction. Manipulations can be assisted by a "drop" mechanism of the treatment table. A section of the table under the pelvic/hip region is activated and raised 2–3 cm with a spring load (tension) mechanism. The level of tension can be set pending the weight of the patient and the force applied by the therapist. Three different techniques are directed at distracting the joint. One places the leg in a position of 10–15° abduction and 20–30° flexion; the other in a "loose packed" position of 25–35° of abduction, 20–30° of flexion and 30–40° of external rotation, and the third in a position with 20–25° of abduction and 0–10° of flexion with the knee in slight flexion. To achieve distraction of the hip joint, the therapist's hands are placed either around the distal ankle or distal femur. The technique is described by Peterson and Bergmann[27]. Each manipulation can be applied 1–3 times pending evaluation by the therapist.

MCI

Patients receive a pamphlet advising them not to initiate or alter their use of pain medication, nonsteroidal anti-inflammatory drugs or glucosamine products during the intervention period and instructing them not to initiate other treatment for their hip in the same period. The pamphlet includes the sheet with the stretching program from the PE group and patients receive 5–10 min of instruction on the program.

Appendix 2. Non-included or excluded patients prior to randomization

Reason for exclusion	(*n*)	
Not meeting inclusion criteria		37
- Age <40 or >80 years	12	
- Duration of hip pain <3 months	2	
- No radiographic OA	22	
- Not able to read or write Danish	1	
Meeting exclusion criteria		148
- Bilateral hip pain	45	

(*continued on next page*)

Appendix 2 (*continued*)

Reason for exclusion	(*n*)	
- Low back pain >hip pain	18	
- Hip dysplasia: center edge angle <25 and acetabular index angle >10	14	
- Polyarthritis	11	
- Indication of hip surgery expected within 6 months	7	
- MT <12 months	20	
- Previous hip or knee arthroplasty	8	
- Severe cerebrovascular disease	3	
- Lower leg neuropathy	2	
- Malignancies	2	
- Rheumatoid arthritis	1	
- Local knee pain on same side of hip pain	2	
- Pain severity <3 on a NRS	8	
- Conditions other than hip OA appearing to be the cause of pain	5	
- Spinal stenosis	2	
- Trochanteric bursitis		
Not wanting to participate		7
Other reasons		15
- Outside of recruitment area	10	
- Contraindication for MT	2	
- Not able to perform exercises due to severe asthma	1	
- Fear of hospitals	1	
- BMI >45	1	
Referral after end of inclusion		6
Total		213

Appendix 3. Mean scores of pain, HOOS and ROM at baseline, 6 weeks, 3 and 12 months for the three intervention groups: PE, PE + MT and MCI. Means, SDs.

Variable	PE means (SD)	PE + MT means (SD)	MCI means (SD)
NRS pain			
Baseline	5.1 (2.0)	5.4 (2.4)	5.8 (1.6)
6 Weeks	5.3 (2.3)	3.4 (2.4)	5.3 (1.7)
3 Months	5.5 (2.5)	4.0 (2.2)	5.6 (2.0)
12 Months	4.9 (2.5)	4.0 (2.5)	4.6 (2.2)
HOOS pain			
Baseline	64 (14)	62 (17)	59 (14)
6 Weeks	64 (16)	80 (16)	64 (13)
3 Months	64 (18)	76 (16)	61 (17)
12 Months	66 (21)	77 (15)	69 (15)
HOOS symptoms			
Baseline	62 (17)	61 (18)	59 (15)
6 Weeks	61 (19)	76 (18)	63 (16)
3 Months	59 (20)	74 (17)	58 (18)
12 Months	64 (25)	72 (17)	67 (18)
HOOS function in daily living			
Baseline	68 (15)	68 (20)	64 (15)
6 Weeks	69 (18)	84 (16)	70 (15)
3 Months	69 (18)	80 (17)	66 (18)
12 Months	69 (21)	79 (16)	73 (17)
HOOS sport and recreation			
Baseline	53 (22)	55 (21)	49 (21)
6 Weeks	56 (23)	76 (20)	60 (18)
3 Months	54 (23)	73 (19)	55 (18)
12 Months	60 (26)	69 (21)	54 (16)
HOOS hip-related QoL			
Baseline	53 (18)	52 (17)	46 (12)
6 Weeks	51 (18)	64 (17)	51 (12)
3 Months	52 (20)	62 (16)	49 (17)
12 Months	56 (22)	59 (15)	54 (16)
ROM – flexion			
Baseline	106 (15)	105 (13)	109 (13)
6 Weeks	106 (14)	110 (13)	113 (11)
3 Months	107 (13)	111 (13)	110 (13)
12 Months	107 (16)	109 (18)	113 (11)

Appendix 3 (*continued*)

Variable	PE means (SD)	PE + MT means (SD)	MCI means (SD)
ROM – abduction–adduction			
Baseline	41 (8)	41 (8)	42 (9)
6 Weeks	40 (8)	44 (8)	42 (8)
3 Months	41 (9)	44 (9)	42 (9)
12 Months	43 (9)	45 (7)	43 (10)
ROM – internal–external rotation			
Baseline	64 (15)	65 (14)	65 (12)
6 Weeks	67 (17)	67 (18)	71 (11)
3 Months	64 (18)	71 (14)	69 (12)
12 Months	67 (16)	69 (13)	68 (12)

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