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Document:
Study Protocol & Statistical Analysis Plan

Official Study Title:
Association of Pre-operative Cryoneurolysis of the Genicular Nerves with Improved Pain and Function in Patients Following Total Knee Arthroplasty

Date:
December 20, 2025

NCT Number: Not yet assigned

Administrative Information

Protocol version: 1.0

Ethics approval: Approved by the Institutional Review Board of the National and Kapodistrian University of Athens (Approval ID: A9, 10/09/2025).

Sponsor: Attikon Hospital

Funding: No external funding. Supported by institutional resources.

Introduction

Persistent postoperative pain following total knee arthroplasty (TKA) remains a significant clinical problem, affecting approximately 20–30% of patients despite advances in surgical technique and perioperative analgesia. Cryoneurolysis, a percutaneous image-guided technique that temporarily interrupts peripheral nerve conduction by inducing axonal degeneration through extreme cold, has emerged as a promising modality for pain management. Preoperative cryoneurolysis of the genicular nerves may reduce postoperative pain intensity, enhance mobility, and improve quality of life outcomes following TKA.

Objectives

The primary objective of this study is to evaluate whether preoperative CT-guided cryoneurolysis of three genicular nerves (upper medial, upper lateral, and lower medial) improves postoperative pain, mobility, and quality of life compared with standard care in patients undergoing total knee arthroplasty.

Primary hypothesis: Preoperative cryoneurolysis of genicular nerves will result in superior postoperative pain control, enhanced mobility, and improved life quality scores compared with control patients.

Trial Design

This is a prospective, randomized, comparative, single-center, two-arm trial with parallel assignment. Participants will be randomized (1:1) to either the intervention (cryoneurolysis) or control (standard care) group. Outcome assessors will be blinded to group allocation.

Participants

Inclusion criteria:

- Adults (≥18 years) undergoing primary total knee arthroplasty for osteoarthritis.
- Cognitively normal individuals able to self-assess pain and function.
- Willing and able to provide informed consent.

Exclusion criteria:

- Cancer-related knee pain.
- Neurological, psychiatric, or medical conditions interfering with self-assessment.
- Chronic opioid use.

Interventions

Participants randomized to the intervention arm will undergo CT-guided cryoneurolysis of the upper medial, upper lateral, and lower medial genicular nerves at least 24 hours before surgery. Local anesthesia will be administered. Each nerve will be treated with a cryoprobe (up to three per patient), induced to -20°C to -100°C, to achieve axonal degeneration.

The control group will undergo standard total knee arthroplasty without preoperative cryoneurolysis.

Outcomes

Primary outcome:

• Change in pain severity as measured by the Brief Pain Inventory (BPI) from baseline to 1 month postoperatively.

Secondary outcomes:

- Knee Injury and Osteoarthritis Outcome Score (KOOS).
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).
- Complications graded according to the CIRSE classification system.
- Quality of life improvement at 3, 6, and 12 months postoperatively.

Sample Size

A total of 100 patients will be enrolled and randomized equally between the two study arms (50 per group). Sample size is based on feasibility and prior literature estimating a moderate effect size for cryoneurolysis in postoperative pain reduction.

Assignment of Interventions (Randomization and Blinding)

Randomization will be performed using computer-generated random numbers in a 1:1 ratio. Outcome assessors and statisticians will be blinded to treatment allocation.

Data Collection and Management

Clinical data will be collected at baseline, and at 1, 3, 6, and 12 months postoperatively using validated questionnaires (BPI, KOOS, WOMAC). Data will be anonymized, stored securely on institutional servers, and accessible only to the research team.

Statistical Methods

All statistical analyses will be performed using IBM SPSS Statistics version 25 (licensed to the National and Kapodistrian University of Athens). Continuous variables will be expressed as mean ± standard deviation or median (IQR), as appropriate. Comparisons between groups will be made using t-tests or Mann–Whitney U tests for continuous variables and

chi-square tests for categorical variables. A p-value <0.05 will be considered statistically significant.

Monitoring and Harms

Adverse events and complications related to cryoneurolysis or TKA will be monitored throughout the study. Complications will be graded according to the CIRSE classification system.

Ethics and Dissemination

This study has received ethics approval from the Institutional Review Board of the National and Kapodistrian University of Athens (Approval ID: A9, 10/09/2025). All participants will provide written informed consent. Results will be submitted to peer-reviewed journals (target: CVIR) and presented at international conferences.

References

1. Mont MA et al. Cryoneurolysis Associated With Improved Pain, Function, and Sleep in Patients Following Total Knee Arthroplasty. J Arthroplasty. 2025;40:92–101.
2. Filippiadis D, Efthymiou E, Tsochatzis A, Kelekis A, Prologo JD. Percutaneous cryoanalgesia for pain palliation: current status and future trends. Diagn Interv Imaging. 2021;102:273–8.
3. Ashoorion V et al. Predictors of persistent post-surgical pain following total knee arthroplasty: a systematic review and meta-analysis. Pain Med. 2023;24:369–81.
4. Ilfeld BM et al. Ultrasound-guided percutaneous cryoneurolysis for treatment of acute pain: could cryoanalgesia replace continuous peripheral nerve blocks? Br J Anaesth. 2017;119:709–12.
5. Dasa V et al. Percutaneous freezing of sensory nerves prior to total knee arthroplasty. Knee. 2016;23:523–8.