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The effect of instruction in analgesic use compared with neuromuscular exercise on knee-joint load in patients with knee osteoarthritis: a randomized, single-blind, controlled trial

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SUMMARY

Objective: To investigate the effect of a neuro-muscular exercise (NEMEX) therapy program compared with instructions in optimized analgesics and anti-inflammatory drug use (PHARMA), on measures of knee-joint load in people with mild to moderate knee osteoarthritis (OA). We hypothesized that knee joint loading during walking would be reduced by NEMEX and potentially increased by PHARMA.
Design: Single-blind, randomized controlled trial (RCT) comparing NEMEX therapy twice a week with PHARMA. Participants with mild-to-moderate medial tibiofemoral knee OA were randomly allocated (1:1) to one of two 8-week treatments. Primary outcome was change in knee load during walking (Knee Index, a composite score from all three planes based on 3D movement analysis) after 8 weeks of intervention. Secondary outcomes were frontal plane peak knee adduction moment (KAM), Knee Injury and Osteoarthritis Outcome Scores (KOOS) and functional performance tests.
Results: Ninety three participants (57% women, 58 ± 8 years with a body mass index [BMI] of 27 ± 4 kg/m^2 (mean ± standard deviation [SD])) were randomized to NEMEX group ($n = 47$) or PHARMA ($n = 46$); data from 44 (94%) and 41 (89%) participants respectively, were available at follow-up. 49% of the participants in NEMEX and only 7% in PHARMA demonstrated good compliance. We found no difference in the primary outcome as evaluated by the Knee Index −0.07 [−0.17; 0.04] Nm/%BW HT. Secondary outcomes largely supported this finding.
Conclusions: We found no difference in the primary outcome; knee joint load change during walking from a NEMEX program vs information on the recommended use of analgesics and anti-inflammatory drugs.
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Background

Clinical guidelines advocate nondrug management strategies as first-line treatment for knee osteoarthritis (OA)[1,2]. These include patient education, exercise, and weight loss, and are preferred for their anticipated negligible adverse effects while still having relevant clinical effect. Despite this, analgesics and anti-inflammatory agents are widely and more commonly used treatments for knee OA in primary health care[3]. Although these are preferred for their pain-relieving effect[4], they also have dose-dependent adverse effects[5–7]. Furthermore, pharmacologic pain relief, by eliminating the protective mechanism of the pain itself, may increase/alter knee-joint load[8–13] which has a central role in symptoms and OA progression[14].

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Neuromuscular exercise (NEMEX), that emphasizes balance, muscle activation, functional alignment, and joint stability, has in pilot studies shown potential to reduce knee-joint loads and improve cartilage matrix quality in those at risk or with mild OA[15,16]. NEMEX is currently used effectively in physiotherapy practice[17] and for prevention and rehabilitation in OA patients before total joint replacement[18,19]. However, only few studies have investigated the effect from this type of exercise on knee joint load[15,20,21]. An uncontrolled pilot study consisting of 13 patients with mild knee OA[15] found a 14% reduction in external peak knee adduction moment (KAM; a surrogate of medial compartment load[22]) during one-leg rise after 8 weeks of NEMEX. Thus, it is possible that NEMEX, targeting the efficiency of lower-limb movement and muscle-activation patterns can be effective in improving dynamic knee-joint loading[14,23], whereas interventions providing pain relief through pharmacologically mediated pathways may be associated with an increase in knee-joint load[8,24].

Using outcomes composed by one plane solely, such as KAM or knee flexion moment (KFM) alone, may not provide the best assumption of medial compartment loading and risk of OA progression[25,26]. Thus, biomechanical outcome measures of total knee loading incorporating all three planes (frontal, sagittal and transversal) may be beneficial in OA research. Recently, the Knee Index, which is a relative novel biomechanical variable that incorporates all three planes into one single outcome, has been shown to be sensitive to the effects of anti-inflammatory and opioid treatments in knee OA patients[13].

The primary objective was to compare the effect of a NEMEX program with instructions on optimized analgesics and antiinflammatory drug use on knee loads in participants with mild to moderate medial tibiofemoral knee OA. We hypothesized that the first peak Knee Index during walking would be reduced by NEMEX as opposed to a potential increase by analgesic use.

Methods

Study design

A single-center, randomized (1:1), single-blind, controlled trial approved by the Regional Scientific Committees for Southern Denmark (identifier: S-20110153) compliant with the Helsinki Declaration. The study protocol[27] conforms to the SPIRIT statement[28], and the reporting follows the recommendations from CONSORT for nonpharmacologic studies[29,30].

Participants

Men and women with a clinical diagnosis of knee OA aged 40–70 years were recruited via general practitioners in the communities of Odense and Middelfart, Denmark, and from advertisements in local clubs, libraries, print media, and Facebook. For a full list of inclusion and exclusion criteria, see Appendix 1. In summary, included subjects had persistent knee pain, a clinical diagnosis of knee OA in accordance with The American College of Rheumatology criteria (ACR)[31], were with/without radiographic changes, had no contraindication for exercise, non-steroidal anti-inflammatory drugs (NSAIDs), or X-ray, and had not had any leg surgery/trauma within the last 6 months. Subjects demonstrating radiographic signs of lateral compartment OA (greater joint space narrowing in the lateral compared to medial compartment assessed qualitatively) and/or at clinical examination (area of pain and bony tenderness) were excluded.

Participants were assessed for eligibility by a general practitioner or by a project manager via e-mail or telephone. Subsequently, participants were invited to a formal information meeting, during which the signing of an informed-consent form, and clinical assessments were performed.

Randomization

Eligible participants were randomly allocated in permuted blocks of four to six computer generated *a priori* by the trial biostatistician (RC) to either exercise (NEMEX) or instruction in analgesic use (PHARMA). The allocation was concealed in a computer file only accessible by the biostatistician. Individual allocations were held in sealed, opaque, consecutively numbered envelopes; i.e., after the participant had been tested at baseline, the envelope was opened and the participant was informed about the allocation.

Interventions

NEMEX

NEMEX has been described in detail[27]. In brief it consisted of five parts: warming up (10 min of aerobic activity at “rather strenuous level”[32]), functional, proprioceptive, endurance strengthening, and cooling down. The functional part comprised five exercises with focus on: core stability/postural function, postural orientation, and lower-extremity muscle strength. The proprioceptive part comprised three exercises, with focus on balance and functional stability. The endurance strengthening part comprised three exercise circuits, with focus on postural and functional stability of the trunk and knee.

The training took place in groups (up to 10 participants) twice a week (each session 60 min) for 8 weeks, and was supervised by NEMEX-educated physiotherapists. To allow for progression, three to four levels of difficulty were given for each exercise. The cooling down included walking/jogging (forward, backwards, sideways and cross-over) with emphasis on quality of alignment and symmetric and uniform weight bearing, and stretching exercises for the lower extremity muscles (10 min)[19,33]. No restrictions on home exercises or participation in additional exercise programs besides the supervised NEMEX were provided.

The physiotherapist recorded the date for each attended session. The participant reported the level of perceived exertion (Borg RPE CR-10[50]), and pain (visual analogue scale for pain [VAS]-scale, 0–10 cm) before and after each training session. During exercise, the supervising therapist assessed pain including flares to progress/regress level of exercise difficulty. Pain up to 2 on the VAS-scale was considered “safe”; between 2 and 5 as “acceptable”; and pain >5 as “avoid”. “Acceptable pain” (between 2 and 5) was allowed during and immediately after training, and increase in resting pain compared with normal was accepted as long as the increase had subsided to normal resting pain level at 24 h after the training session[33,34]. Participants were informed to expect muscle soreness and slight irritation of the joints. While participants were allowed over-the-counter and prescribed pain-relieving drugs, this was not recommended.

Good compliance was defined as $\geq$12 sessions.

PHARMA

The PHARMA group received information on how best to use acetaminophen and oral NSAIDs, in doses consistent with Danish guidelines[1]. The information was described in details in the study protocol[27]. In brief, participants were provided with a pamphlet and a video outlining the recommended use of mild analgesics and antiinflammatory drugs (that is, acetaminophen and oral NSAIDs). Participants were encouraged to take their medication according to their need and to adjust the medication according to their pain levels.