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ORIGINAL RESEARCH

Genicular Nerve Ultrasound-Guided Cryoanalgesia for the Treatment of Chronic Knee Joint Pain: An Observational Retrospective Study

Giuliano Lo Bianco · Francesco Paolo D'angelo · Guillherme Ferreira Dos Santos · Agnes Stogicza · Matteo Luigi Giuseppe Leoni · Andrea M. Trescot · Robert Jason Yong · Christopher L. Robinson

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ABSTRACT

Introduction: Chronic knee pain caused by osteoarthritis (OA) is a prevalent source of disability in the adult population. Total knee arthroplasty (TKA) is an effective surgical treatment for advanced disease, but many patients continue to suffer from chronic post-surgical pain (CPSP). In recent years, minimally invasive techniques targeting peripheral nerves have been explored. Cryoanalgesia of the genicular nerves (GNCryo) is one such intervention that disrupts sensory input by applying extremely low temperatures to the target nerves, potentially leading to sustained pain relief without the need for neurodestructive heat lesions. This study aims to evaluate the effectiveness of ultrasound-guided GNCryo in patients with chronic knee pain due to primary OA or CPSP after TKA.

Methods: This retrospective, single-center study included 90 patients who underwent GNCryo between September 2021 and February 2023. Inclusion criteria were patients over 18 years of age, symptomatic knee OA or CPSP after TKA, and a positive response (≥ 50% pain relief) to diagnostic genicular nerve blocks. Ultrasound guidance was used to optimize needle placement and reduce complications. Clinical outcomes were assessed at baseline and at 1, 3, 6, and 9 months post-procedure. Outcome measures included the Visual Analog Scale (VAS, 0–10) for pain intensity, the Western Ontario and McMaster Universities Arthritis Index (WOMAC, 0–100) for assessing pain, stiffness, and physical function related to OA, the

G. L. Bianco (✉)
Anesthesiology and Pain Department, Foundation G. Giglio Cefalù, Via Pietrapollastra, 90015 Palermo, Cefalù, Italy
e-mail: giulianolobianco@gmail.com

F. P. D'angelo
Department of Anaesthesia, Intensive Care and Emergency, University Hospital Policlinico Paolo Giaccone, Palermo, Italy

G. F. Dos Santos
Division of Pain Medicine, Department of Anesthesiology, Reanimation, and Pain Medicine, Hospital Clínic de Barcelona, University of Barcelona, Barcelona, Spain

A. Stogicza
Department of Anaesthesia and Intensive Care, University of Szeged, Szeged, Hungary

M. L. G. Leoni
Department of Medical and Surgical Sciences and Translational Medicine, Sapienza University of Rome, Rome, Italy

A. M. Trescot
Orles Pain and Regenerative Medicine, Jacksonville, FL, USA

R. J. Yong · C. L. Robinson
Anesthesiology, Perioperative, and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Douleur Neuropathique en 4 Questions (DN4, 0–10) for neuropathic pain, and the EuroQol 5-Dimension (EQ-5D, 0–100) for quality of life.
Results: Ninety patients completed the 9 months follow-up. The median VAS score decreased from 7.0 (6.0, 8.0) at baseline to 4.0 (3.0, 5.0) at 1 month, remained at 4.0 (3.0, 5.0) at 3 months, and increased slightly to 5.0 (4.0, 5.0) at 6 months and 5.0 (4.0, 6.0) at 9 months, yet pain relief remained lower than baseline. WOMAC scores decreased from 65 (55, 71) at baseline to 35 (30, 40) at 1 month and 35 (30, 40) at 3 months, increased to 40 (35, 50) at 6 months and 55 (45, 65) at 9 months. DN4 scores decreased from 7 (5, 8) at baseline to 4 (3, 4) at 1 month and 3 (2, 4) at 3 months, increased to 3.5 (3, 5) at 6 months and 5 (4, 6) at 9 months, yet remained lower than baseline. EQ-5D scores increased from 64.5 (47, 84) at baseline to 42 (32, 58) at 1 month, 43.5 (31, 59) at 3 months, 45.5 (35, 60) at 6 months, and 52 (41, 72) at 9 months.
Conclusions: Ultrasound-guided GNCryo is a promising minimally invasive treatment for chronic knee pain, providing pain relief and improved quality of life for up to 9 months. Although some outcomes showed a trend toward baseline over time, pain relief remained lower than baseline, consistent with potential nerve regeneration or recovery. Larger prospective, controlled trials are necessary to confirm these findings and to refine patient selection and technique optimization.

Keywords: Chronic knee pain; Osteoarthritis; Genicular nerve; Cryoanalgesia; Ultrasound guidance; Minimally invasive procedures

Key Summary Points

Why carry out this study?

Chronic knee pain resulting from osteoarthritis (OA) or following total knee arthroplasty (TKA) remains an unmet clinical challenge, as many patients continue to experience pain despite surgery and conventional therapies.

This study evaluated whether ultrasound-guided genicular nerve cryoanalgesia (GNCryo) provides meaningful and sustained pain relief for patients with chronic knee pain from OA or post-TKA chronic post-surgical pain, with a focus on reductions in pain intensity and improvements in function and quality of life over 9 months.

What was learned from this study?

GNCryo led to significant reductions in pain, functional limitations, and neuropathic symptoms, peaking at 1–3 months and remaining better than baseline at 9 months. A clinically significant proportion of patients achieved ≥ 50% pain relief and surpassed minimal clinically important differences (≥ 2-point reduction on the Visual Analog Scale).

Although some pain and functional scores trended back toward baseline after six months, overall improvements remained clinically meaningful, suggesting that cryoanalgesia may need to be repeated for prolonged relief.

Ultrasound guidance combined with sensory stimulation addressed anatomical variability of the genicular nerves, enhancing procedural accuracy. Larger, controlled trials are necessary to validate these findings, refine patient selection—including those with neuropathic components—and establish the long-term role of GNCryo in managing chronic knee pain.

INTRODUCTION

Chronic knee pain resulting from degenerative osteoarthritis (OA) is recognized as a major cause of disability worldwide, particularly among adults over 40 years of age [1]. When conservative measures prove inadequate in managing advanced knee OA, total knee arthroplasty (TKA) is often considered the gold-standard intervention, offering notable improvements in pain and quality of

life. Despite technical advancements in joint replacement, however, a substantial proportion of individuals, approximately 15–30%, continue to experience chronic post-surgical pain (CPSP) after TKA [2–4]. Factors such as younger age, women sex, higher preoperative pain intensity, and psychological comorbidities have all been correlated with increased risk for CPSP [5–8].

Given the growing prevalence of knee OA and correspondingly high numbers of TKA procedures, there is a parallel rise in patients seeking treatments for persistent or recurrent knee pain after surgery [9]. As an alternative or complement to repeated surgeries, minimally invasive approaches targeting the genicular nerves of the knee have garnered attention [10–12]. Radiofrequency ablation (RFA) of these sensory nerves can reduce pain transmission; however, anatomical variability of the genicular nerves and the potential for nerve regeneration may lead to incomplete or short-lived symptom relief [11, 12].

In contrast, genicular nerve cryoanalgesia (GNCryo) applies extremely low temperatures (– 78°) to the targeted sensory nerves (superomedial, superolateral, and inferomedial branches) innervating the knee joint [13, 14]. Unlike RFA, which produces a thermal lesion through heat-induced coagulation, cryoanalgesia preserves the connective tissue (endo-, peri- and epineurium) of the nerve while inducing Wallerian degeneration within the axon, and myelin [13, 14]. Moreover, incorporating ultrasound guidance (US) into GNCryo allows for real-time visualization of soft tissues and vascular structures, potentially improving the accuracy and safety of needle placement compared to fluoroscopy alone [14].

Building on these advantages, US-guided GNCryo has been recognized as a valuable therapeutic modality for chronic knee pain due to OA or CPSP [15–17]. Nevertheless, clinical data on its efficacy, particularly in prolonged follow-up intervals, remain scarce. Therefore, this retrospective observational study aims to evaluate the safety, feasibility, and effectiveness of US-guided GNCryo for patients with persistent knee pain.

METHODS

This retrospective observational study was conducted at Foundation G. Giglio–Cefalù in Palermo, Italy. Patient charts were reviewed for all individuals who underwent percutaneous US-guided GNCryo for chronic knee pain between September 2021 and February 2023.

Ethical Approval

The study protocol was approved by the Local Ethics Committee and Hospital Scientific Committee (Palermo 1 Verbale No. 17 of the 04/07/2024). It was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments. Written informed consent was obtained from all participants before enrollment in the study. Each patient was informed about the objectives and procedures of the study, as well as their right to withdraw at any time without any effect on their clinical care.

Patients were eligible if they were over 18 years of age, had a clinical diagnosis of symptomatic knee OA or CPSP, and had demonstrated at least a 50% reduction in pain intensity after diagnostic genicular nerve blocks [11, 12]. Additional requirements included available and complete follow-up records for at least 9 months after the procedure. Patients were excluded if their medical records were incomplete, if they had active infection or coagulopathy, or if they had previously undergone unsuccessful knee denervation procedures.

Data collected from the electronic medical records included age, sex, type of GNCRYO procedure, use of analgesics (opioids and/or nonsteroidal anti-inflammatory drugs), previous knee replacement surgery, and pain intensity scores [(Visual Analog Scale (VAS) and the Douleur Neuropathique en 4 Questions (DN4)], the Western Ontario and McMaster Universities Arthritis Index (WOMAC), and the EuroQol-5 Dimension (EQ-5D) at baseline and follow-up. Specifically, the VAS was used to assess pain intensity at rest and during movement [18], the WOMAC score evaluated the

impact of knee pain on daily life by measuring pain, stiffness, and physical function related to osteoarthritis [19], the DN4 questionnaire was employed to determine the presence of neuropathic pain, with scores ≥ 4 indicating neuropathic pain [20], and the EQ-5D index measured health-related quality of life at baseline and during follow-up [21]. Pain intensity difference (PID) was calculated as the difference between VAS scores at each follow-up and baseline. Data collection at the 1-month follow-up was performed by the treating physician, while subsequent follow-ups were conducted by telephone through an independent investigator to minimize in-person hospital visits [22–25]. All records were screened for early and late adverse events. Three independent investigators (F.P.D., G.L.B. and M.L.G.L.) verified data accuracy. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [26].

Technical Procedure

Diagnostic Genicular Nerve Block

Patients were placed supine with the knee slightly flexed. After skin antisepsis, a 22-gauge spinal needle was inserted under US guidance to the superomedial, superolateral, and inferomedial genicular nerve targets (Figs. 1, 2) [27]. The needle was placed initially out-of-plane onto the junction of tibial/ femoral shaft and condyle from anterior to posterior (Fig. 3), then visualized in plane and advanced posteriorly, making sure the tip was as parallel to the bony surface as possible, and 1 mL of 1% lidocaine was injected at each location [28]. A positive test was defined as ≥ 50% pain reduction within 30–90 min, lasting at least 2 h. Some 3–5 weeks later, a second diagnostic block was performed using 0.25% bupivacaine, with a positive response defined as ≥ 50% pain reduction lasting at least 3 h.

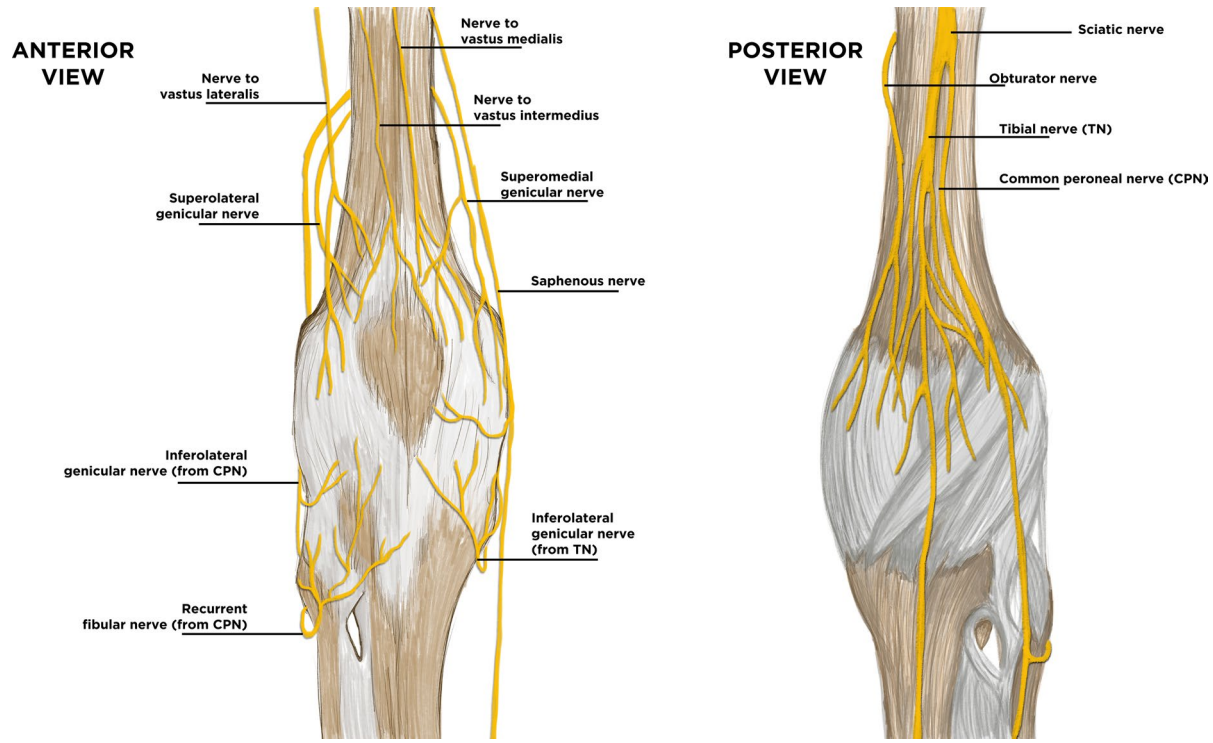

Fig. 1 The nerve anatomy of the knee in both the anterior and posterior view. Anterior view highlights the superolateral genicular nerve, inferolateral genicular nerve (from the common peroneal nerve; *CPN*), saphenous nerve, and recurrent fibular nerve. Posterior view highlights the tibial nerve (*TN*), obturator nerve, CPN, and sciatic nerve

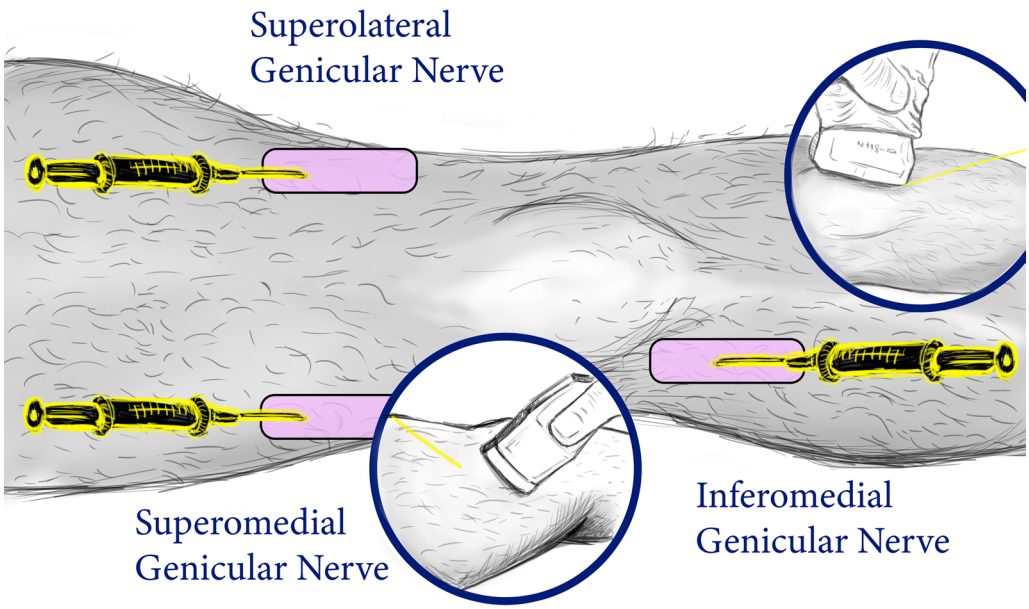

Fig. 2 Ultrasound-guided genicular nerve block technique (superolateral, superomedial, and inferomedial branches). This schematic demonstrates a knee with three distinct injection sites for the ultrasound-guided genicular nerve block procedure. Each *pink rectangular area* represents the target zone for anesthetic infiltration aimed at the superolateral, superomedial, and inferomedial branches of the genicular nerves. *Yellow syringes* indicate the trajectory of the needle toward these injection sites. *Two circular insets* provide close-up views of the ultrasound probe on the skin and the needle pathway

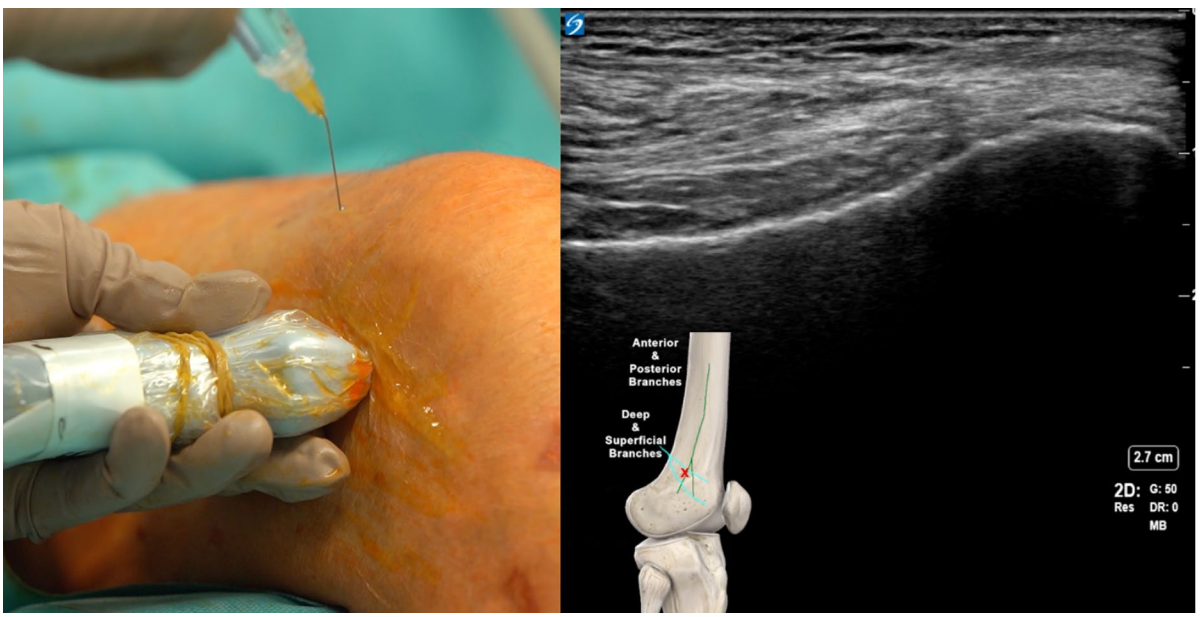

Fig. 3 A 25-gauge local needle was inserted under US guidance to the superolateral genicular nerve targets. (Image courtesy of Agnes Stogicza, MD)

Patients who showed positive responses to both blocks were deemed candidates for GNCryo [29].

Although ultrasound guidance was used for needle placement, we sometimes encountered suboptimal visualization of the needle tip and small genicular nerve branches due to anatomical variability or patient habitus. To mitigate this, we employed a multimodal approach by also using sensory stimulation, which confirmed accurate needle localization when ultrasound imaging was limited. Specifically, eliciting paresthesia in the distribution of the patient's typical knee pain enabled us to verify that the target nerve had been effectively identified.

Genicular Nerve Cryoneurolysis

Following appropriate antiseptic preparation, patients were positioned supine, and vital signs were continuously monitored. US guidance was used to localize the superomedial, superolateral, and inferomedial genicular nerves in relation to the femoral and tibial epicondyles [14, 30]. When needed, mild IV sedation (midazolam 0.05 mg/kg) was administered. After infiltrating 2 mL of 2% lidocaine at each entry site, a 14G introducer needle was inserted to facilitate the insertion of the probe. A 1.3 mm Metrum Cryoflex (Łomianki/Warsaw, Poland) cryoprobe was then advanced toward the target genicular nerve under continuous US visualization (Fig. 4). The probe position was carefully adjusted based on anatomical landmarks, with the ultrasound probe oriented perpendicular to the shaft in the out-of-plane, then in the in-plane approach to optimize visualization (as with the diagnostic block). Sensory stimulation at ≤ 0.4 mV/50 Hz confirmed accurate placement by reproducing paresthesia in the distribution of the patient's typical knee pain. Motor stimulation (0.9–3 V/2 Hz) was performed to exclude unintended motor nerve involvement [31]. Cryoneurolysis was achieved by cooling the probe tip to − 78 °C for approximately 90 s at each targeted nerve location (Fig. 5). The freeze cycle was repeated two times to ensure a robust conduction block [13, 14, 32, 33]. Patients were observed briefly and discharged the same day.

In instances where needle or nerve visibility was limited, real-time ultrasound guidance was again complemented by sensory stimulation. This allowed us to confirm paresthesia in the exact distribution of the patient's knee pain, ensuring accurate cryoprobe placement on the intended nerve. By integrating ultrasound imaging with elicited sensory responses, we addressed any potential ambiguity regarding needle guidance and target nerve localization.

Statistical Analysis

Quantitative data are reported as mean ± standard deviation (SD) or median and interquartile ranges (IQR), depending on distribution. Categorical variables are summarized as frequencies and percentages. Data normality was tested with the Shapiro–Wilk test. The nonparametric Friedman test was applied for repeated measures (baseline, 1, 3, 6, and 9 months), with pairwise Wilcoxon signed-rank tests and Bonferroni correction for multiple comparisons. Changes in DN4 and EQ-5D were similarly assessed using repeated-measures analysis. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism software (GraphPad Software, San Diego, CA, USA) [33].

RESULTS

A total of 90 patients met the study's inclusion criteria and completed the 9 months follow-up. Of these, 65% were woman, and their mean (± SD) age was 68 ± 9 years. A total of 38 patients (42%) had CPSP following TKA, while 52 patients (58%) had chronic knee pain due to primary OA without prior TKA. At baseline, the median VAS for knee pain was 7.0 (6.0, 8.0). Following cryoneurolysis, VAS scores improved to 4.0 (3.0, 5.0) at 1 month ($p < 0.0001$), remained at 4.0 (3.0, 5.0) at 3 months ($p < 0.0001$), and demonstrated slight increases to 5.0 (4.0, 5.0) at 6 months and 5.0 (4.0, 6.0) at 9 months—both values still significantly better than baseline ($p < 0.0001$) (Fig. 6a).

Additionally, we evaluated the proportion of patients achieving clinically significant pain relief. At the 1-month follow-up, 58% of

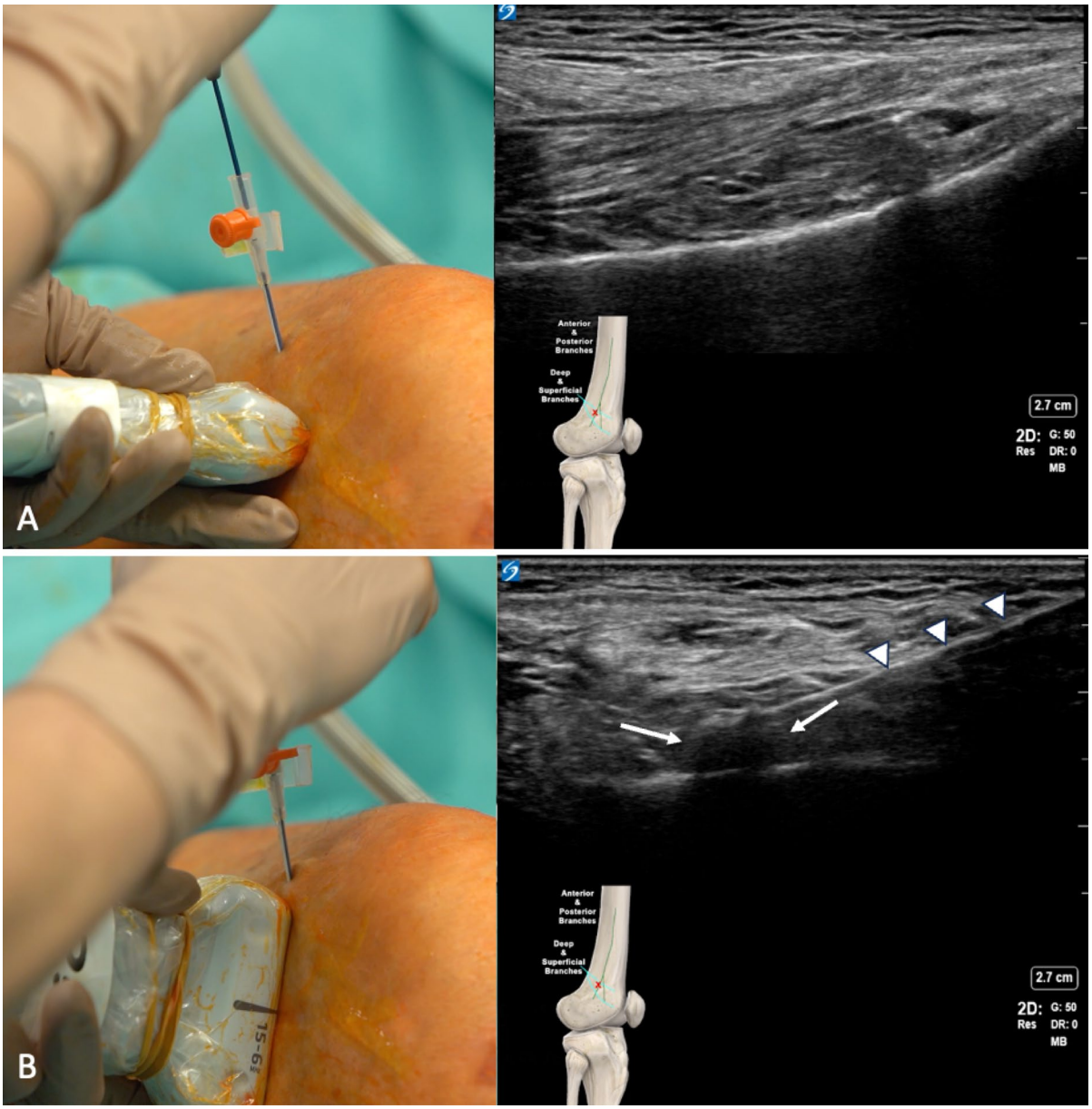

Fig. 4 Cryoablation of the superolateral genicular nerves. The cryoprobe is first placed to the junction of the femoral epiphysis and diaphysis, and the bony surface is approached by the cryoprobe (**A**). Next, the ultrasound probe is rotated 90°, so the cryoprobe is visualized in-plane, as it approaches the bony surface (**B**). *Arrows* mark the ice-ball at the tip of the cryoprobe (*arrowheads*). The superomedial and inferomedial genicular nerves are targeted based on the same concept. (Image courtesy of Agnes Stogicza, MD)

patients (52/90) experienced ≥ 50% reduction in VAS scores, and 64% (58/90) reported an improvement of more than 3 VAS points. At 3 months, these proportions were 56% (50/90) and 61% (55/90), respectively. The percentages decreased somewhat at 6 and 9 months, but still remained higher than at baseline, underscoring the sustained clinical impact of the intervention. WOMAC scores similarly improved from a median of 65.0 (55.0, 71.25) at baseline to 35.0 (30.0, 40.0) at 1 and 3 months ($p < 0.0001$); scores rose moderately at 6 months [40.0 (35.0,

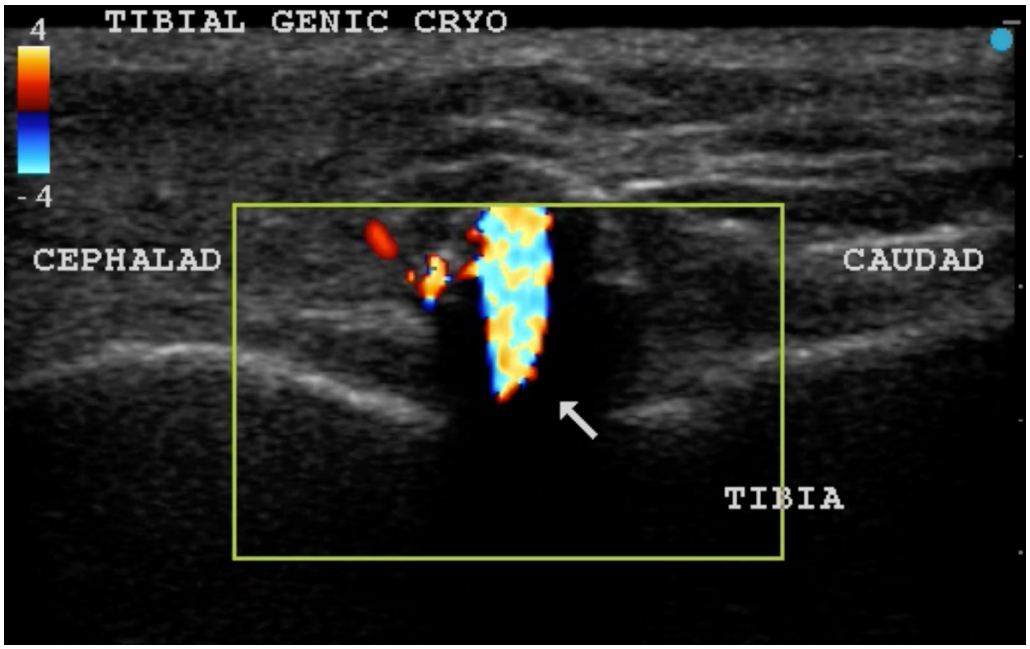

Fig. 5 Hypoechoic shadow of the ice is marked by the *arrow* and the *color* at the junction of the tibial shaft and condyle. The color doppler picks up on the CO_2 flow within the cryo probe. The size of the ice ball typically measures around 6 × 4 mm with the 1.3-mm probe. (Image courtesy of Agnes Stogicza, MD)

50.0)] and at 9 months [55.0 (45.0, 65.0)] but remained significantly lower than baseline values ($p < 0.0001$) (Fig. 6b).

DN4 scores, initially 7.0 (5.0, 8.0), improved to 4.0 (3.0, 4.0) at 1 month and 3.0 (2.0, 4.0) at 3 months ($p < 0.0001$), and a trend towards baseline was observed at 6 [3.5 (3.0, 5.0)] and 9 months [5.0 (4.0, 6.0)], but these values were still markedly better than baseline ($p < 0.01$) (Fig. 6c). EQ-5D, increased from 64.5 (47.0, 84.0) at baseline to 42.0 (32.0, 58.25) at 1 month ($p < 0.01$), and, although scores at 6 and 9 months shifted to 45.5 (35.0, 60.25) and 52.0 (41.0, 72.0), respectively, they remained improved relative to baseline ($p < 0.05$). No major complications were identified, and no patient required additional surgical intervention during the 9 months follow-up (Fig. 6d).

DISCUSSION

Our findings indicate that US-guided GNCryo yields statistically significant and clinically meaningful, improvements in pain, function, neuropathic symptoms, and quality of life in patients suffering from chronic knee pain. Improvements were most pronounced at 1 and 3 months, after which a slight decline was observed at 6 and 9 months; nonetheless, all measured outcomes remained significantly better than baseline at the 9-month mark. These trends are broadly consistent with prior evidence demonstrating the value of genicular nerve interventions for chronic knee pain [9–12, 34–38].

Unlike thermal RFA, cryoanalgesia achieves a conduction block by applying subzero temperatures, potentially reducing the risk of permanent nerve damage and offering an alternate mechanism of analgesia that may benefit selected patient populations [13–15, 33]. The present study's use of US guidance for nerve localization likely increased procedural accuracy, because the ice-ball created by the cryoprobe can directly be visualized on target, minimized technical variability, and contributed to the observed clinical successes [14, 16, 30].

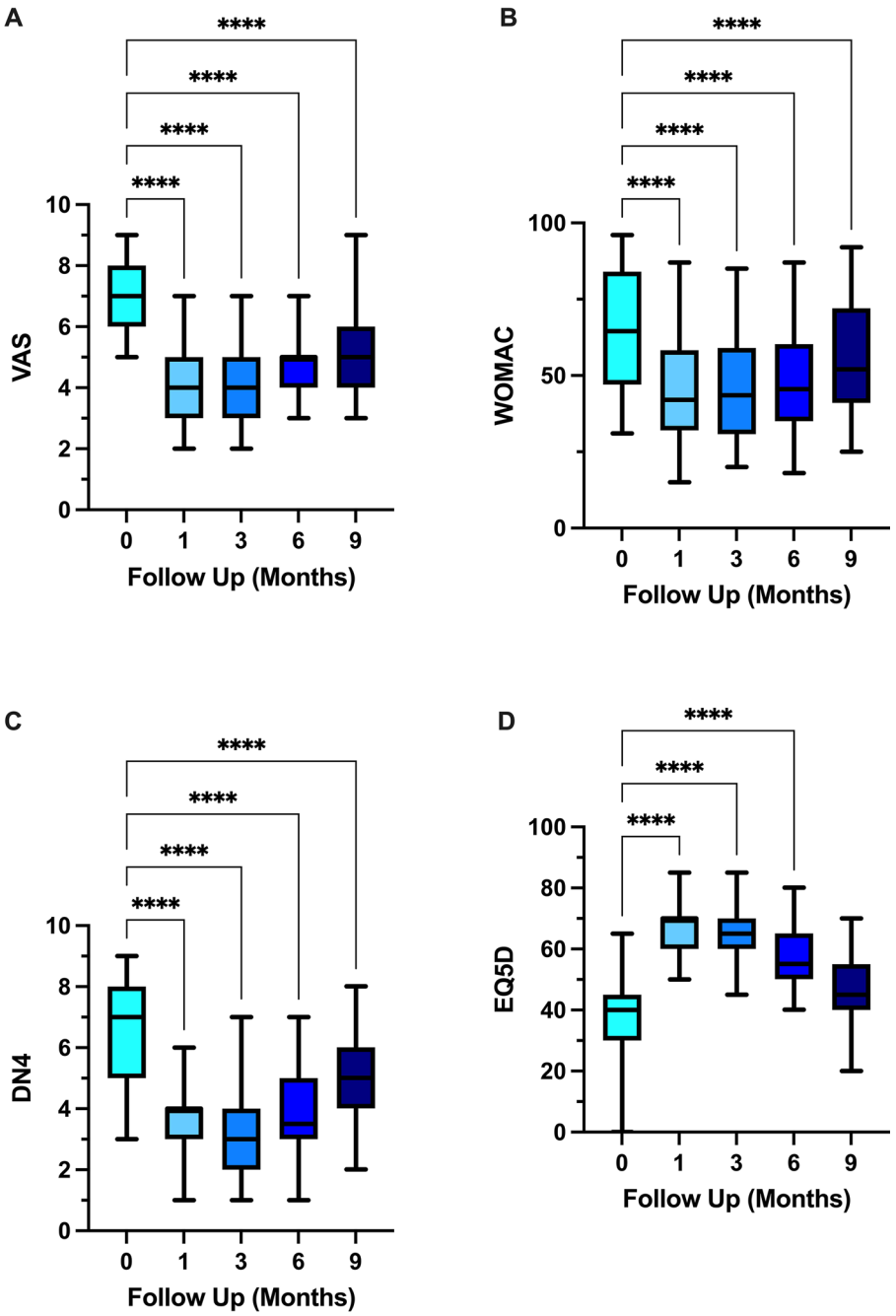

Fig. 6 *Box-and-whisker plots* showing changes in four outcome measures at baseline (0) and 1, 3, 6, and 9 months post-procedure. **A** Visual Analog Scale (VAS, 0–10) represents pain intensity, with lower scores indicating less pain. **B** Western Ontario and McMaster Universities Arthritis Index (WOMAC, 0–100) assesses pain, stiffness, and physical function in osteoarthritis, where lower scores signify fewer symptoms. **C** Douleur Neuropathique en 4 Questions (DN4, 0–10) measures neuropathic pain components, and higher scores suggest more pronounced neuropathic features. **D** EuroQol 5-Dimension (EQ-5D, 0–100) reflects health-related quality of life, where higher scores denote better perceived health. Statistically significant differences compared to baseline: $^{****}p < 0.0001$; $^{**}p < 0.01$

In terms of neuropathic assessment, the DN4 questionnaire could provide a more detailed characterization of neuropathic components in both OA- and CPSP-related knee pain. In this retrospective study, we used DN4 primarily as a screening tool to identify potential neuropathic features, without stratifying the results by neuropathic versus non-neuropathic pain. Future prospective studies should incorporate a more granular approach to differentiating neuropathic and nociceptive components, enabling more individualized treatment strategies.

We acknowledge the concern regarding the possibility of missing additional articular branches when positioning the cryoprobe close to the joint capsule. However, the commonly targeted superomedial, superolateral, and inferomedial genicular nerve branches are widely recognized as primary contributors to knee joint innervation. Although some anatomical variability may exist, we combined detailed ultrasound visualization with sensory stimulation to help ensure adequate coverage of the critical nerve pathways. Future prospective studies could investigate alternative or more lateralized probe placements to further broaden coverage of potential articular branches and examine whether adjunct imaging (e.g., MRI or contrast arthrography) might improve accuracy in locating all relevant genicular nerve branches.

The observed partial recurrence of symptoms after 6–9 months highlights the possibility that repeated cryoneurolysis sessions might be required for sustained pain relief, given that cryo-induced nerve damage is not permanent. This underscores the importance of future work to optimize treatment protocols, refine patient selection (including psychological and clinical factors), and explore whether adjunctive therapies can extend the analgesic duration. In addition, emerging data suggest that the larger lesion area associated with cryo-procedures can help accommodate the anatomical variability of genicular nerves, potentially enhancing and prolonging pain relief [12, 25, 32, 33, 39].

Overall, GNCryo offers a promising, minimally invasive approach to chronic knee pain secondary to osteoarthritis or post-surgical etiologies.

Limitations

This retrospective observational study did not include a control or comparison group (e.g., placebo, conventional nerve blocks, or other minimally invasive techniques such as thermal radiofrequency ablation), which limits our ability to infer causation and directly compare the efficacy of genicular nerve cryoanalgesia to alternative interventions. The single-center design and relatively small sample size may also affect the external validity of our findings. Moreover, psychological and expectation-driven factors can influence patient-reported outcomes, raising the possibility of a placebo effect. Another potential source of bias is our reliance on diagnostic genicular nerve blocks, which are susceptible to technical, anatomical, and psychological confounders, and may produce false-positive results. Finally, we did not control for adjunctive therapies (e.g., physical therapy, psychological support, or education programs) which patients may have pursued during the follow-up period, introducing additional confounding effects [9, 22–24]. Future prospective, randomized, and multicenter studies with sham or comparator arms will be necessary to more definitively establish causality, validate these findings, and improve generalizability.

CONCLUSION

US-guided GNCryo appears to be a safe and minimally invasive procedure that provides significant and sustained pain relief, enhanced function, and improved quality of life for patients with chronic knee pain due to OA or CPSP. While the maximal benefit diminished slightly toward the 9-month mark, patients nonetheless maintained improvements over baseline. These findings suggest that GNCryo may serve as a valuable addition to the therapeutic options for managing OA-related knee pain and CPSP following TKA. Further prospective and comparative studies—including randomized controlled trials—are necessary

to clarify its long-term durability and optimal role relative to alternative genicular nerve interventions, such as thermal radiofrequency ablation [17, 34, 40–43].

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Giuliano Lo Bianco is a speaker for Abbott and Stryker.—Francesco Paolo D'Angelo has nothing to disclose.—Guillherme Ferreira Dos Santos has no relevant financial conflicts of interest.—Agnes Stogicza has nothing to disclose.—Matteo Luigi Giuseppe Leoni has nothing to disclose.—Andrea M. Trescot is an Editor-in-Chief of Pain and Therapy. Andrea Trescot was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.—Robert Jason Yong has nothing to disclose.—Christopher L. Robinson has nothing to disclose.

Ethical Approval. This study was approved by the Local Ethics Committee, Palermo 1 (Verbale N° 17 of the 04/07/2024). It was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments. Written informed consent was obtained from all participants before enrollment in the study. Each patient was informed about the objectives and procedures of the study, as well as their right to withdraw at any time without any effect on their clinical care.

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