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Primary Knee

Cryoneurolysis before Total Knee Arthroplasty in Patients With Severe Osteoarthritis for Reduction of Postoperative Pain and Opioid Use in a Single-Center Randomized Controlled Trial

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ABSTRACT

Background: We hypothesized that preoperative cryoneurolysis of the superficial genicular nerves in patients with osteoarthritis would decrease postoperative opioid use relative to standard of care (SOC) treatment in patients undergoing total knee arthroplasty (TKA).
Methods: Patients received either cryoneurolysis (intent-to-treat [ITT]: n = 62) or SOC (ITT: n = 62). The cryoneurolysis group received cryoneurolysis of the superficial genicular nerves 3–7 days before surgery plus a similar preoperative, intraoperative, and postoperative pain management protocol as the SOC group. The primary end point was cumulative opioid consumption in total daily morphine equivalents from discharge to the 6-week study follow-up assessment. Secondary end points included changes in pain and functional scores. Primary and secondary end points were assessed using ITT and per-protocol (PP) analyses.
Results: The primary end point was not met in the ITT analysis (4.8 [cryoneurolysis] vs 6.1 [SOC] mg; $P = .0841$) but was met in the PP analysis (4.2 vs 5.9 mg; $P = .0186$) after excluding patients with medication deviations or missing follow-up data. Compared with the SOC group, the cryoneurolysis group had improved functional scores and numerical improvements in pain scores across all follow-up assessments, with significant improvements observed in current pain from baseline to the 72-hour and 2-week follow-up assessments and pain in the past week from baseline to the 12-week follow-up assessment.
Conclusion: Findings from the PP analysis suggest that preoperative cryoneurolysis in patients with knee osteoarthritis can reduce opioid consumption and improve functional outcomes after TKA.

Knee arthroplasty is a commonly performed surgical procedure in the United States, with >600,000 procedures performed annually [1]. Total knee arthroplasty (TKA) can result in severe postoperative pain, and opioids are a primary component of perioperative pain management [2]. However, persistent postoperative opioid use is an important concern. Clinical evidence from patients undergoing TKA indicates that approximately one-third of patients still consume opioids 3 months after surgery [3,4]. The risk of developing persistent postoperative opioid use is evident in patients undergoing TKA who are opioid naive at the time of surgery and is exacerbated in those consuming opioids preoperatively [5]. For this reason, it is critical that orthopedic surgeons balance effective pain management with the minimization of the risk of persistent opioid use.

Over the past decade, orthopedic surgeons have implemented multimodal pain management protocols because they have been

Note: Primary TKA was performed by five orthopedic surgeons (WMM, MCF, JRC, JWH, JLG), with fellowship training in lower extremity adult reconstruction, using a medial parapatellar surgical approach with either a cruciate-retaining or posterior-stabilized TKA, including patella resurfacing in all patients.

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shown to reduce opioid prescriptions [6], thereby decreasing opioid-related complications. In May 2019, the United States Department of Health and Human Services published a report recommending cryoanalgesia (cryoneurolysis) as part of a multidisciplinary approach to treat knee pain due to osteoarthritis [7]. Cryoneurolysis is the nonpermanent treatment of peripheral nerves with temperatures below −20°C [8], which causes Wallerian degeneration of the nerve axons [9], resulting in a long-acting nerve block [10]. Results of a multicenter, randomized, double-blind, sham-controlled trial demonstrated that cryoneurolysis reduced the pain and symptoms of knee osteoarthritis for 90 days [11]. A retrospective study of 100 patients undergoing TKA demonstrated that preoperative cryoneurolysis of the superficial genicular nerves (infrapatellar branches of the saphenous nerve [ISN] and anterior femoral cutaneous nerve [AFCN]) resulted in a significantly shorter length of hospital stay, significantly fewer opioids prescribed 12 weeks after TKA, and significantly less pain 6 weeks after TKA [12]. On the basis of these findings, we hypothesized that preoperative cryoanalgesia could decrease the total daily morphine equivalents (TMEs) required for postoperative pain management in patients undergoing TKA.

Material and Methods

Study Design and Patients

From November 6, 2017, through February 19, 2019, we conducted an unblinded randomized controlled trial to evaluate the efficacy and safety of cryoneurolysis treatment before TKA for reducing postoperative opioid use at a single study center. The study was performed in accordance with the provisions of the Declaration of Helsinki, and the protocol was approved by an institutional review board. Written informed consent was obtained from all participants before inclusion. The trial was registered before patient enrollment at ClinicalTrials.gov (NCT03327220). The study was funded by the sponsor, Pacira Cryotech, Inc. (Supplemental Table 2).

Eligible patients were between the ages of 22 and 79 years and were scheduled to undergo primary unilateral TKA as a result of osteoarthritis with anticipated discharge to home. Exclusion criteria were daily or almost daily use of opioids (defined as habitual use of opioids on the basis of clinical judgment) for >3 months before enrollment, a concurrent painful physical condition that required analgesic treatment during study follow-up, large lower extremity deformities (ie, varus or valgus malalignment of >15° on preoperative radiograph), previous cryoneurolysis treatment, body mass index ≥40 kg/m^2, previous surgery in the region to be treated, history of a clotting disorder, and anticoagulant medication within 7 days before treatment.

Patients (n = 124) were assigned 1:1 via a computerized random number generator process (Microsoft Excel) to receive either cryoneurolysis 3-7 days before TKA or current preoperative standard of care (SOC) treatment. Primary TKA was performed by five orthopedic surgeons, with fellowship training in lower extremity adult reconstruction, using a medial parapatellar surgical approach with either a cruciate-retaining or posterior-stabilized TKA, including patella resurfacing in all patients. Patients in both groups received similar preoperative, intraoperative, and postoperative pain management, except that the SOC group did not receive preoperative cryoneurolysis, and periarticular local infiltration analgesia was not permitted in the cryoneurolysis group except for in the posterior capsule, in an effort to attribute treatment outcomes to cryoneurolysis alone and because cryoneurolysis does not treat this pain.

Cryoneurolysis was administered using the iovera° device (Pacira CryoTech, Inc., Fremont, CA, USA). Cryogen (nitrous oxide) flows from the disposable cartridge through the handpiece to the Smart Tip, an assembly of closed-ended needles. As the nitrous oxide enters the needles, a highly localized cold zone is formed.

Cryoneurolysis was administered to conscious patients following local anesthesia with lidocaine. Cryoneurolysis was focused on freezing the superficial genicular nerves, more specifically referred to as the ISN and the AFCN. These nerves innervate the anterior aspect of the knee [13], which is subject to pain from the surgical incision and soft tissue damage during TKA. Treatment was performed unilaterally along a treatment line, the location of which was guided by visualization and palpation of anatomic landmarks (Fig. 1). The ISN treatment line was 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 was 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. Adjacent insertions were placed along the treatment line until the entire line was treated.

Medications administered for pain management before, during, or after TKA were recorded in the medical record. Patients received spinal anesthesia and a single-injection adductor canal block before surgery. In a few cases, general anesthesia was used instead of spinal anesthesia because of a lack of supplies; however, these deviations were not considered clinically significant by the investigators. The SOC group could receive local infiltration analgesia (periarticular and posterior capsule; 1% lidocaine along the two lines of treatment, with 5 cc administered along each treatment line) during surgery. Periarticular local infiltration analgesia was not permitted in the cryoneurolysis group, although these patients could receive local infiltration analgesia (eg, liposomal bupivacaine)

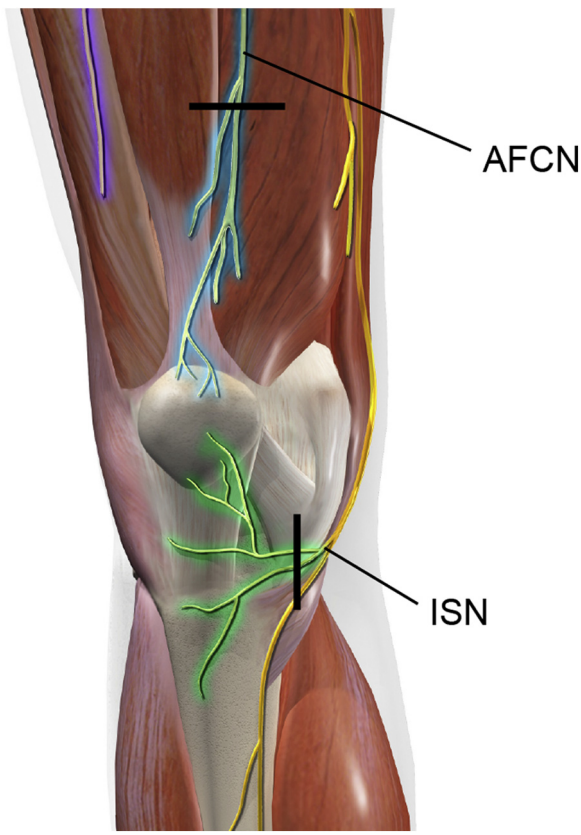

Fig. 1. Cryoneurolysis ISN and AFCN treatment lines. AFCN, anterior femoral cutaneous nerve; ISN, infrapatellar branches of the saphenous nerve.

in the posterior capsule because cryoneurolysis of the superficial genicular nerves does not affect this region of the knee. Postoperative discharge criteria included the ability to tolerate fluids, ambulate with a physical therapist for the first ambulation, and void >200 cc, with adequate pain control.

Patients were discharged within ~1 day. After discharge, postoperative analgesia included 1000 mg of acetaminophen (40 pills) three times daily and 100 mg of gabapentin (40 pills) three times daily, 15 mg of meloxicam once daily (15 pills), 50 mg of tramadol every 6 hours (40 pills), and 5 mg of oxycodone taken as needed, but not more often than every 4 hours, as rescue medication (40 pills).

Assessments and Outcomes

Study follow-up assessments occurred at 72 hours, 2 weeks, 6 weeks, and 12 weeks after the day of surgery. The 72-hour assessment was conducted by telephone; all others were conducted at the study site. The primary efficacy end point was cumulative opioid consumption in TMEs from the time at discharge to the 6-week study follow-up assessment. Tramadol was not included in the calculation of the primary efficacy end point. Patients self-reported the number of opioids used during the first 72 hours after the day of surgery as pill counts by phone call. Subsequently, pill counts were performed by the study coordinator or a designee at the 2-week, 6-week, and 12-week assessments; patients were required to bring all unused prescription opioids dispensed during study participation to each assessment.

Secondary efficacy end points were numerical rating scale (NRS) for pain, Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOS JR), and Timed Up and Go (TUG) test results from baseline. Baseline measures for pain score, KOOS JR score, and TUG test score were collected during screening; scores were also collected at the 72-hour, 2-week, 6-week, and 12-week follow-up assessments. NRS is a well-validated instrument for assessing pain [14]. With the NRS, patients were asked to verbally rate their worst pain "right now" and "in the past 7 days" on a scale ranging from 0 to 10, where 0 = "no pain" and 10 = "the worst imaginable pain," when standing from a seated position. The KOOS JR is a shorter, 7-question version of the 42-item KOOS developed for patients undergoing joint replacement [15]. The KOOS JR represents a unidimensional construct of "knee health," combining pain, symptoms, and functional ability into a single score, with higher scores indicating greater knee health. The TUG test consisted of timing patients as they stood from a seated position, walked to a line on the floor 10 feet away, returned to their chair, and sat back down; in this assessment, a shorter time to complete the task indicates better mobility [16]. The exploratory analysis included an assessment of the range of motion at 6 and 12 weeks. A patient was considered lost to follow-up and discontinued from the study after the site made three attempts to contact the patient.

Statistical Analysis

The sample size was determined on the basis of providing at least 80% power for the primary end point using a 1-sided, 2-independent sample Satterthwaite *t*-test to test for superiority of cryoneurolysis vs SOC treatment with a significance level of 0.025, assuming a 1:1 allocation to treatment, a true treatment effect ($\mu_{1,\text{cryoneurolysis}} - \mu_{1,\text{SOC}}$) of −12.0 mg, and true standard deviations (SDs) of 16.9 and 26.0 mg for the cryoneurolysis and SOC treatments, respectively. On the basis of these specifications, the required sample size was 57 individuals per group. To account for individuals withdrawing early or not having data available for analysis, the required sample size was increased to 124 individuals.

Analyses were completed using SAS software, version 9.4 (SAS Institute, Cary, NC). All participants who met screening criteria and underwent randomization were included in the intent-to-treat (ITT) population. The per-protocol (PP) population was defined as the group of patients who were randomized, received the treatment to which they were randomly assigned, and completed their 6-week assessment without any major protocol deviations. Primary and secondary efficacy analyses were each performed for the ITT and PP populations. The mean difference (MD) and 95% confidence interval (CI) in TMEs between the 2 groups were calculated, and a one-sided, 2-independent sample Satterthwaite *t*-test was used to test the null hypothesis, with a one-sided α level of 0.025.

The secondary efficacy end points were analyzed as the area under the curve (AUC)/time (calculated as the AUC of change scores from baseline to the 6-week follow-up assessment divided by the number of days from TKA until the week-6 assessment) on the basis of the change from baseline to the 6-week follow-up assessment in pain NRS, KOOS JR, and TUG test. Items on the KOOS JR for which individuals did not provide a numerical response were blindly imputed with a value of "extreme" for severity and difficulty. Range of motion was assessed with descriptive statistics. The safety population consisted of all patients who were randomized, met all eligibility criteria, and received the study treatment.

Results

Patient Disposition

A total of 124 patients were randomized to cryoneurolysis (n = 62) or SOC treatment (n = 62; Fig. 2 and Table 1) and constituted the ITT population. Because of major protocol deviations, some patients were excluded from the ITT population to form the safety and PP populations. Major protocol deviations that resulted in exclusion from the safety population included 4 patients (3 cryoneurolysis; 1 SOC) who either did not have surgery at all (1 patient lost to follow-up after an open wound on the heel led to surgery rescheduling outside of the cryoneurolysis treatment window, 1 patient presented with fungal infection and did not receive treatment or surgery, and 1 patient was lost to follow-up) or were not within the window for administering cryoneurolysis (n = 1) and 1 patient who was discharged to a rehabilitation facility (SOC group). Major protocol deviations that resulted in exclusion from the PP population were the same as those for the safety population, in addition to 21 patients with medication deviations (excess opioid prescriptions of 50 pills: 2 cryoneurolysis and 3 SOC; excess opioid prescriptions of 60 pills: 4 cryoneurolysis and 6 SOC; insufficient opioid prescriptions: 2 cryoneurolysis and 0 SOC; no tramadol prescribed: 2 cryoneurolysis and 2 SOC) and 2 patients who did not have follow-up data through 6 weeks (1 in each group). The safety population consisted of 119 patients (cryoneurolysis, n = 59; SOC, n = 60) (Fig. 2) and the PP population consisted of 96 patients (cryoneurolysis, n = 48; SOC, n = 48). Patient characteristics in the PP population were similar between the treatment groups (Table 1).

Opioid Consumption

The primary efficacy end point was not met for the ITT analysis because cumulative opioid consumption in TMEs from discharge to the 6-week follow-up assessment was not significantly different between the cryoneurolysis and SOC groups (MD, 1.3 mg [95% CI, −0.6 to 3.2 mg]; $P = .0841$) (Supplemental Table). However, when patients who were prescribed an incorrect amount of opioids, did not receive a tramadol prescription, or lacked follow-up data through 6 weeks were excluded from both the

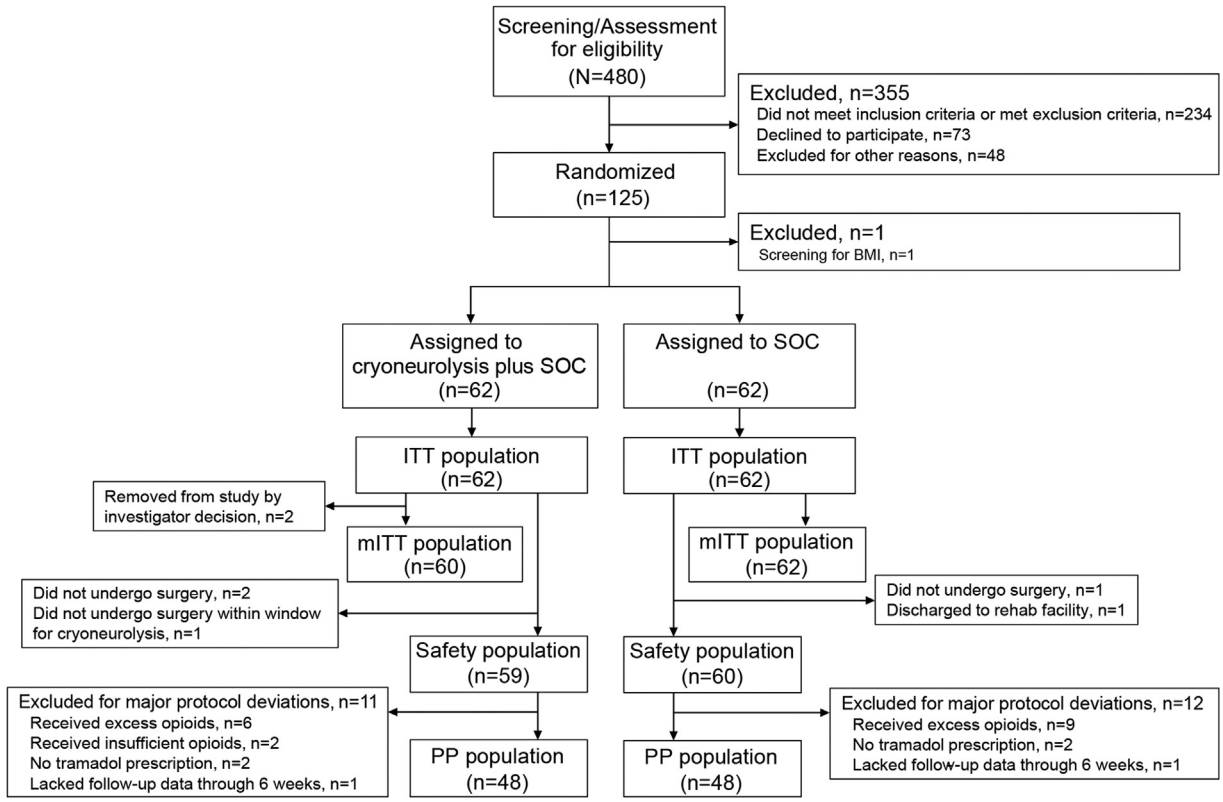

Fig. 2. Patient disposition, including enrollment, treatment assignment, and analysis populations. BMI, body mass index; ITT, intent-to-treat; PP, per protocol; SOC, standard of care.

cryoneurolysis and SOC groups for the PP analysis, the cryoneurolysis group consumed significantly fewer cumulative opioids in TMEs than the SOC group at the 72-hour (MD, 4.0 mg [95% CI, −0.5 to 8.4 mg]; $P = .0389$), 6-week (MD, 1.6 mg [95% CI, 0.1 to 3.2 mg]; $P = .0186$), and 12-week (MD, 1.0 mg [95% CI, 0.0 to 2.0 mg]; $P = .0234$) follow-up assessments, but not at the 2-week follow-up assessment (MD, 0.6 mg [95% CI, −2.3 to 3.5 mg]; $P = .3461$) (Table 2 and Fig. 3). From discharge to the 12-week follow-up assessment, the cryoneurolysis group consumed 29% fewer opioids than the SOC group. From discharge to the 6-week follow-up assessment, a significantly smaller percentage of patients receiving cryoneurolysis continued to consume opioids vs those receiving SOC treatment for the PP population (15% vs 40%; $P = .0059$) (Table 2).

Table 1
Patient Characteristics (PP Analysis).

	Cryoneurolysis (n = 48)	SOC (n = 48)
Age, y		
Mean (SD)	66.1 (7.7)	65.5 (6.8)
Median	65.5	67.5
Range	49–79	51–77
Gender, n (%)		
Female	25 (52.1)	26 (54.2)
Male	23 (47.9)	22 (45.8)
Race, n (%)		
White	40 (83.3)	36 (75.0)
Black	8 (16.7)	12 (25.0)
Asian	1 (2.1)	0 (0)
Ethnicity, n (%)		
Hispanic or Latino	0 (0)	0 (0)
Not Hispanic or Latino	48 (100)	48 (100)
Body mass index, mean (SD), kg/m^2	30.1 (4.3)	31.5 (4.7)

PP, per protocol; SD, standard deviation; SOC, standard of care.

Secondary and Exploratory End Points

Numerical improvements in NRS scores were observed from baseline to each follow-up assessment as measured by AUC/time for a change in pain in the past week and in current pain from baseline, but significant reductions were not observed at all assessments (Tables 3 and 4). The cryoneurolysis group reported better outcomes on KOOS JR scores relative to the SOC group, with significantly greater improvement in scores from baseline on the KOOS JR at the

Table 2
Opioid Consumption in PP Analysis.

	Cryoneurolysis (n = 48)	SOC (n = 48)	Mean Difference Between Groups (95% CI)[a]	*P* Value
Opioid consumption in TMEs, mean (SE), mg				
Discharge to 72 h	10.9 (1.4)	14.9 (1.7)	4.0 (−0.5, 8.4)	0.0389
Discharge to 2 wk	9.2 (1.0)	9.8 (1.1)	0.6 (−2.3, 3.5)	0.3461
Discharge to 6 wk	4.2 (0.5)	5.9 (0.6)	1.6 (0.1, 3.2)	0.0186
Discharge to 12 wk	2.4 (0.3)	3.4 (0.4)	1.0 (0.0, 2.0)	0.0234
Patients who were not opioid free, n (%)[b]				
Discharge to 6 wk	7 (15)	19 (40)		0.0059

Study follow-up assessments occurred at 72 hours, 2 weeks, 6 weeks, and 12 weeks after the day of surgery.
CI, confidence interval; PP, per protocol; SE, standard error; SOC, standard of care; TKA, total knee arthroplasty; TME, total daily morphine equivalent.
[a] Difference calculated as standard of care group mean − cryoneurolysis group mean. [b]Patients were classified as opioid free if they did not take any opioid medication between 6 and 12 weeks after TKA.

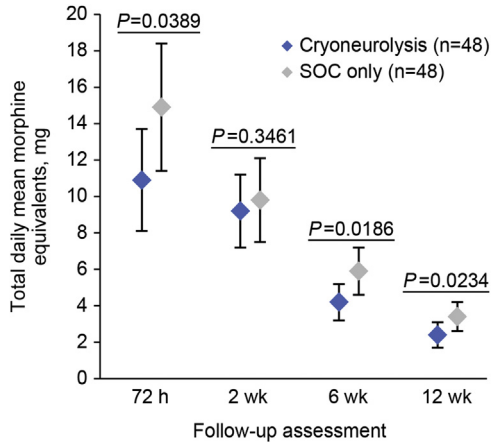

Fig. 3. Cumulative opioid consumption in total daily mean morphine equivalents from discharge to each follow-up assessment for the PP analysis. Study follow-up assessments occurred at 72 hours, 2 weeks, 6 weeks, and 12 weeks after the day of surgery. Error bars are the 95% confidence interval. PP, per protocol; SOC, standard of care.

2-week, 6-week, and 12-week follow-up assessments (Fig. 4). There were no significant between-group differences for change from baseline in AUC/time for the TUG test at any follow-up assessment. Mean (SD) range of motion was comparable between groups at 6 weeks (cryoneurolysis: 111.6° [9.4°]; SOC: 107.9° [10.0°]) and 12 weeks (cryoneurolysis: 114.3° [7.6°]; SOC: 112.1° [9.1°]). Mean (SD) change in range of motion from baseline was also comparable between groups at 6 weeks (cryoneurolysis: −1.6° [16.6°]; SOC: −4.2° [11.6°]) and 12 weeks (cryoneurolysis: 1.3° [15.4°]; SOC: −0.3° [12.8°]), with no significant differences observed at either 6 weeks (MD, 2.6° [95% CI, −3.2° to 8.5°]; $P = .3750$) or 12 weeks (MD, 1.6° [95% CI, −4.3° to 7.4°]; $P = .5892$).

Safety

As shown in Table 5, the percentage of patients who experienced an adverse event (AE) was similar in both treatment groups (16.9% in the cryoneurolysis group; 35% in the SOC group). Most AEs in both groups were related to the surgery and were of mild (61%) or moderate (27%) severity. There were no serious AEs in the cryoneurolysis group attributed to the treatment. There were no device-related or cryoneurolysis procedure–related AEs, and no patient who received cryoneurolysis withdrew from the study because of an AE. The most frequently reported AEs for the study were deep vein thrombosis and wound issues associated with the surgical incision (Table 5).

Table 3
AUC Change From Baseline in Pain in the Past Week as Measured by NRS Pain Scores in the PP Analysis.

	Cryoneurolysis (n = 48)	SOC (n = 48)	Mean Difference Between Groups (95% CI)[a]	*P* Value
Baseline to 72 h	0.2 (1.4)	−0.2 (1.1)	0.4 (−0.1, 0.9)	0.0642
Baseline to 2 wk	1.0 (2.1)	0.4 (1.8)	0.6 (−0.2, 1.4)	0.0615
Baseline to 6 wk	2.2 (2.2)	1.6 (2.0)	0.6 (−0.2, 1.5)	0.0680
Baseline to 12 wk	3.2 (2.3)	2.3 (2.0)	0.9 (−0.0, 1.7)	0.0256

Values are mean (standard deviation) unless otherwise specified. Study follow-up assessments occurred at 72 hours, 2 weeks, 6 weeks, and 12 weeks after the day of surgery.
AUC, area under the curve; CI, confidence interval; NRS, numerical rating scale; PP, per protocol; SOC, standard of care.
[a] Difference calculated as standard of care group mean − cryoneurolysis group mean.

Table 4
AUC Change From Baseline in Current Pain as Measured by NRS Pain Scores in PP Analysis.

	Cryoneurolysis (n = 48)	SOC (n = 48)	Mean Difference Between Groups (95% CI)[a]	*P* Value
Baseline to 72 h	0.5 (1.7)	−0.4 (1.3)	0.9 (0.3, 1.5)	0.0023
Baseline to 2 wk	1.3 (2.6)	0.1 (2.0)	1.2 (0.2, 2.1)	0.0074
Baseline to 6 wk	2.1 (2.6)	1.4 (2.0)	0.8 (−0.2, 1.7)	0.0568
Baseline to 12 wk	2.9 (2.6)	2.3 (2.0)	0.6 (−0.3, 1.6)	0.1045

Values are mean (standard deviation) unless otherwise specified. Study follow-up assessments occurred at 72 h, 2 wk, 6 wk, and 12 weeks after the day of surgery.
AUC, area under the curve; CI, confidence interval; NRS, numerical rating scale; PP, per protocol; SOC, standard of care.
[a] Difference calculated as standard of care group mean − cryoneurolysis group mean.

Discussion

Cryoneurolysis before TKA is a novel modality that could be incorporated into a multimodal pain management protocol to reduce opioid consumption while maintaining good pain control and improving function during the first 12 weeks following surgery. Although cryoneurolysis did not result in significantly reduced opioid consumption from discharge to the 6-week follow-up assessment in comparison to SOC treatment in the ITT population, it did result in significantly reduced opioid consumption in the PP population at multiple assessments (72 hours, 6 weeks, and 12 weeks) (Supplemental Table 1). This difference in statistical significance between the ITT and PP populations reflects the possible confounding role of not adhering to a standardized multimodal pain management regimen, suggesting results from the PP analysis may be more relevant than the ITT analysis in interpreting how cryoneurolysis alone affected outcomes related to pain. Specifically, some patients in this study received opioid prescriptions in excess of the prespecified pain management protocol, while others did not receive a prescription for tramadol. This could have influenced outcomes; previous work has demonstrated that the volume of opioids prescribed may influence subsequent consumption. For example, one study found that, among patients who lived in states with regulations to restrict initial amounts of opioids dispensed, opioid consumption over the 6 weeks following TKA was reduced,

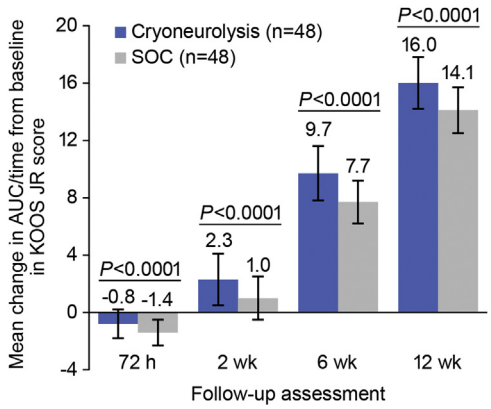

Fig. 4. Improvement in KOOS JR from baseline to each follow-up assessment for the PP analysis. Study follow-up assessments occurred at 72 hours, 2 weeks, 6 weeks, and 12 weeks after the day of surgery. AUC/time, area under the curve/time (calculated as the AUC of change scores from baseline to the 6-week follow-up assessment divided by the number of days from TKA until the 6-week assessment); KOOS JR, Knee Injury and Osteoarthritis Outcome Score for Joint Replacement; PP, per protocol; SOC, standard of care; TKA, total knee arthroplasty.

Table 5
TEAEs (Safety Population).

System Organ Class Preferred Term	Cryoneurolysis (n = 59)	SOC (n = 60)
Any TEAE	10 (16.9)	21 (35.0)
Any serious TEAE[a]	2 (3.4)	2 (3.3)
Any TEAE resulting in study withdrawal	0 (0)	1 (1.7)
Any opioid use–related TEAE	0 (0)	2 (3.3)
Cardiac disorders	0 (0)	1 (1.7)
Congestive heart failure	0 (0)	1 (1.7)
Infections and infestations	0 (0)	2 (3.3)
Urinary tract infection	0 (0)	1 (1.7)
Wound infection	0 (0)	1 (1.7)
Musculoskeletal and connective tissue disorders	0 (0)	3 (5.0)
Blisters around knee dressing	0 (0)	1 (1.7)
Inflammatory/Soft tissue	0 (0)	1 (1.7)
Wound drainage	0 (0)	1 (1.7)
Psychiatric disorders	0 (0)	2 (3.3)
Depression	0 (0)	1 (1.7)
Neuropsychotic/Seizure	0 (0)	1 (1.7)
Renal and urinary disorders		
Urinary retention due to benign prostatic hyperplasia	1 (1.7)	0 (0)
Skin and subcutaneous tissue disorders	0 (0.0)	3 (5.0)
Anaphylaxis	0 (0)	1 (1.7)
Blisters from wound dressing	0 (0)	1 (1.7)
Rash over lateral aspect of knee	0 (0)	1 (1.7)
Rash/Allergy to oxycodone	0 (0)	1 (1.7)
Surgical and medical procedures	3 (5.1)	7 (11.7)
Aseptic necrosis of surgical wound	0 (0)	1 (1.7)
Bleeding/Inflammation under dressing	0 (0)	1 (1.7)
Edema	0 (0)	1 (1.7)
Inflammation	0 (0)	1 (1.7)
Nerve hypersensitivity from surgery	1 (1.7)	0 (0)
Right knee manipulation (manipulation under anesthesia)	1 (1.7)	0 (0)
Stretched nerve resulting in foot drop	0 (0)	1 (1.7)
Surgical incision dehiscence	0 (0)	1 (1.7)
Surgical wound bleeding	1 (1.7)	1 (1.7)
Vascular disorders	6 (10.2)	4 (6.7)
Bilateral pulmonary embolisms	1 (1.7)	0 (0)
Deep vein thrombosis	0 (0)	1 (1.7)

Values are number (percentage).
SOC, standard of care; TEAE, treatment-emergent adverse event.
[a] Serious TEAEs in the cryoneurolysis group included 1 patient who reported shortness of breath on exertion and was given a computed tomography scan to rule out pulmonary embolism, and 1 patient diagnosed with deep vein thrombosis in the right lower extremity who was treated with apixaban. Serious TEAEs in the SOC group included 1 patient who had a severe allergic reaction later attributed to allergy to sulfur contained in celecoxib, and 1 patient admitted to the hospital with general weakness, confusion, lethargy, hallucinations, and slurred speech. The patient was discontinued from tramadol because of its interference in controlling preexisting epilepsy and increased seizure activity and was also discontinued from oxycodone because of its sedating effects.

while another study found that for every 1 pill prescribed, patients were likely to consume an additional ~0.5 pill after total joint arthroplasty [17,18]. Further, standardized opioid prescription protocols have been previously shown to facilitate reduced opioid use [19]. Together, these data suggest that a standardized multimodal pain management regimen is important for improving patient outcomes. Moreover, although standardized protocols do not necessarily reflect real-world practice, future studies that continue to use standardized multimodal pain management regimens to isolate the potential benefits of investigational treatments (eg, NCT04191031) are necessary.

Additionally, we observed consistent improvements in knee function in the PP population, suggesting that the cryoneurolysis group experienced a more active recovery process in the first weeks after TKA than patients who received SOC treatment, which further supports the therapeutic benefit of preoperative cryoneurolysis in this procedure. The more active recovery period observed in patients who received cryoneurolysis may have also contributed to the lack of significant 2-week findings, given that the increased functionality during this time may have led to additional activity-related pain, thereby leading to additional opioid use.

It should be noted that in the PP analysis, patients who received cryoneurolysis were ~3 times more likely to not be opioid-free from discharge to the 6-week follow-up visit vs those receiving SOC treatment (15% vs 40%). The percentage of patients continuing to consume opioids 6 weeks after the day of surgery in the SOC group is also comparable with findings at ≥12 weeks (≥3 months) in two other studies of >137,000 patients undergoing TKA [3,4]. Clinically meaningful changes in opioid use have not been routinely studied, although one study of patients undergoing laparoscopic cholecystectomy reported that a clinically meaningful change in opioid use was ~3 mg of morphine equivalent dose after meeting a threshold of 10.6 mg of morphine equivalent dose [20]. Given that it is unclear how these findings translate to TKA, future studies assessing clinically meaningful changes in this therapeutic area are needed. This underscores the need for introducing novel methods of analgesia to minimize high levels of long-term opioid use observed in standard practice and the associated complications, such as infection, stiffness, and aseptic revision [3].

In the present study, cryoneurolysis was well tolerated, as indicated by the absence of device- or procedure-related AEs and the similar rate of AEs observed in both groups. A limitation of this study was the lack of a sham control group. Although we cannot discount the possibility that the improved outcomes in the cryoneurolysis group were partially attributable to a placebo effect, we note that results from a sham-controlled study of cryoneurolysis for the treatment of knee osteoarthritis pain demonstrated a statistically significant reduction in pain in patients who received

cryoneurolysis [11]. Additionally, for the KOOS JR scores, the highest (worst) score was imputed for questions that patients did not answer; regardless of this imputation that would bias against the study intervention, cryoneurolysis improved knee function outcome scores across multiple time points. The use of a single site allowed for greater control over pain management and physical therapy protocols. Because this study was conducted at a single clinical site, the findings may not be generalizable to larger, more diverse populations, especially given that there appears to be wide variation in postoperative opioid prescribing habits even within a single healthcare system, necessitating system-wide quality improvement programs. Some patients in the present study did not receive spinal anesthesia and instead received general anesthesia. General anesthesia is associated with a higher rate of infection and a longer length of hospital stay compared with spinal anesthesia [2]. Given these data, it may be expected that the use of general anesthesia could bias against the outcomes assessed in this study. However, despite the numerically larger number of patients in the cryoneurolysis group who received general anesthesia compared with the SOC group, improved pain management and function were observed with this intervention. Additionally, while patients who were not prescribed tramadol were excluded from the PP analysis, tramadol use was not directly measured; as such, it is not possible to assess how patient nonadherence could have affected observed outcomes. Furthermore, patient satisfaction measures and cost efficiency were not analyzed, and future studies incorporating these analyses may help provide a comprehensive understanding of treatment effects beyond clinical outcomes. Finally, given the number of medical deviations that could have confounded patient outcomes, results from the PP analysis are likely more meaningful than the ITT analysis; however, the PP analysis should be interpreted with caution because of the small sample size and because it was more likely to be biased toward the null hypothesis than the ITT analysis.

Conclusions

Preoperative cryoneurolysis may be considered as a part of multimodal pain management to minimize opioid use while reducing pain and improving knee function after surgery. Future studies can assess the analgesic efficacy, safety, and opioid-sparing benefits of cryoneurolysis in patients with prior long-term opioid use undergoing TKA. Collectively, these data indicate that cryoneurolysis can be an important component to multimodal postoperative pain strategies and address the growing concern of long-term postoperative opioid use.

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Pacira BioSciences, Inc. participated in the study conception and design; collection, analysis, and the interpretation of the data; and review of the manuscript. The authors were responsible for review and final approval to submit for publication.

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Appendix

Supplemental Table 1
Opioid Consumption in Total Daily Morphine Equivalents (ITT Analysis).

	Cryoneurolysis, mg (n = 62)	SOC, mg (n = 62)	Mean Difference Between Groups (95% CI), mg[a]	*P* Value
Discharge to 72 h	11.2 (1.4)	14.6 (1.6)	3.3 (−0.9, 7.6)	0.0604
Discharge to 2 wk	9.7 (1.2)	10.2 (1.2)	0.5 (−2.8, 3.9)	0.3766
Discharge to 6 wk	4.8 (0.7)	6.1 (0.7)	1.3 (−0.6, 3.2)	0.0841
Discharge to 12 wk	2.7 (0.4)	3.4 (0.4)	0.7 (−0.4, 1.8)	0.0968

Values are mean (standard error) unless otherwise specified. Study follow-up assessments occurred at 72 h, 2 wk, 6 wk, and 12 wk after the day of surgery.
[a] Difference calculated as SOC group mean − cryoneurolysis group mean. CI, confidence interval; ITT, intent-to-treat; SOC, standard of care.

Supplemental Table 2
CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial*.

Section/Topic	Item No	Checklist Item	Reported on Page No
Title and abstract			
	1a	Identification as a randomized trial in the title	Title Page Document p1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts)	Manuscript Document p3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Manuscript Document p5-p6
	2b	Specific objectives or hypotheses	P6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio	Manuscript Document p7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	Manuscript Document p7
	4b	Settings and locations where the data were collected	Manuscript Document p7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Manuscript Document p7-p9
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	Manuscript Document p9-p10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	Manuscript Document p10-p11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomization:			Manuscript Document p9
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	Manuscript Document p9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Manuscript Document p9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Manuscript Document p9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Manuscript Document p11-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Manuscript Document p10-12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned received intended treatment and were analyzed for the primary outcome	Manuscript Document p13
	13b	For each group, losses and exclusions after randomization, together with reasons	Manuscript Document p13
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Manuscript Document p7
	14b	Why the trial ended or was stopped	Manuscript Document p11, p13 (met sample size)
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Manuscript Document p23 (Table 1)
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Manuscript Document p13/ Figure 2

(*continued on next page*)

Supplemental Table 2 (*continued*)

Section/Topic	Item No	Checklist Item	Reported on Page No
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Manuscript Document p13-15; Tables 2-4, Fig 3-4, Supp Tables 1-3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	Manuscript Document p15, Supp Table 4
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Manuscript Document p15-16; Table 5
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Manuscript Document p18-19
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	Manuscript Document p18-19
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Manuscript Document p17-19
Other information			
Registration	23	Registration number and name of trial registry	Manuscript Document p7
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Manuscript Document p19-20

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for randomized cluster trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.