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ORIGINAL RESEARCH

A Randomized Controlled Pilot Study Using Ultrasound-Guided Percutaneous Cryoneurolysis of the Infrapatellar Branch of the Saphenous Nerve for Analgesia Following Total Knee Arthroplasty

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ABSTRACT

Introduction: Total knee arthroplasty (TKA) is frequently associated with severe, prolonged postsurgical pain, and therefore local anesthetic-based peripheral nerve blocks are commonly used for postoperative analgesia. Cryoneurolysis involves the use of freezing temperatures to provide a reversible sensory (and motor) block with a duration measured in weeks and months, more commensurate with the typical period of post-TKA pain. We therefore conducted a randomized controlled pilot study to evaluate the use of this modality for the treatment of pain following TKA to (1) determine the feasibility of and optimize the study protocol for a subsequent definitive clinical trial; and (2) estimate analgesia and opioid reduction within the first 3 postoperative weeks.

Methods: A convenience sample of 16 patients undergoing primary TKA with a single-injection and/or continuous adductor canal nerve block were randomized to receive either active cryoneurolysis or a sham procedure targeting the infrapatellar branch of the saphenous nerve, in a participant-masked fashion. This was a pilot study with a relatively small number of participants, and therefore resulting data were not analyzed statistically.

Results: Compared with participants receiving sham, the active treatment group reported slightly lower average and worst pain scores as well as opioid consumption and sleep disturbances due to pain at a majority of postoperative time points between postoperative days (POD) 4–21.

Conclusions: Preoperative ultrasound-guided cryoneurolysis of the infrapatellar branch of the saphenous nerve is feasible and may provide analgesic benefits for multiple weeks following TKA. A definitive randomized controlled trial appears warranted.

Keywords: Cryoneurolysis; Infrapatellar branch of the saphenous nerve; Nerve block; Regional anesthesia; Total knee arthroplasty

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Key Summary Points

Total knee arthroplasty is frequently associated with severe, prolonged postsurgical pain, and ultrasound-guided cryoneurolysis of the infrapatellar branch of the saphenous nerve may lead to more prolonged analgesia after surgery

We conducted a randomized controlled pilot study to evaluate the use of this modality for the treatment of pain following total knee arthroplasty to assess feasibility and analgesia/opioid reduction for 3 weeks after surgery

Preoperative ultrasound-guided cryoneurolysis of the infrapatellar branch of the saphenous nerve is feasible and may provide analgesic benefits for multiple weeks following TKA

A definitive randomized controlled trial appears warranted

INTRODUCTION

Total knee arthroplasty (TKA) is frequently associated with severe, prolonged postsurgical pain, and therefore local anesthetic-based peripheral nerve blocks are commonly used for postoperative analgesia. However, the duration of benefit from single-injection and catheter-based techniques is limited to hours or a few days. Acute and chronic pain are associated, and despite perioperative local anesthetic administration, the incidence of chronic pain following TKA is 20% or greater 3–24 months after surgery [1]. An analgesic modality better matching the duration of post-TKA pain may both decrease pain in the immediate postoperative period and hopefully decrease the risk of subsequent chronic pain.

Ultrasound-guided percutaneous cryoneurolysis is such a possible modality [2]. Cryoneurolysis involves the application of extreme cold to a peripheral nerve, leading to Wallerian degeneration of the distal axon and subsequent regeneration of the axon over the course of weeks to months. Percutaneous cryoneurolysis for TKA analgesia was first described by Dasa et al. in 2016 with a "blind" landmark-based technique targeting the anterior femoral cutaneous nerve and the infrapatellar branch of the saphenous nerve (IPBSN) [3]. While case reports of perioperative ultrasound-guided percutaneous cryoneurolysis—including of the IPBSN [4]—suggest substantial analgesic and opioid-sparing benefits after painful surgical procedures [5], only a single randomized controlled pilot study involving the lateral femoral cutaneous nerve after skin grafting has been published [6].

We therefore conducted a randomized controlled pilot study to evaluate the use of this modality for the treatment of pain following TKA to (1) determine the feasibility of and optimize the study protocol for a subsequent definitive clinical trial; and (2) estimate analgesia and opioid reduction within the first 3 postoperative weeks.

METHODS

This study followed Good Clinical Practice and was conducted within the ethical guidelines outlined in the Declaration of Helsinki. The protocol was approved by the Institutional Review Board (#180863, University of California, San Diego, CA) and prospectively registered (clinicaltrials.gov NCT03578237; Principal Investigator Brian M. Ilfeld, MD, MS; initial posting July 6, 2018). Written, informed consent was obtained from all participants.

Enrollment

Adults, age 18 years or older, presenting for unilateral primary total knee arthroplasty with a planned single-injection or continuous adductor canal block were evaluated for enrollment in this study between August 2019 and September 2021. Exclusion criteria included chronic opioid use (daily use within the previous 2 weeks and for a duration of at least 4 weeks), morbid

obesity (body mass index > 40 kg/m^2), infection at the cryoneurolysis site, incarceration, pregnancy, and individuals with a medical condition that is a contraindication to cryoneurolysis (e.g., cryoglobulinemia, cold urticaria, and Raynaud's syndrome).

Preoperative Procedures

Patients had standard American Society of Anesthesiologists monitors applied in the supine position. Ultrasound examination of the adductor canal and IPBSN was performed to confirm adequate visualization of both targets. After confirmation of visualization, light sedation with intravenously administered midazolam and/or fentanyl was provided for the procedures. Single-injection adductor canal nerve blocks were performed at the mid-sartorius level in relation to the superficial femoral artery. After skin preparation with chlorhexidine gluconate, a 17-gauge Tuohy needle was advanced in-plane under ultrasound guidance into the adductor canal, and 30 mL of ropivacaine 0.5% with 1:400,000 epinephrine was injected around the superficial femoral artery. For continuous techniques, an 18-gauge catheter was threaded through the Tuohy needle into the adductor canal space, and the tip of the catheter was confirmed to be in the correct space with injection of 30 mL of ropivacaine 0.5% with 1:400,000 epinephrine. Patients also received preoperative multimodal analgesia in the form of orally administered acetaminophen, celecoxib, and/or gabapentin based on patient's age, allergies, and comorbidities.

Treatment Group Allocation

After confirmation of successful peripheral nerve block administration defined by sensory changes in the saphenous nerve distribution, participants were randomly allocated to one of two treatments: (1) *active* cryoneurolysis, or (2) *sham*. Computer-generated randomization lists were used by the University of California San Diego Investigational Drug Service (San Diego, CA) to create sealed, opaque randomization envelopes enclosing the treatment group assignment. The investigator administering the study intervention opened the randomization envelope. Therefore, other investigators, participants, and clinical staff were masked to treatment group assignment, with the exception being the unmasked individual who performed the procedure.

Study Intervention

The IPBSN was identified in short-axis along the medial aspect of the proximal tibia using a 13- to 6-MHz linear ultrasound transducer (HFL38, Edge-II, SonoSite, Bothell, WA) (Fig. 1) [7]. After skin preparation with chlorhexidine gluconate and infiltration of the skin with 1% lidocaine, a 14-gauge angiocatheter was introduced into the subcutaneous tissue under ultrasound guidance. Subsequently, a 14-gauge cryoneurolysis probe connected to a console-based cryoneurolysis machine (PainBlocker, Epimed International, Farmers Branch, TX) was introduced through the angiocatheter. The tip of the cannula was advanced under in-plane ultrasound guidance to within 0.3 cm of the IPBSN and the cryoneurolysis machine activated for three cycles of 2 min on and 1 min of defrost. For the active cryoneurolysis group, an ice ball was visualized at the tip of the cryoneurolysis probe enveloping the IPBSN (Fig. 1). For the sham procedure group, the sham probe vented the nitrous oxide at its proximal end, and therefore no freezing occurred at the distal tip. The difference between the active and sham cannulas is imperceptible for the patient, although the physician operator is aware of the treatment assignment because of the lack of ice ball visualization by ultrasound.

After the study interventions, patients were taken to the operating room and underwent general or neuraxial anesthesia. Intraoperative opioids were administered by the anesthesiology team at their discretion. Postoperatively, on the basis of age, allergies, and comorbidities, patients were prescribed oral multimodal analgesia, including scheduled acetaminophen, celecoxib, and gabapentin. Oxycodone 5–10 mg was provided, as needed, every 4 h based on numeric rating scale (NRS) pain score with

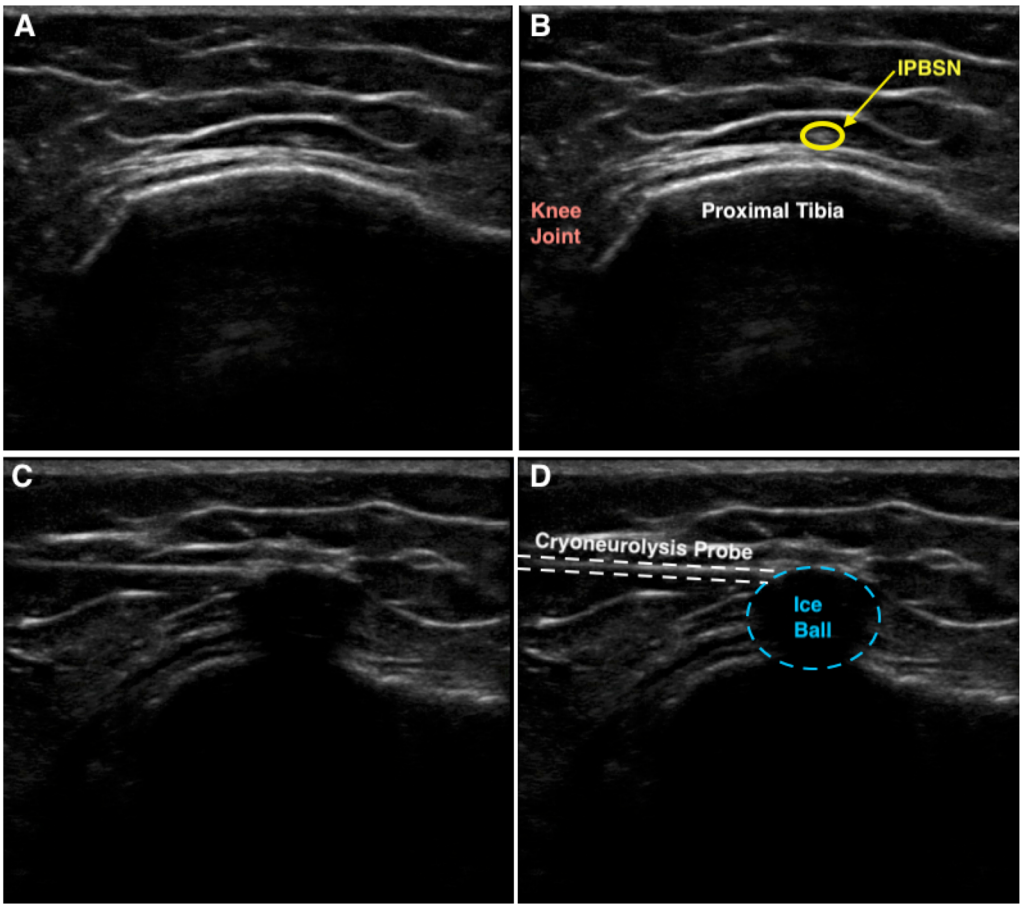

Fig. 1 Ultrasound images of percutaneous cryoneurolysis of the infrapatellar branch of the saphenous nerve (used with permission from Matthew W. Swisher, MD, MS)

intravenously administered hydromorphone 0.5 mg every 3 h for breakthrough rescue pain not alleviated by oxycodone. Discharge readiness was assessed by the primary orthopedic team and physical therapy.

Outcome Measures

Participants were contacted by an unmasked investigator on postoperative days (POD) 1, 2, 3, 4, 7, 14, and 21 either in person if hospitalized or via phone following discharge. For each time point, worst and average pain using an NRS of 0–10 with 0 corresponding to "no pain" and 10 corresponding to "worst imaginable pain" were collected. Opioid consumption was recorded from the electronic medical record while the subjects remained in the hospital. Following discharge, this information was asked of the patients during the follow-up phone calls. Day of discharge was also recorded. Additionally, subjects were asked at each follow-up time point about difficulty sleeping due to pain (binary outcome: yes or no), number of awakenings due to pain, and nausea on a Likert scale of 0 representing "no nausea" to 10 representing "vomited." As a pilot study, primary and secondary outcome measures were not specified.

Statistical Analysis

This was a pilot study designed to determine the feasibility and estimate analgesic effects of percutaneous cryoneurolysis after TKA, and therefore resulting data were not analyzed statistically. Descriptive statistics were used to

describe or summarize characteristics or results of a sample or data set, such as a mean or frequency. A convenience sample of 16 participants was enrolled.

RESULTS

Between August 2019 and September 2021, a total of 16 participants were enrolled, had successful adductor canal peripheral nerve blocks/catheters administered, and randomized to either active ($n = 8$) or sham ($n = 8$) cryoneurolysis (Table 1). Compared to the sham group, the active cryoneurolysis group reported lower average and worst pain scores as well as opioid consumption for the majority of time points from POD 4 to POD 21 (Figs. 2, 3). Mean pain scores peaked on POD 3 or 4 for both groups and subsequently downtrended through POD 21. By POD 14, five subjects in the active cryoneurolysis group no longer required opioids, versus three subjects in the sham group, although a week later, five subjects in both groups were opioid-free. Difficulty sleeping, awakenings due to pain, and hospital length of stay were lower in the active treatment group (Table 2).

Table 1 Patient characteristics and procedural information

	Cryoneurolysis ($n = 8$)	**Sham ($n = 8$)**
Age (years)	68 (64–72)	67 (63–77)
Female (%)	43% (3)	88% (7)
Height (cm)	174 (164–177)	165 (162–170)
Weight (kg)	78 (74–81)	81 (70–87)
Body mass index (kg/m^2)	26 (25–28)	28 (27–30)
Perineural catheter insertion (#)	25% (2)	13% (1)

Values are reported as median (interquartile) or percentage (number of subjects)

Adverse Events and Protocol Violations

There were no observed treatment-related adverse events. Overall follow-up was satisfactory between both groups (98% follow-up rate in active group versus 93% in the sham group). One subject in the active group could not be contacted on POD 7, seven subjects in the sham group could not be contacted at one time point (POD 3 and 4), and one subject in the sham group could not be contacted at two time points (POD 3 and 14).

DISCUSSION

This randomized, patient-masked, sham-controlled pilot study provides evidence that a single preoperative application of ultrasound-guided percutaneous IPBSN cryoneurolysis is feasible and modestly improves analgesia while reducing opioid requirements following TKA. While the overall decrease in pain scores is modest—between 1 and 2 points on the 10-point numeric rating scale—this is similar to improvements achieved with a continuous femoral nerve block, often described as the gold-standard analgesic following TKA [8]. In general, the smallest relevant improvement between *groups* of patients (e.g., active vs. placebo) will be smaller than for *individual* patients [9]. And the smallest relevant improvement for interventions with few side effects and adverse events (among other variables) can be exceedingly small: for example, acetaminophen decreases pain scores and/or opioid requirements to such a small degree as to be rarely even detectable following knee arthroplasty [10], but is nonetheless frequently included in "multimodal analgesia" regimens. Cryoneurolysis lacks the potential systemic toxicity of acetaminophen with a far longer duration of action [5]; and therefore if the relatively small improvements we detected in this pilot study are validated in a definitive trial, this modality *may* ultimately be deemed advantageous as is acetaminophen.

Our data may suggest a benefit of cryoneurolysis' prolonged duration without requiring external equipment or physician/patient

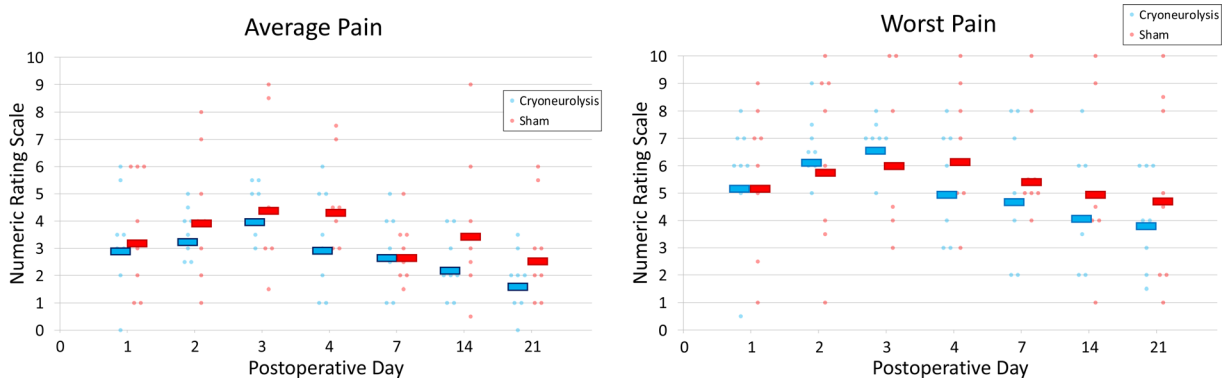

Fig. 2 Effects of percutaneous cryoneurolysis on average and worst pain following total knee arthroplasty measured using a numeric rating scale with 0 equivalent to no pain and 10 being the worst imaginable pain. Each circle represents one participant and the mean for each group at each time point is denoted with a horizontal line

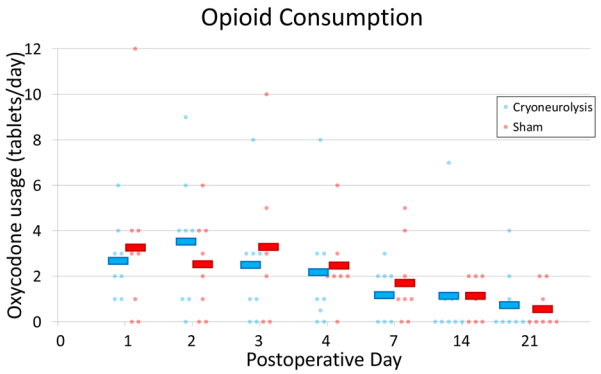

Fig. 3 Effects of percutaneous cryoneurolysis on opioid consumption following total knee arthroplasty. Each circle represents one participant and the mean for each group at each time point is denoted with a horizontal line

management: differences between the active and placebo groups began to increase on POD 4 and continued through the follow-up period of 3 weeks. The smaller differences in the early period may have been due to the single-injection and continuous adductor canal blocks.

As a result of the limited nature of this pilot study, participants were not followed past 3 weeks; but, since the duration of cryoneurolysis effects is often measured in months, it is possible that analgesic benefits continued. In one *retrospective* investigation, preoperative ultrasound-guided percutaneous cryoneurolysis of the IPBSN and branches of the femoral cutaneous nerves was associated with decreased opioid consumption through 6 weeks following TKA [11]. And while a recent randomized placebo-controlled trial comparing a "blind" landmark-based cryoneurolysis technique for TKA was negative for its primary end point, secondary outcomes suggested a similar reduction in opioid consumption through 6 weeks [12]. Unfortunately, landmark-based targeting of the genicular nerves may not reliably block the individual nerves given anatomic variations, and ultrasound visualization of small genicular nerves can be challenging [13]. Thus, prospective studies investigating ultrasound-guided targeting of these nerves for cryoneurolysis are warranted. This pilot study confirms the feasibility of ultrasound-guided cryoneurolysis of the IPBSN and provides a preliminary estimate of the potential analgesic treatment effect.

Limitations

As a pilot study assessing the feasibility of ultrasound-guided IPBSN cryoneurolysis with a limited sample size of 16 subjects, statistical analysis was not performed. No prior data were available to estimate any possible treatment effect, thus a convenience sample of 16 subjects was used. Given this limited sample size, our results should be interpreted as preliminary with the goal of guiding a future adequately powered randomized controlled trial. In addition, while participants were masked to

Table 2 Outcome measures

	Cryoneurolysis (n = 8)	Sham (n = 8)
Day of discharge[a]		
1	63% (5)	38% (3)
2	38% (3)	63% (5)
Nausea and/or vomiting		
POD 1	0 (0–0)	0 (0–0)
POD 2	0 (0–0)	0 (0–0)
POD 3	0 (0–0)	0 (0–0)
POD 4	0 (0–0)	0 (0–0)
POD 7	0 (0–0)	0 (0–0)
POD 14	0 (0–0)	0 (0–0)
POD 21	0 (0–0)	0 (0–0)
Difficulty sleeping due to pain		
POD 1	25%	38%
POD 2	50%	75%
POD 3	63%	83%
POD 4	50%	42%
POD 7	57%	38%
POD 14	38%	57%
POD 21	13%	50%
Awakenings due to pain (#/subject)		
POD 1	0 (0–1)	0 (0–0)
POD 2	0 (0–0)	1 (0–2)
POD 3	1 (0–2)	3 (0–4)
POD 4	1 (0–2)	2 (0–3)
POD 7	0 (0–1)	0 (0–0)
POD 14	0 (0–1)	0 (0–3)
POD 21	0 (0–0)	0 (0–2)

Values are reported as percentage of the group or median (interquartile)
POD postoperative day
[a]Totals not equal to 100% due to rounding error

treatment group, the investigator collecting data was not, adding possible bias to the results.

As previously mentioned, post-TKA pain can be associated with multiple terminal nerves. The degree of sensory innervation of the IPBSN to the knee and its associated degree of attributed pain may be modest. This pilot study did not investigate the analgesic effect of cryoneurolysis of other genicular nerves. If pain attributed to the IPBSN after TKA is truly small in comparison to the total innervation to the knee, the overall treatment effect in a future prospective study may be similarly small. However, it is important to quantify the contribution of each terminal genicular nerve on post-TKA analgesia to guide future interventions.

CONCLUSION

This pilot study demonstrates that preoperative ultrasound-guided percutaneous cryoneurolysis of the IPBSN is feasible and may provide analgesic benefits for multiple weeks following TKA. A definitive, highly powered randomized trial is warranted to further understand the treatment effect.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Matthew W. Swisher, MD MS: this author helped with literature search, data collection, study design, analysis of data, manuscript preparation, and review of manuscript. Scott T. Ball, MD: this author helped with literature search, study design, manuscript preparation, and review of manuscript. Francis B. Gonzales, MD: this author helped with literature search, study design, manuscript preparation, and review of manuscript. Krishna R. Cidambi, MD: this author helped with literature search, study design, manuscript preparation, and review of manuscript. Andrea M. Trescot, MD: this author helped with literature search, study design, manuscript preparation, and review of manuscript. Brian M. Ilfeld, MD MS: this author helped with literature search, data collection, study design, analysis of data, manuscript preparation, and review of manuscript.

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Compliance with Ethics Guidelines. This study followed Good Clinical Practice and was conducted within the ethical guidelines outlined in the Declaration of Helsinki. The protocol was approved by the Institutional Review Board (#180863, University of California, San Diego, CA) and prospectively registered (clinicaltrials.gov NCT03578237; Principal Investigator Brian M. Ilfeld, MD, MS; initial posting July 6, 2018). Written, informed consent was obtained from all participants.

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

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