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Effects of 6 weeks of cryotherapy plus compression therapy after total or unicompartmental knee arthroplasty: protocol for a single-centre, single-blind randomised controlled trial

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ABSTRACT

Introduction Effective rehabilitation after total knee arthroplasty (TKA) and unicompartmental knee arthroplasty (UKA) is often impeded by pain and swelling. Beneficial short-term effects in terms of pain and opioid use after a short period of cryotherapy (±compression therapy) have been demonstrated. The effectiveness of a longer intervention period on longer-term postoperative outcomes is unclear. This study aims to assess the effects of 6 weeks of cryotherapy plus compression therapy on pain, functioning and patient satisfaction after TKA or UKA.

Methods and analysis A single-centre, single-blind randomised controlled trial will be conducted at a teaching hospital in the Netherlands. Patients over age 18 with end-stage osteoarthritis planned for a TKA or UKA are eligible; 104 UKA and 104 TKA patients will be included. Both groups will be randomly allocated (1:1) into an intervention group receiving 6 weeks of cryotherapy plus compression therapy (commencing after discharge from hospital) or a control group (usual care). The primary endpoint is perceived pain at rest at 6 weeks postoperatively. Secondary outcomes include compliance with cold protocol, pain at rest during the first six postoperative weeks and at 6 and 12 months postoperatively, pain on weight bearing, opioid use, functioning, patient satisfaction and complications.

Ethics and dissemination The local medical ethics committee MEC-U approved the study protocol (R22.095/NL-number NL81956.100.22). The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice regulations, and personal data will be handled in agreement with the Dutch Personal Data Protection Act (AGV). Written informed consent will be obtained prior to performing any of the study procedures. We will disseminate study results through multiple peer-reviewed publications and through conference presentations.

Trial registration number NCT05572359.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A low-cost and easy-to-use cooling brace is used in the study.
⇒ Effectiveness is studied using a broad range of instruments; in addition to patient-reported questionnaires, physical examination tests will be performed to measure functional recovery as patients tend to overestimate their functioning shortly after surgery.
⇒ Little is known so far about the effects of cryotherapy after unicompartmental knee arthroplasty (UKA); this study will investigate the outcomes of cryotherapy plus compression therapy in total knee arthroplasty and UKA patients, making a comparison possible.
⇒ A limitation is the single-blind design, which could result in a placebo effect that may introduce a small bias in the outcomes, since several of these are subjective.
⇒ Cryotherapy will be used in combination with compression therapy; it will not be possible to differentiate between the effects of cryotherapy and compression therapy separately.

INTRODUCTION

Total knee arthroplasty (TKA) and unicompartmental knee arthroplasty (UKA) are well-established treatment options for osteoarthritis (OA) of the knee, as long-term improvement in pain, functioning and quality of life are reported in literature.[1] Effective rehabilitation in the early period may be hampered by pain and swelling due to inflammatory reaction following tissue damage.[2] Especially considering the increasing opioid abuse with its accompanying side effects, alternative analgesic techniques are desirable.[3]

Cryotherapy plus compression therapy may be an effective and non-invasive way to enhance postoperative rehabilitation. Cryotherapy reduces intra-articular temperature, which in turn reduces blood flow and sensory nerve transmission, leading to less swelling and perceived pain.[4 5] Adequate compression on the skin reduces postoperative intra-articular bleeding, in turn reducing swelling.[6] Kullenberg *et al* showed that concurrent use

of both cryotherapy and compression therapy is beneficial in terms of pain control and haemarthrosis.[7]

There are several ways to apply cryotherapy and compression therapy, such as ice bags, a cold-compression brace or a computer-assisted cryotherapy device. The effectiveness of cryotherapy (±compression therapy) on recovery after joint arthroplasty has been extensively studied, mostly finding a beneficial effect on pain.[8–10] A review by Chughtai *et al* including 16 randomised controlled trials (RCTs) using cryotherapy after knee arthroplasty demonstrated that the majority of studies favour the use of cryotherapy for postoperative pain compared with standard care.[9] This review concluded furthermore that the most optimal device would be one with continuous cold flow, including compression. The added value of compression was confirmed by a recently updated Cochrane review that showed a trend favouring the combination of cold and compression over cryotherapy alone.[11] A systematic review by Wyatt *et al*, (2022), who included six recent RCTs between 2017 and 2022 showed not only decreased perceived pain but also a reduction in opioid consumption in the cryotherapy group within the first post-TKA week.[8] Thijs *et al* (2018) demonstrated in their RCT that the use of cold therapy (computer-assisted device set on 12 degrees) during the first postoperative week resulted in 2.6 less opioid use as a rescue medication compared with the control group (device set on 21 degrees)[12]; in the RCT of Brouwers *et al* a significant reduction of opioid escape medication use was found in the cryotherapy group compared with the usual care group (21% vs 40%).[13] No clear longer-term benefits of cryotherapy were found.[8 9] The recent Cochrane review concluded that there is low-certainty evidence for a beneficial effect of cryotherapy on blood loss, pain, range of motion and swelling in the short-term, but not on the longer-term.[11]

Studies so far have only had an intervention period using cryotherapy (±compression therapy) for a week. This relative short duration could explain the beneficial effects only being demonstrated in the short-term. A longer intervention period may have a prolonged beneficial effect. To our knowledge, no study has been conducted on the effects of multiple weeks of cryotherapy plus compression therapy. The primary aim of this study is to investigate the effects of 6 weeks of cryotherapy plus compression therapy on pain in rest 6 weeks after TKA and UKA. Secondary aims are to study the effectiveness in both groups of patients on pain in rest (other time points), pain during loading, opioid use, functioning, patient satisfaction, complications and compliance with the cold protocol instructions.

METHODS AND ANALYSIS

Project period

The start of inclusion of this study was in May 2023 and the inclusion of patients is expected to take approximately 1 year. With 1 year of follow-up, the planned end date of the study is June 2025.

Study design and setting

A single-centre, single-blind, parallel-group RCT will be conducted into the effects of 6 weeks of cryotherapy plus compression therapy after TKA and UKA at the Orthopaedic Surgery Department of Martini Hospital, a teaching hospital in the Netherlands. A flow chart of the study procedures for patients in time is presented in figure 1.

Eligibility criteria and patient recruitment

Inclusion criteria are patients with end-stage OA over age 18 who are planned for a TKA or UKA at Martini Hospital. Exclusion criteria are revision TKA implant (only for the TKA patients), perioperative conversion to TKA (only for the UKA patients), rheumatoid arthritis, comorbidities on which cryotherapy plus compression therapy may have a negative impact (as judged by the orthopaedic surgeon) and inability to read and understand Dutch. Since the cool pack—part of the cold and compression brace—needs to be cooled in a freezer, patients are required to have access to a freezer. Treating surgeons will inform eligible patients about the study by handing out a patient information letter explaining all the study details, including the informed consent form (online supplemental appendix 1). Written informed consent will be required prior to performing any of the study procedures. Patients are asked to return the signed informed consent form by mail. This form will subsequently be signed by a physician involved in the trial.

Randomisation and blinding

Participants will be separated into two groups, according to their planned procedure (TKA or UKA). Both groups will be randomly allocated into an intervention group or a control group—randomisation is stratified by surgery type. The randomisation procedure (block, ratio 1:1) for the intervention and control groups will be based on sequentially numbered opaque sealed envelopes; the order of the sequence will be computer-generated. Allocation to the control or intervention group will take place after the baseline measurements to ensure blinding. These baseline measurements and allocation will be performed by the research staff of the Orthopaedics department of the Martini Hospital (study coordinator (AJdV) or one of the two research nurses). Follow-up physical examination measurements will be performed by a blinded assessor (trained nurses with experience in orthopaedics). Patients are instructed not to talk about the intervention they received during this visit until these measurements are performed.

Study intervention

The intervention group will receive cryotherapy plus compression therapy after hospital discharge for 6 weeks postoperatively. The U-sport ultimate recover knee cold compression brace will be used to apply the cryotherapy plus compression therapy. Cold is applied by a reusable gel package. With a hand pump the amount

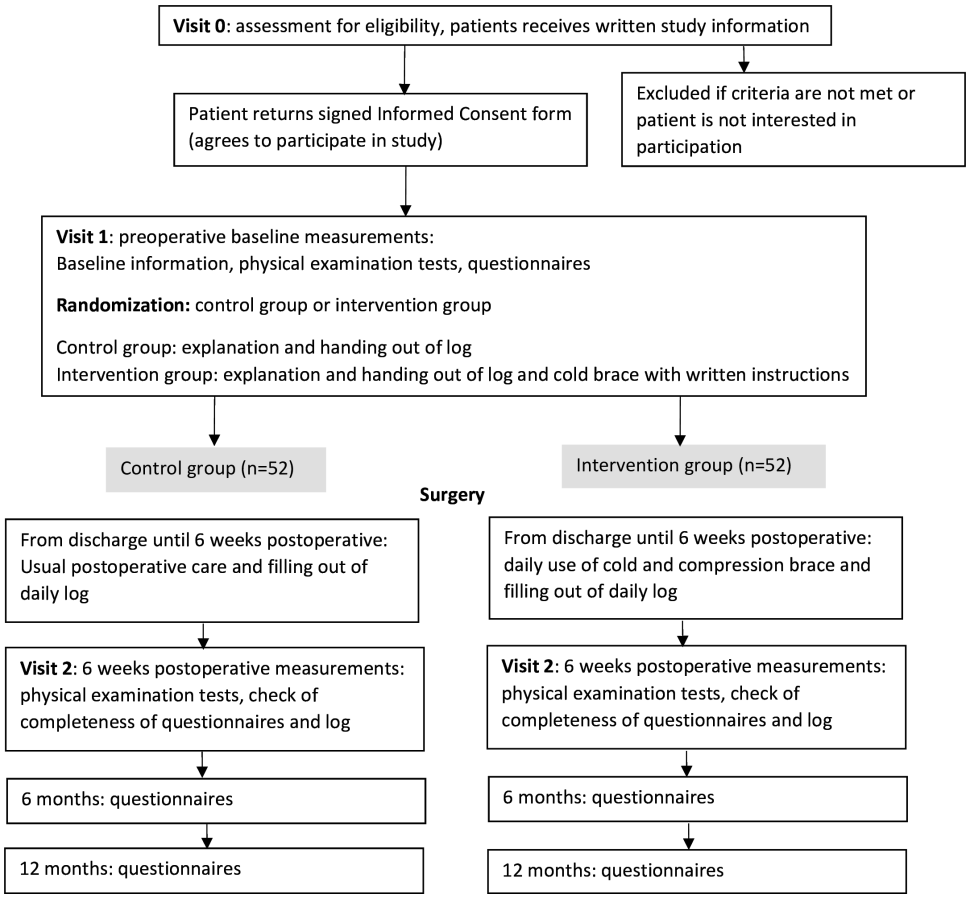

Figure 1 Flowchart of the study procedures.

of compression can be adjusted by the patient itself. Patients will be instructed to use the cool brace five times a day for a maximum of 20 min, as was done in the study of Demoulin *et al*.[14] Patients will be instructed to use compression too, by using a hand pump to force air in the brace, but the amount of compression will depend on the patient's preference and will not be graded. Both control and intervention groups will receive during hospitalisation standardised postoperative care according to the rapid recovery protocol from Martini hospital, which consists of early full weight-bearing mobilisation and range of motion exercises guided by a physiotherapist, cold packs and 24-hour postoperative compressive bandaging. According to standard protocol, after discharge, postoperative pain will be managed with paracetamol and a non-steroidal anti-inflammatory drug (NSAID, eg, diclofenac/naproxen/ibuprofen). For patients with NSAID intolerance, the naproxen is replaced by oxycodone. In both the standard and adapted protocol, patients can use extra oxycodone (up to 5 mg four times a day and/or 10 mg extended release one time a night) in case of excessive pain. There are during hospitalisation as well as after discharge no restrictions on co-interventions regarding analgesics and cold packs as used in regular care for either the intervention or control groups.

Evaluation

To evaluate recovery after surgery several questionnaires and physical examination tests are assessed preoperatively and postoperatively (for an overview see table 1). During the first six postoperative weeks patients fill out a daily log. In this daily log patients are asked to document the frequency of the use of cold packs (control groups)/cold brace including use of compression (intervention groups), and to document additional opioid use in case of excessive pain and the daily perceived pain in rest and during loading. To promote patient retention and completeness of the log, patients will be contacted by phone after 2–3 weeks after surgery by a researcher to ask if there are questions or problems and to remind the patient to fill out the daily log.

Outcome measures

Primary outcome

Primary endpoint of this study is the 11-point Numerical Rating Scale (NRS) pain scale (where 0 indicates no pain and 10 indicates extreme pain) to rate perceived pain at rest 6 weeks postoperatively.

Secondary outcomes

Pain

The 11-point NRS pain scale at rest will be assessed postoperatively as a secondary outcome daily during the first 6

Table 1 Overview of time points of study procedures and evaluation measures

	Preoperative	Surgery	6 weeks	6 months	12 months
Randomisation	X				
Log - opioid use, NRS pain scores (rest and while loading) and use of cold packs (control groups) or cold brace with or without compression (intervention groups)		Starting from discharge: daily during first 6 weeks			
Satisfaction with brace (intervention groups)			X		
Physical examination					
AROM	X		X		
TUG	X		X		
Knee circumference	X		X		
Questionnaires					
NRS pain rest	X		X	X	X
NRS pain loading	X		X	X	X
EQ5D-5L	X		X	X	X
KOOS-PS	X		–	X	X
OKS	X		X	X	X
KOOS*	X		X	–	–
WORQ	X		X	–	–
Anchor questions (pain and ADL)			X	X	X
Satisfaction with surgery			X	X	X

*Except for the sports and recreation subscale.
ADL, activities daily living; AROM, active range of motion; EQ5D-5L, EuroQol-5 dimension, 5-point Likert scale; KOOS(-PS), the Knee injury and Osteoarthritis Outcome Score (Physical Functioning Short Form); NRS, Numerical Rating Scale; OKS, Oxford Knee Score; TUG, Timed Up and Go; WORQ, Work, Osteoarthritis and joint-Replacement Questionnaire.

weeks and at 6 and 12 months. At the same postoperative time points (daily during the first 6 weeks, after 6 weeks and at 6 and 12 months) the 11-point NRS pain score for pain during loading will be assessed. An anchor question for perceived pain will be used to determine improvement at 6 weeks and 6 and 12 months postoperatively compared with the preoperative situation (7-point Likert scale, range: much worse—much improved). The need for 5 and 10 mg oxycodone as escape medication will be asked to document daily during the first six postoperative weeks as an additional outcome measure.

Functioning

Physical examination tests will be assessed preoperatively and at 6 weeks postoperatively, and consist of measuring active range of motion (AROM) using a goniometer for maximal flexion and extension (in degrees), measuring knee circumference (in cm, mid-patella, 7 cm proximally and 7 cm distally of the patella) and the Timed Up and Go (TUG, in seconds). With the TUG, patients will be asked to sit down in a chair, walk 3 m to the mark and walk back again to sit down in the chair. Time will be measured from the point of standing up to the point of sitting down again. Patients will be allowed to use walking aids. Both AROM and knee circumference assessment are shown to be reliable measurements in terms of knee motion and swelling, respectively.[15] The TUG is shown to be a sensitive method to quantify functional performance after TKA.[16]

Several questionnaires will be used to assess functional outcomes in this study—preoperatively and at 6 weeks and at 6 and 12 months postoperatively. The Knee injury and Osteoarthritis Outcome Score (KOOS) (42 items) contains of five different subscales (pain, symptoms, activities of daily living, recreational activities and sports and knee-related quality of life) with scores ranging from 0 (extreme knee problems) to 100 (no knee problems) per subscale. As this questionnaire will be assessed preoperative and after 6 weeks, the subscale recreational activities and sports will not be assessed (with items like running, kneeling and jumping being not valid). The Short Form (KOOS-Physical Functioning, 7 items) which is comprised of items of the subscales activities of daily living and recreation and sports, will be used at the 6 and 12 months postoperative time points.[17] The Work, Osteoarthritis and joint-Replacement Questionnaire is a valid instrument to evaluate the impact of knee problems following TKA on work, using a 0–100 scale (0 indicating no ability to work).[18] The Oxford Knee Score (score range 0–48, with 0 indicating maximal functional limitations) will be used to measure functional limitations of the knee in different activities.[19] Last, the anchor question of daily functioning will be scored to determine improvement compared with

the preoperative situation (7-point Likert scale, range: much worse—much improved).

Patient satisfaction, quality of life, complications and compliance

Patient satisfaction using an 11-point NRS (0 indicating no satisfaction and 10 complete satisfaction) and quality of life using the EuroQol-5 dimension questionnaire, which measures health-related quality of life in five different dimensions will be evaluated at 6 weeks and 6 and 12 months postoperatively.[19] Complications using the cold compression brace (frostbite, other inconveniences) will be documented during the first six postoperative weeks; other complications after surgery (infections, reoperations) during the first postoperative year. Compliance with use of the cold compression brace in the intervention group according to protocol during the first six postoperative weeks will be obtained based on the daily log. Last, patient satisfaction (using an 11-point NRS scale) with use of the brace will be assessed 6 weeks postoperatively.

Baseline characteristics

To describe the study sample, sex (male/female), age (in years), height (in cm), weight (in kg), body mass index calculated based on height and weight (in kg/m^2), side of TKA/UKA ((index knee) left/right), Kellgren and Lawrence OA classification system (range 0–4) of the index knee (determined by one experienced orthopaedic surgeon, RWB), presence of issues on other knee (contralateral side, yes/no), whether patient already had a TKA/UKA on the other side (yes/no), presence of symptoms in the hip joint or in other lower extremities (yes/no) and length of stay (hours) will be obtained.

Sample size

An a priori sample size calculation is performed. For both study groups this sample size calculation is based on the pain score 6 weeks postoperatively, found by Brouwers *et al* (2020), which is 3.2 (SD 2.4) on an NRS pain scale in the control group.[13] A minimal clinical difference of 1.4 is used for this calculation.[20] Two-sided testing, a power of 80%, and an alpha of 0.05 led to a sample of 47 patients per arm. With an expected drop-out rate of 10%, a sample of 52 patients per arm will be needed for the TKA as well as the UKA patients—so in total 104 TKA patients and 104 UKA patients. As was agreed with the ethical committee, in case of a drop-out all data that are gathered until that moment can be used in the analysis.

Statistics

An intention-to-treat analysis will be performed, where patients allocated to one of the two groups will be analysed in that group, independently of their compliance with the protocol. Descriptive statistics will be used to present the data: means and SD when data are interval/ratio and normally distributed, and medians and IQRs when data distribution is considered not normal. Frequencies and percentages will be used for categorical variables. Analysis will be performed using IBM SPSS V.25.0. An alpha of 0.05 will be considered statistically significant.

Primary outcome

For the primary outcome, NRS pain score at rest an analysis of covariance will be used at 6 weeks to assess the difference between the two study groups within one patient category (UKA or TKA), where will be corrected for the baseline NRS pain score in rest by including this variable as a covariate. To assess if the intervention is more effective in one patient category (UKA or TKA), a linear regression analysis will be performed with NRS pain score in rest at 6 weeks as the dependent variable and the baseline NRS pain score in rest, the patient category (UKA/TKA), group (intervention/control) and the interaction effect (patient category * group) as predictors.

Secondary outcomes

For the ratio/interval outcome variables that will be assessed multiple times (eg, the questionnaires and NRS pain scores), the generalised estimated equations analysis (exchangeable data structure) will be used to analyse if there are differences between groups, in time and between groups in time (interaction group * time). 'Groups' are considered the intervention and the control group within a patient category (UKA or TKA), to assess whether there is a difference on that particular outcome between intervention and control group (in time). A possible difference between the effectiveness of the intervention between the patient categories (UKA and TKA) will also be assessed. This will be done by adding patient category (UKA/TKA) as an additional factor to the model and to investigate the interaction 'patient category * group' and 'patient category * group * time'. To investigate if there are differences between groups for the other outcome variables with a nominal or ordinal measurement level (eg, analgesic use), a Pearson χ^2 test will be used.

Patient and public involvement

The feedback of patients in our previous trial studying the effect of cryotherapy after TKA,[13] as well as the feedback from one patient that used the cold and compression brace as a pilot during 6 weeks and filled out the log, was taken into consideration in the design and conduct of our study. Patient and/or public were not involved in the reporting or dissemination plans of this trial.

ETHICS AND DISSEMINATION

Prior to the start of the inclusion, this trial was registered at ClinicalTrials.gov. The local medical ethics committee MEC-U approved the study protocol (R22.095/NL-number NL81956.100.22). The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice regulations, and personal data will be handled in agreement with the Dutch Personal Data Protection Act (AGV). Written informed consent will be obtained from all participants prior to performing any of the study procedures. In this project we process and store personal (identifiable) patient data only in the key list. The key list

is kept in our electronical patient dossier where only those persons who have interference with the research project have access. All other paper documents, the Case Report Form (CRF), questionnaires and the log are coded and do not contain patient identifiable data. All the data will ultimately be collected digitally using an electronical CRF (research manager) with the code as the identifier. An independent monitor will evaluate this trial prior to the first inclusion, two times during the execution of the trial and at close-out. No interim analysis or stopping guidelines are described, considering the non-invasive nature of the intervention.

We aim to facilitate data-sharing in line with the FAIR (Findability, Accessibility, Interoperability and Reuse) principles, and data-sharing will be considered on reasonable request. Study results will be disseminated by multiple peer-reviewed publications and through conference presentations. After completion of the trial, all participating patients will receive a summary of the study results.

Contributors AJdV: design of the work, handling of ethical applications; drafting of the manuscript. HKA: drafting and revision of the manuscript. RWB: design of the work and revision of the manuscript. All the authors contributed to the content of the protocol and approved the final version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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