PROTOCOL

The effect of cryoneurolysis for the treatment of acute postoperative pain following total knee arthroplasty in high pain responders – A randomized, participant- and observer-masked, sham-controlled trial

(Cryoanalgesi til behandling af smerter efter total knæalloplastik – Et randomiseret, blindet og shamkontrolleret studie)

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The sponsor hereby confirms, always, to follow the protocol and work in accordance with the principles for Good Clinical Practice.

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1. Introduction

1.1 Background

Total knee arthroplasty (TKA) is a frequently performed procedure and is expected to increase in numbers due to the aging population and growing obesity rates [1-6]. Fast-track regimes with multimodal opioid-sparing analgesia have improved postoperative outcomes [7, 8]. However, a subset of patients still experiences unsatisfactory levels of postoperative pain in the weeks following surgery [9-12], potentially delaying mobilization and recovery as well as increasing the need for opioid analgesics. Current recommendations for pain management following TKA according to the Procedure Specific Postoperative Pain Management (PROSPECT) Working Group include paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, local infiltration analgesia, and single shot adductor canal block (ACB) [12]. However, the role of ACBs for pain after TKA has been under extensive debate in recent years. While an ACB may provide some pain relief, the duration of pain control is usually less than 24 h and the effect on length of stay (LOS) and opioid consumption is questionable [12].

In the past decades, cryoneurolysis has been used to treat acute pain following herniorrhaphy [13], tonsillectomy [14], and thoracotomy [15] via the surgical incision. The emergence of percutaneous cryoprobes and the use of ultra-sound guided techniques has allowed for an increase in potential applications [16]. Recently, the use of cryoneurolysis has gained attention as a potential regional anesthetic technique for the treatment of knee pain. Cryoneurolysis works by freezing peripheral nerves with temperatures in the range of -20^{o}C to -100^{o}C, causing a Wallerian degeneration of nerve axons distal to the treatment site [17]. This process involves loss of the relative continuity of the axon and its covering of myelin but with a preservation of the surrounding endo-, peri-, and epineurium, thus allowing normal axonal regeneration and remyelination. Axons regenerate at a rate of 1-2 mm/day. Thus, resulting in a nerve block that typically will resolve with full recovery within weeks to months depending on the site of treatment [17].

The effect of cryoneurolysis on knee pain has been documented in a few studies. A randomized, double-blind, sham-controlled trial found that cryoneurolysis reduced symptoms of knee osteoarthritis for up to 150 days [18]. A retrospective chart-review of 100 patients undergoing TKA found that cryoneurolysis significantly lowered LOS, reduced opioid consumption until 12 weeks after surgery, and reduced pain at the 2- and 6-weeks follow-up [19]. Another retrospective analysis in 267 patients undergoing TKA found a comparable reduction in opioid requirements, pain, and LOS in patients treated with cryoneurolysis compared with historic controls [20]. A recent RCT comparing cryoneurolysis to standard of care in 124 patients undergoing TKA found that cryoneurolysis reduced opioid consumption at 72 h, 6 weeks and 12-week follow-ups [21].

Although these findings are promising, cryoneurolysis is expensive and comprehensive, and might not be relevant in all patients receiving multimodal analgesia with COX-2 inhibitors, paracetamol, local infiltration analgesia, and high-dose steroid in a fully implemented enhanced recovery program [22, 23]. Several risk factors have been associated with a high pain response including age, gender, preoperative pain, psychological profile, and quantitative sensory testing (QST) [24-26]. However, when including postoperative pain in

the prediction of acute pain, movement-evoked pain 24 h postoperatively is the best predictor for pain the week following surgery [Springborg AH et al. – IN PREPARATION].

Using postoperative pain 24 h after surgery as a predictor of a sustained high pain response, we hypothesized that postoperative cryoanalgesia compared to a local anesthesia (LA) block with sham cryo treatment would reduce pain in patients with moderate to severe pain following TKA 2-7 days after surgery.

2. Aim

To compare the effect of postoperative cryoanalgesia with a sham treatment consisting of LA block only on postoperative pain in the first week after surgery in TKA patients with moderate to severe pain on the first postoperative day.

3. Outcomes

3.1 Primary outcome

Cumulated pain (VAS 0-100 mm) upon ambulation in a 5-meter walk test on days 2-7 postoperatively after TKA surgery.

3.2 Secondary outcome

- Pain (VAS 0-100) during rest and during 5-meter walk test at the 2 weeks, 4 weeks, 12 weeks, and 24 weeks follow-up
- Pain relief immediately following blockade evaluated as ΔVAS 0-100 during a 5-meter walk test before and after the blockade
- Cumulated pain at rest and during night from days 2-7
- Quality of sleep and nausea postoperatively from days 2-7
- Cumulative use of rescue-analgesics from days 2-7, and at 2 weeks, 4 weeks, 12 weeks, and 24 weeks follow-up
- Oxford knee score at 12 weeks
- LOS in hospital, and reasons for prolonged stay (>1 postoperative day) registered as “Why still in hospital”
- Reasons for re-admissions within 12 weeks
- Morbidity and mortality (4-, 12-, and 24 weeks follow-up by Electronic Patient Journal (EPJ) or telephone)

4. Study design

Randomized, participant- and observer-masked, sham-controlled trial.

4.1 Intervention groups

Patients eligible for participating in the study will be evaluated 24 h after surgery for the presence of moderate to severe pain. Patients with pain (VAS 0-100 mm) ≥ 45 during a 5 m walk test are included.

The study will include the following intervention groups:

Sham cryo (sham-group): Postoperative sham cryoneurolysis of the lower extremity.

Cryoneurolysis (cryo-group): Postoperative cryoneurolysis of the superficial genicular nerves, i.e., the infrapatellar branches of the saphenous nerve (ISN) and the anterior femoral cutaneous nerve (AFCN).

Both cryoneurolysis and the sham block will be performed using ultrasound and a nerve stimulator (*see 8.2 Intervention page 11*). An injection of ropivacaine around the nerves will be administered in both groups preceding the intervention. The patient will be blinded but the anesthetist performing the intervention will be unblinded.

4.2 Number of patients

44 patients, 22 in each group (sham-group vs. cryo-group).

4.3 Number of visits to the hospital

The patients will follow the standard fast-track protocol in our specialized arthroplasty unit. There will be no additional visits at the study site.

5. Selection criteria

5.1 Inclusion criteria

- Age $\geq$ 18
- Primary unilateral TKA
- Ability to participate in the study (understand written and spoken Danish language, self-reported pain and satisfaction)
- Signed written informed consent form
- Pain (VAS 0-100 mm) ≥ 45 during a 5-meter walk test at 24 h (20-28h) postoperatively

5.2 Exclusion criteria

- Ongoing treatment of systemic glucocorticoids or other immunosuppressant treatment apart from inhaled steroids
- Insulin-dependent diabetes
- Pregnancy or breastfeeding*
- Mental disability that could impair a patient's decision-making capability of giving informed consent and not enabling valid data collection.
- Patients with known diagnoses of schizophrenia, ongoing psychosis, bipolar disease and/or a history of ongoing anti-psychotic treatment.
- Patients with modulated pain-reception (experience) based on other diseases or injuries, e.g. spinal cord or brain injury, severe polyneuropathies or neurologic disorders.
- Posttraumatic osteoarthritis as reason for TKA
- Bleeding disorder
- Localized infection in the treatment area

- Cryoglobulinemia, cold urticaria, paroxysmal cold haemoglobinuria, or Raynaud's syndrome
- Perioperative peripheral nerve block

*Pregnancy: No women with suspected or proven pregnancy are eligible for inclusion. The following will be considered as safe contraception: intrauterine device or hormonal contraception. For women aged between 18-50 years, a urine HCG test for pregnancy will be performed.

6. Randomization and blinding

6.1 Randomization

Using https://www.sealedenvelope.com/, a randomization will be carried out using 2:2 block-randomization, half of which will be allocated to the sham-group and the other half to the cryo-group.

It is not possible to perform the cryoneurolysis while being blinded. Thus, the anesthetist performing the intervention will be unblinded. However, the patient and all personnel involved in study-specific assessments will be blinded to the allocation.

Group 1: sham-group	Postoperative ultrasound guided nerve block with LA followed by sham cryoneurolysis of the superficial genicular nerves.
Group 2: cryo-group	Postoperative ultrasound and guided nerve block followed by cryoneurolysis of the superficial genicular nerves.

https://www.sealedenvelope.com/ will generate unique randomization codes to be imported to REDCap. Two lists containing the unique randomization codes will be made and stored at the Dept. of Anesthesiology, Hvidovre Hospital.

6.2 Blinding

The patient, the investigators performing study-specific assessments, and the sponsor will all be blinded to the intervention allocation, until all data processing is finished. However, one anesthetist performing the intervention will be unblinded to the allocation.

Sealed coding-envelopes containing data on randomization are stored in a locked cabinet at the Dept. of Anesthesiology, Hvidovre Hospital. If an unblinding of a randomized patient is deemed necessary by the attending physician, to secure health and patient-safety, unblinding will be made by opening the sealed patient-specific randomization envelope, containing set patient's allocation. The on-site investigator can always also be contacted to assist in unblinding and guidance. In case of unblinding, the reason for unblinding is noted, dated, and signed by the investigator in the specific patient CRF.

6.3 Procedures in case of emergency

The investigator will ensure that emergency procedures and the necessary expertise will be available for the patient during the study.

7. Statistics

7.1 Power calculation

Data from our previous study showed that pain during a 5-meter walk test at 24 h was the best predictor of cumulated pain on days 2-7 after TKA surgery [Springborg AH et al. – IN PREPARATION]. With the optimal cut-off of VAS ≥ 45, the mean (SD) cumulated pain during a 5-meter walk test on days 2-7 was 390 (208). A 50 % reduction in cumulated mean VAS upon mobilization days 2-7 postoperatively is clinically relevant. In a two-sided superiority design with a level of significance of 0.05 and a power of 80% we need two groups of 18 patients each. Assuming a small number of dropouts, 22 patients will be included in each of the two groups resulting in inclusion of 44 patients in total.

7.2 Data analysis

All participants who meet the inclusion criteria and undergo randomization will be included in the intention-to-treat (ITT) population. The per-protocol (PP) population is defined as the group of patients who are randomized, receive the treatment to which they were randomly assigned, and complete their assessments without any major protocol deviations. The primary and secondary outcome analyses will each be performed for the ITT and PP populations. The primary endpoint along with other continuous data will be tested using independent samples t-test or Mann-Whitney U test as appropriate. The secondary outcomes will also be analyzed relative to the pain relief during the initial LA injection in the cryo group versus the remaining patients from both groups. A *P*-value < 0.05 is considered significant. Dichotomized data will be tested using Chi-square or Pearson's exact test. Uni- and/or multivariate analysis, where appropriate, will be made to test for independent variables. Missing values will be accounted for in the final statistical plan. Statistical calculations will be made using either R statistical software (Open source) or SPSS statistics (IBM, New York, USA).

The study will be registered at Clinicaltrials.org and will include a complete statistical analysis plan submitted to publication.

8. Study plan

A general layout of the study is provided in Appendix 1. In the outpatient clinic, the screening procedure will be performed among patients planned for TKA by the surgeons. Patients will be asked by orthopedic staff whether they may be contacted regarding the research project. The research staff will then contact potential patients either in person or via telephone. The written study information will be explained – either at the outpatient clinic or via telephone by the investigator.

All patients receive both spoken and written information. Information is given in a separate closed room without interruptions. All patients are given the chance of an additional meeting with the chance of bringing a relative. All patients must give a signed informed consent on paper prior to inclusion to participate in the study. The patient will sign the consent form on day 1 after surgery.

8.1 Perioperative treatment

The pre-, intra-, and postoperative treatment-course follows the local operating procedures and common clinical guidelines implemented at the Dept. of Orthopedic Surgery, Hvidovre Hospital.

8.1.1 Preoperative standard treatment

Preoperatively, the patient is examined by a specialized arthroplasty surgeon, and a basic preoperative health examination is done, along with a specialized anesthesiologic assessment planning the anesthesia for the TKA operation.
On the morning of surgery the patient will be given:

Celebra	400 mg
Paracetamol	1 g

8.1.2 Anesthesia

All included patients will receive general anesthesia or a neuraxial blockade in the form of a spinal anesthesia administered at level L2-L4, by injecting 2-3 ml of hyperbaric bupivacaine 0.5%. If spinal anesthesia is performed, perioperative sedation with propofol or other sedatives is optional and done in agreement with the patient. According to local guidelines, dexamethasone 0.3 mg/kg or 1 mg/kg IV rounded up to nearest 10 mg will be administered prior to surgery to patients with a pain catastrophizing scale score ≤ 20 or > 20, respectively [27]. A supplement of local infiltration analgesia is administered directly into the surrounding tissue of the knee at the end of surgery, according to local operating procedure.

Tranexamic acid is administered as 1 g preoperatively, 1 g 3 h postoperatively, and 1 g in the surgical ward according to local operating procedure to prevent bleeding.

8.1.3 Surgical procedure

A medial parapatellar approach will be used. No tourniquet is used. Following insertion of the prosthesis, local infiltration analgesia (LIA) with 200 mL 0.2% Ropivacaine will be injected in the posterior capsule, periarticular tissues and subcutaneous tissue. Joint capsule, subcutis and skin are closed with standard 3-layer closure and a compression bandage is applied. No drains are used. All patient will be operated with cemented components and patella resurfacing.

8.1.4 Standard postoperative treatment

The postoperative multimodal analgesic regimen consists of:

Celebra 200 mg x 2, for 7 days.
Paracetamol 1 g x 4, for 7 days.
Morphine 10-20 mg or opioid equivalents administered only as rescue opioids.

8.2 Intervention

The intervention will take place after the inclusion at 20-32 h after TKA surgery. The procedure will be performed at the Dept. of Anesthesiology.

8.2.1 Cryoneurolysis mechanism of action

Cryoneurolysis will be performed on the superficial genicular nerves (Cryo-S, Metrum Cryoflex, Blizne Laszczynskiego, Poland). The cryoprobe works by passing carbon dioxide at a relatively high pressure down the shaft, through a small orifice and into a closed tip at a much lower pressure. According to the Joule-Thomson effect, this drop in pressure causes a dramatic decrease in temperature which leads to a rapid expansion and absorption of heat. Afterwards the gas moves back up through a larger diameter tube. Importantly, this closed loop allows no gas to escape into the surrounding tissue. The intense cold created (approximately -70^{o}C) causes a Wallerian degeneration, thereby reversibly destroying the nerve axon with retention of the endo-, peri-, and epineurium. Since the architecture of the nerve remains intact, the nerve axon can grow out along its normal path which occurs with approximately 1-2 mm/day [28]. The drop in temperature cannot be lower than the boiling point for the gas used, which for carbon dioxide is -79^{o}C. Irreversible degeneration of nerve tissue occurs at about -100^{o}C which allows for a wide safety margin.

8.2.2 Procedure technique

Cryo-group:

The patient is placed in a supine position with a sheet between the upper and lower part of the body, thus blinding the patient from the intervention allocation. The procedure is performed using a linear array ultrasound probe. Local anesthesia is injected in the skin. The superficial genicular nerves, more specifically the ISN and the AFCN, are visualized. A nerve stimulator (Stimuplex HNS 12, B Braun, Melsungen, Germany) is used to verify the visualized nerves., 2-3 ml of ropivacaine 5 mg/ml is injected around the nerves. After 5-15 minutes the effect is evaluated by assessing pain in the surgical area and asking the patient whether there is a pain relief. Following this evaluation, cryoneurolysis (Cryo-S, Metrum Cryoflex, Blizne Laszczynskiego, Poland) is performed unilaterally along a treatment line, the location of which was guided by visualization and palpation of anatomic landmarks. The ISN treatment line is located along the line that connects a point located 5 cm medial to the lower pole of the patella and a point located 5 cm medial to the tibial tubercle. The AFCN treatment line is located at one-third the length of the distance from the center of the patella to the top of the femur, with a width equal to the width of the patella.

Sham-group:

The exact same procedure as in the cryo-group is performed, except that the nerves are not frozen with the cryoneurolysis apparatus. Sound effects from the machine are replicated to give the patient the same experience as in the active intervention group.

8.3 Study specific

Pain is rated by the patient before the intervention, after the initial LA injection, at home on days 2-7 and at the 2-, 4-, 12-, and 24 weeks follow-up via telephone.

A Visual Analog Scale (VAS 0-100) is used. On days 1-7 patients mark their pain in the electronic CRF twice a day (Appendix 5). If the patient is not able to complete the ratings electronically, a physical pain diary will be provided. Pain is rated by the patient at rest, during a 5-meter walk test, and during sleep. At the hospital and at the follow-ups patients are asked to rate their pain at rest and during a 5-meter walk test.

Use of rescue-analgesics (opioids) or other specific pain-relieving actions that differ from standard treatment is noted in the CRF.

The presence of dysesthesia or other side effects will be evaluated at each follow-up.

8.4 Other clinical data

- Demographical data (gender, age, height, weight, co-morbidity, American Society of Anesthesiologist (ASA) score)
- Preoperative opioids/strong analgesics
- Pain Catastrophizing Scale (PCS)
- Surgical data (date of surgery, indication, surgical time, procedure information, intraoperative bleeding, transfusion data, perioperative analgesics)
- Type and dosage of analgesics.
- Deviations from standard treatment
- Quality of sleep, lethargy, dizziness, and nausea, pre- and postoperative registration, on a NRS (0-10)
- Adverse events throughout the hospitalization and at each follow-up
- Neuropathic Pain Scale for Postsurgical Patients (NeuPPS)

8.4.1 Pain Catastrophizing Scale

The PCS consists of 13 questions divided into three sections: rumination, exaggeration, and helplessness [27, 29, 30]. The questions are answered in accordance with a scale of 0 to 4. At Hvidovre Hospital all patients undergoing major lower limb arthroplasty fill out this form prior to surgery.

8.4.1 Neuropathic Pain Scale for Postsurgical Patients

The NeuPPS consists of 5 yes/no questions about the presence of sensory disturbances [31, 32]. A score of 1 will be assigned for a ‘yes’ and a score of 0 will be assigned for a ‘no’. The summed scores are used. The patients will fill out this questionnaire preoperatively and at every follow-up.

8.5 Study location

The inclusion will take place at the Dept. of Orthopedic Surgery, Arthroplasty unit at Hvidovre Hospital, Capital Region of Denmark. Study personnel include employees from the Dept. of Orthopedic Surgery, the Surgical Wards and the Dept. of Anesthesiology, at Hvidovre Hospital.

The sponsor and investigators are employees at the Research Unit at the Dept. of Anesthesiology, Hvidovre Hospital.

8.6 Timespan

The study is expected to start inclusion during the fall of 2023.
The expected end of inclusion is in the spring of 2024.

9. Study drugs

9.1 Ropivacaine

The cryoneurolysis intervention itself does not involve any study drugs. However, ropivacaine 5 mg/ml will be administered preceding the cryoneurolysis or the sham block. The ropivacaine is contained in plastic ampules.

9.2 Rescue drugs

It is not expected that any specific rescue drugs are needed. However, drugs that the investigator may find necessary to use include adrenaline, atropine, intralipid, midazolam, or ondansetron. The administration of rescue drugs will be recorded in the patient's CRF

10. Data recording, management, and quality

The study is to be conducted in accordance with the current guidelines for quality management and control for clinical investigations with human subjects. The study will follow Good Clinical Practice (GCP) guidelines at all times.

The sponsor is associated with Hvidovre Hospital, and is responsible for handling and storage of data, in accordance with current updated guidelines including the Danish Data Protection Act, the General Data Protection Regulation and the Health Act.
Data belongs to the sponsor and will be kept 5 years after the end of the trial.
The study is submitted to the Data Protection Agency for approval.

Signed informed consent from participating patients at Hvidovre Hospital will be stored in a locked cabinet at the Anesthesiologic Dept. 542, in the office 500.50.401, cabinet F. All other data will be stored in REDCap.

10.1 Case report form

Every patient included in the study will have an electronic CRF in the data-monitoring system REDCap. The following will be considered as source data and registered directly in REDCap: Pain scoring at all time points, evaluation of sleep quality, lethargy, dizziness, and nausea in the 7 days following surgery, use of rescue analgesics after discharge, and presence of side effects at follow-ups.

10.2 Blood samples

No study-specific blood samples will be taken.

10.3 Education

The primary investigator will ensure that the personnel, and patients participating in the study, have received correct and sufficient education regarding the study. Procedural descriptions will be made for different types of personnel, accounting for different types of tasks.
An overview of the entire study and study plan will be accessible for the participating personnel on site.

11. Ethical considerations

11.1 General ethics

The study will be carried out in accordance with the principles in the Helsinki Declaration, and the protocol will be submitted the Local Ethics Committee (LEC), the Danish Medical Agency (DKMA) and the Data Protection Authorities (DPA) for approval. The investigators are required to inform the relevant authorities (LEC, DKMA, DPA) on substantial or essential changes in the protocol.
All patients participating in the study must provide a signed informed consent form before inclusion in the study. The patients will be informed that the consent includes access to information in relevant EPJ in relation to their surgery and during the follow-up time until End-of-Trial. This information will also be provided to the authorities in case of inspection. This is in accordance with the Health Act (Sundhedsloven), § 43, stk. 1.

It is the responsibility of the investigators to ensure that all patients receive written information about the study in connection with their hospitalization, and to ensure that all patients are informed about the study. This is to ensure that the patient is fully aware of all aspects of participating in the study. The patient can at any time withdraw their consent to participating in the study, and this will not have any consequences on the treatment the patient receives or deteriorate the relationship between the patient and the treating personnel. The patient will continue to receive the best treatment the facility can offer.

11.2 Study-specific considerations and risks

The study assumes that a further reduction in postoperative pain and rescue-opioid consumption after TKA is possible with postoperative cryoneurolysis compared to a sham block. This could secure a better postoperative convalescence and rehabilitation as well as lower the risk of complications.

Cryoneurolysis has been used to treat acute pain following herniorrhaphy [13], tonsillectomy [14], and thoracotomy [15] via the surgical incision. Recently, cryoneurolysis has been used for the treatment of knee pain. In May 2019, the United States Department of Health and Human Services published a report recommending the use of cryoanalgesia as a treatment option for knee pain due to osteoarthritis [33]. At Hvidovre Hospital cryoneurolysis is offered to selected patients with chronic post-herniorrhaphy pain. However, it is not part of standard care for acute post-TKA pain but the anesthetist performing the procedure is well trained.

Patients will receive cryoneurolysis of the ISN and ACFN nerves or a sham block at the same locations. The procedure will be performed with conscious patients after the injection of local anesthesia. The patient may experience tingling and slight pain in the area, but the procedure may be stopped at any time should the patient wish to. The control group will receive a sham-block using only local anesthesia and the insertion guide of the cryoprobe without freezing. The cryoprobe will be held close by for blinding purpose.

Generally, side effects following cryoneurolysis are mild and self-limiting [18]. Some patients experience mild to moderate pain involved in the initial application (first freeze sequence), but this usually resolves within 30 s. The most commonly reported side effects are bruising, numbness, redness, tenderness upon palpation, and swelling [20]. Due to the risk of

bleeding, patients with anticoagulation therapy without adequate pause or bleeding disorders are excluded. If the ice ball involves the skin, risks may include frostbite, alopecia, depigmentation and/or hyperpigmentation. Infection appears to be extremely rare [28]. Damage to the surrounding tissue may occur if the probe is moved before adequate thaw period, as the tissues can adhere to the probe. This may theoretically cause permanent nerve damage. However, there are no published reports of permanent nerve damage or neuroma formation [34]. There are reports of patients experiencing severe dysesthesia interfering with sleep and daily activities. This has been observed between 2-14 days after the treatment. In one study severe dysesthesia occurred in 2 out of 169 patients (1.2%) treated for postoperative pain after TKA [20]. Another retrospective study on 50 patients receiving cryoanalgesia for postoperative pain after TKA found no significant side effects in the treated group [19]. In a study on post-herniorrhaphy pain, no patients experience allodynia but three out of 24 patients experienced some degree of hyperalgesia following cryoanalgesia [13]. It is noteworthy that two randomized controlled trials reported a significantly higher incidence of neuropathic pain for subjects treated with cryoneurolysis at 8 weeks [35] and 6 months after open thoracotomy [36]. These results are in contrast with studies of post-TKA pain and the reason for this discrepancy remains unknown but may be due to the double crush hypothesis given the high incidence of surgical procedure-related nerve injury during open thoracotomy [34].

Due to the long-lasting effects that cryoneurolysis may have, we study the subjects for up to 6 months after cryoneurolysis.

The study will not bring other changes to the patient's course of treatment in relation to the preoperative preparation, level of information, type of anesthesia, surgical procedure, postoperative care, physiotherapy, and discharge, the exceptions being cryoanalgesia for patients with high levels of postoperative pain. All these other steps will be following our fast-track program.

Participating patients help investigate the effect of cryoanalgesia as a potential new treatment for patients with moderate to severe pain after TKA surgery, which can potentially reduce the length of stay, the rate of postoperative complications, and the intake of opioids. This could potentially change the course of treatment and postoperative convalescence for thousands of TKA patients worldwide and lead to changes in national and international clinical guidelines.

Patients participating in the study are not secured a gain by participating in the study, but do not receive inferior treatment compared to patients outside the study.

12 Side effects

12.1 Intervention specific side effects

Possible side effects of cryoneurolysis are discussed above (*see 11.2 Study-specific considerations and risks*). These may include [18]:

- Altered sensation
- Bruising
- Crusting
- Hyperpigmentation

- Itching
- Local pain
- Numbness
- Redness
- Swelling
- Tenderness
- Tingling
- Aggravated pain
- Loss of motor function outside the treatment area
- Infection

12.2 Definitions

Adverse Events (AE) are defined as any unwanted event in a patient or in a study subject in a clinical study after treatment with a drug, without necessarily having any connection to the treatment and the adverse event.

Adverse Reactions (AR) are defined as any harmful and unwanted reaction related to the intervention drug regardless of the dose.
Serious Adverse Events (SAE) are defined as any adverse event, regardless of dose of study-drug, resulting in death, a life-threatening condition (according to the investigator's assessment, the patient was in an immediate risk of dying from the SAE, when it occurred), any event leading to hospitalization or prolonged stay (>2 days after index surgery), significant or persistent disability or incapacity or results in a congenital anomaly or birth defect.
Serious Adverse Reactions (SAR) are defined as any adverse reaction resulting in death, a life-threatening condition (according to the investigator's assessment, the patient was in an immediate risk of dying from the SAE, when it occurred), any event leading to hospitalization or prolonged stay (>2 days after index surgery), significant or persistent disability or incapacity or results in a congenital anomaly or birth defect.
Suspected Unexpected Serious Adverse Reactions (SUSAR) are defined as any suspected adverse reaction which is both serious and unexpected (not consistent with information available to date). The summary of product characteristics for dexamethasone (see link on bottom of page 15) will be used as reference to evaluate if the serious adverse reaction is expected or unexpected.

12.3 Reporting of side effects

As we are testing a relatively new procedure, all AEs will be reported at every follow-up.

All AEs will be assessed by the investigators and sponsor for association with the study drug and possible causality and reported according to present law. The severity of the AE and the possible association to the study drug will be evaluated according to following guidelines by investigators and sponsor:

1. **Not related** – No temporal association, other reasons/etiologies most likely cause of AE
2. **Possibly related** – Lesser clear association, other reasons/etiologies could be cause of AE.

3. **Likely related** – Clear temporal association with improvement in discontinuation of study drug, and not reasonably explained by the clinical condition of the patient.
4. **Related** – Clear temporal association with treatment or clinical assessment.

Patients experiencing AEs will be monitored with relevant clinical assessments and laboratory tests at the discretion of the attending and treating physician. All AEs will be followed until satisfactory restitution or stabilizing of the patient. Time of origin and ending, level of severity and consequences for the patient and study will be reported.

A Serious Adverse Event (SAE) is not dose-dependent and results in a significant risk of death or disability for the participant, including, but not limiting itself, to an event that:

1. causes death.
2. is life-threatening - the participant was at imminent risk of dying from the adverse event, according to the investigator's assessment.
3. requires hospitalization or prolongs already occurring hospitalization.
4. causes permanent disability.

All SAEs must be reported by investigators to sponsor within 24 hours from time of discovery.

Investigators are responsible for the registration, monitoring and reporting of all AEs and SAEs in the patient CRF and in the specific Trial Master File. Sponsor is responsible for the ongoing surveillance of the risk/benefit ratio in the study. If situations with risk or danger for the patient's safety or the execution of the study should occur, this must always and immediately be reported to the Danish Medicines Agency. Reporting of such situations or risks must also be done to all involved investigators and the approving ethics committee.

A safety report including all SAE and SAR must be made once a year and reported to the Danish Medicines Agency and the approving Ethics committee.
In case of a SUSAR, the sponsor must report this to the Danish Medicines Agency, the Ethics Committee and all investigators within 7 days, and within 8 days after the first reporting of the SUSAR, the sponsor must inform and share any relevant information from the sponsor and the investigators follow-up actions to the SUSAR with the Danish Medicines Agency.

Upon finishing the study an elaborate report containing all occurred SAEs must be made and reported to the Danish Medicines Agency and the approving Ethics committee. The sponsor will notify the Danish Medicines Agency no later than 90 days after completion of the trial, and if earlier than planned, reasons for stopping the trial.

13. Information and consent

13.1 Recruitment

Patients planned for TKA are screened in accordance with the inclusion and exclusion criteria and informed at the pre-surgery examination or anesthetist appointment or via phone before the surgery. Patients receive written information about the study before the surgery date and is told to consider their possible participation. If the patient declines all contact to the research personnel, the investigator is informed. If not, the patient is contacted for further information.

Patients who are found fit to participate is given adequate oral information about the study purpose, setting, advantages and risks.

An electronic screening log is kept tracking declining patients and later to fulfill the Consort diagram. This log does not contain names or other person-specific information, which would allow for future identification. The screening log is kept for later examination of the study cohort, and reasons for declining participation. No study related data is part of the screening log.

13.2 Informed consent

The information will be given without disturbance and interruptions and the patient is informed that he/she can schedule a new information interview and to bring a bystander/relative if wished. The information interview will be postponed until the bystander is present if requested. The information interview can be by attendance at the facility or by phone.
The patient receives the written information for participants at the pre-surgery appointment or if needed by secure email. The patient is informed that he/she is entitled to at least one day of reflection/consideration. If the patient does not want to participate, they can do so without informing about the reason for this.

The investigator or research-nurse informs the patient and collect the signed consent form. When needed, in case of sickness or holiday, other research collaborators can collect the signed consent form. The signed consent will be done before the surgery. Both the hospital and the patient will have a signed Consent form. The applicable guidelines and restrictions concerning informed consent brought by the National Ethics Committee is attached to the patient-information. Information for the participant and the Consent form is attached as Appendices 2 and 3.

The patient will be informed that participation is voluntary, and that withdrawal can happen anytime without justification, also after the signed consent, without this affecting their further treatment course and stay at the facility. They will also be informed that the investigator can pull them out of the study anytime at their discretion.

14. Information from the electronic patient journal

All information from the EPJ will be obtained after signing the informed consent form the day after surgery. The consent gives the primary investigator, the sponsor, and sponsor's representatives direct access to gather information from the patient's journal including the EPJ. The information obtained is necessary for the completion of the study and to make sure that the study is carried out correctly, which includes self-control and quality control. After the informed consent, the following information will be obtained from the patient's EPJ:

- Gender
- Age
- Height
- Weight
- Co-morbidities
- American Society of Anesthesiologist (ASA) score

- Pain Catastrophizing Scale (PCS)
- Current medical prescriptions (including glucocorticoids, immunosuppressants, opioids, insulin, and anti-psychotics)
- Surgical data (date of surgery, indication, surgical time, procedure information, intraoperative bleeding, transfusion data, perioperative analgesics)
- Type and dose of rescue-analgesics (opioids) or other specific pain-relieving actions that differ from standard treatment during the in-hospital stay
- Adverse events throughout the hospitalization
- Morbidity and mortality during the in-hospital stay at each follow-up

15. Data protection

The study will be conducted according to the General Data Protection Regulation and The Data Protection Act. All information will be treated confidentially, and all data will be pseudonymized with a code.
All research personnel are subject to professional secrecy. The investigators will keep an ID-list on all patients included in the study, containing full name, social security number and participant-ID.
A screening log is kept electronically in REDCap containing date of screening/surgery, age, reasons for not including in study on all patients screened for participation.

Collected data will be entered in the electronic CRF. This CRF and the EPJ will be made available for third parties in accordance with Danish Law. This means available for inspection by the Danish Medical Agency or other health authorities.

Patients will be informed that results will be stored and analyzed, and that anonymity will be respected. Data will always be stored in accordance with the regulations by DPA. Furthermore, participants will be informed of the possibility of inspection of the data from public authorities. Investigator ensures that the study follows the principles of Good Clinical Practice.

16. Quality monitoring and assessment

At Hvidovre Hospital, the quality related to the study and the treatment of study participants will follow the usual quality monitoring and assessment.

17. Practical information

17.1 Financial conditions

The initiative to the study has been taken by Professor Nicolai Bang Foss and Professor Henrik Kehlet. Expenses are held by Henrik Kehlet and Nicolai Bang Foss who has received funding to the study from the Candys Foundation. The primary investigator Anders Holten Springborg is employed as a ph.d.-student and is paid according to the collective agreement for medical doctors in Denmark. Study specific expenses include cryoneurolysis probes with a total cost of 77,000 DKK (22 probes priced at 3.500 DKK) as well as salary for Anders Holten Springborg (1 year) and costs associated with presentation of results at scientific

conferences. The total amount expected to complete the study is approximately 700,000 DKK. The whole amount is provided by funds from the Candys Foundation.

None of the participating investigators, research personnel, or sponsors have any economical yield/gain from the study.

In case further funding is obtained to this study, the participants and Ethics Committee will be informed.

All funding is managed through an account which is subject to public audit.

17.2 Patient completion and interruption of the study

A patient who has completed the study, must have received the study drug, and the primary outcome registration must have been completed as described in this protocol.

A patient who interrupts the study, must have been included from the start, have given signed consent and have been given the study intervention, but not completed the primary outcome for any reason. If a subject interrupts the study the data collected will be used after acceptance from the patient. If the patient wishes that the collected data from acceptance to withdrawal from the study shall not be used, this data will be deleted. In case of interruption of the study, the patient will continue usual care following the standard fast-track treatment including pain medication.

17.3 Reasons for withdrawal of patients from the study

A study participant can be withdrawn from the study under the following circumstances:

- If an investigator considers it highly important for the patient's treatment or change of treatment to withdraw his or her participation in the study.
- If the patient wishes to exit the trial.
- If there are one or more significant protocol violations.

17.4 Procedure for patient withdrawal from the study

In accordance with the Helsinki Declaration, participants in the study always have the right to withdraw their participation, for any reason they deem reasonable. The reason for untimely withdrawal is to be noted in the patients CRF.

18. Insurance

All participants are, in case of injury or death, insured by the Hospital health insurance, and all participants are covered by the national patient compensation unit, Patienterstatningen.

19. Publication

Based on the data, one or more manuscripts will be made for the purpose of publication in an international peer-reviewed journal. Negative and positive results as well as inconclusive results will be published. Authorship and co-authorship will be distributed according to the Vancouver Recommendations (International Committee of Medical Journal Editors). The order of authors will be as follows:

Anders Holten Springborg, Kirill Gromov, Anders Troelsen, Henrik Kehlet, Nicolai Bang Foss, Kenneth Geving Andersen.

Within 1 year after the end of the trial, the results will be made accessible from the EudraCT database.

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Appendices

Appendix 1: General study plan

Appendix 2: Participant information

Appendix 3: Declaration of consent form

Appendix 4: Protocol summary

Appendix 5: Pain diary