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Percutaneous freezing of sensory nerves prior to total knee arthroplasty

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ABSTRACT

Background: Total knee arthroplasty (TKA) is a common procedure resulting in significant post-operative pain. Percutaneous cryoneurolysis targeting the infrapatellar branch of the saphenous nerve and anterior femoral cutaneous nerve could relieve post-operative knee pain by temporarily blocking sensory nerve conduction.
Methods: A retrospective chart review of 100 patients who underwent TKA was conducted to assess the value of adding perioperative cryoneurolysis to a multimodal pain management program. The treatment group consisted of the first 50 patients consecutively treated after the practice introduced perioperative (five days prior to surgery) cryoneurolysis as part of its standard pain management protocol. The control group consisted of the 50 patients treated before cryoneurolysis was introduced. Outcomes included hospital length of stay (LOS), post-operative opioid requirements, and patient-reported outcomes of pain and function.
Results: A significantly lower proportion of patients in the treatment group had a LOS of ≥2 days compared with the control group (6% vs. 67%, $p < 0.0001$) and required 45% less opioids during the first 12 weeks after surgery. The treatment group reported a statistically significant reduction in symptoms at the six- and 12-week follow-up compared with the control group and within-group significant reductions in pain intensity and pain interference at two- and six-week follow-up, respectively.
Conclusions: Perioperative cryoneurolysis in combination with multimodal pain management may significantly improve outcomes in patients undergoing TKA. Promising results from this preliminary retrospective study warrant further investigation of this novel treatment in prospective, randomized trials.
Level of evidence: III

1. Introduction

Total knee arthroplasty (TKA) is a very common surgery for advanced osteoarthritis of the knee that is unresponsive to conservative treatments. There are approximately 600,000 knee replacements performed each year, and this number is expected to increase in future years [1]. Although knee replacements usually are very successful in the long term, patients often experience a significant amount of pain during the immediate post-operative period, which can be a major hindrance to effective rehabilitation and restoration of function following surgery.

Perioperative pain control has been the focus of considerable attention in recent years. Traditionally, narcotic pain medications have been used to control pain; however, their well-known side effects, such as nausea, emesis, ileus, and dependence, can slow down recovery [2]. Recently, multimodal pain management has been promoted to improve perioperative pain control while minimizing the risk of adverse events in the American Society of Anesthesiologists practice guidelines for acute pain management [3]. Multimodal pain management protocols implemented after total hip and knee arthroplasty (THA and TKA) have been shown to result in better pain control and patient satisfaction, lower overall narcotic consumption, shorter hospital stays, improved function, and fewer complications [4].

The use of cold as an analgesic dates back to the days of Hippocrates and the ancient Egyptians [5]. Recent work has shown the effect of cryoneurolysis on peripheral sensory nerve function. Barnard demonstrated that cryoneurolysis applied to the terminal branches of the trigeminal nerve in rats causes degeneration distal to the site of freezing without disruption of the anatomical architecture followed by structural regeneration of the nerve at about six weeks of post-injury and recovery of normal sensation in two to four months [6]. Histological studies have shown that treatment of nerves with temperatures from −20° to −60 °C results in Wallerian degeneration [6], which occurs distal to the site of injury and involves loss of the relative continuity of the axon and its covering of myelin, but preservation of the surrounding endoneurial, perineurial, and epineurial structure, which allows for normal axonal regeneration and remyelination [6]. Functional recovery of

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the sensory axon will normally occur between several weeks and months after cryoneurolysis depending on the distance of the axon injury site to the target site and rate of axon regrowth [6].

In a preclinical study, Hsu and Stevenson observed significant axonal regeneration and remyelination with concurrent elimination of macrophage infiltration and via histological examination of nerves eight weeks following cryoneurolysis and complete axonal regeneration by 16 weeks post-treatment [7]. Consistent with these findings, cryoneurolysis of peripheral sensory nerves has been shown to be efficacious in attenuating pain symptoms in patients with clinical conditions including trigeminal neuralgia, neuroma, and post-thoracotomy pain [5,8–12], with pain relief ranging from a couple of months to a few years [10,13].

Neuropathic knee pain is an important source of post-operative pain [13]. Percutaneous cryoneurolysis directed at sensory nerves that innervate the knee is a new option for reducing TKA post-operative pain [13]. Cryoneurolysis treatment of knee pain targets the infrapatellar branch of the saphenous nerve (ISN) and anterior femoral cutaneous nerve (AFCN), which lie in a predictable and superficial location as they approach the knee. The ISN and AFCN provide sensory innervation around the anterior knee with no motor involvement. After extensive use by the senior author in treatment of knee osteoarthritis pain, he began using this new treatment to improve post-operative outcomes following TKA. This study was conducted to evaluate whether perioperative cryoneurolysis, in combination with a standard multimodal pain regimen, would shorten hospital stays, decrease narcotic medication use, and improve patient-reported outcomes.

2. Materials & methods

2.1. Patient selection and methods

This was a retrospective chart review of 100 patients who underwent TKA by a single surgeon at a university-based orthopedic practice from 2011 to 2014. The treatment group (cryoneurolysis plus multimodal pain management) included the first 50 patients who were treated with cryoneurolysis after March 31, 2014, when the practice began administering perioperative cryoneurolysis to all TKA patients as part of its standard perioperative pain management protocol. This was the only appreciable change in practice and all other aspects of the treatment protocol (e.g., intraoperative and post-operative pain protocol, surgical technique, implant selection) remained the same. The control group consisted of the first 50 patients who were treated with multimodal pain management alone, preceding the introduction of the cryoneurolysis plus multimodal pain management regimen, who had completed the Western Ontario and McMaster Universities Arthritis Index (WOMAC).

Among the 100 patients included in the study, 70 were females and 30 males. As shown in Table 1, the treatment and control groups were similar in terms of gender ($p = 0.66$), age ($p = 0.24$), and body mass index (BMI) ($p = 0.26$). There were no overall significant differences between groups on baseline patient-reported outcome measures (Wilks' F-test, $p = 0.73$, Table 2). The treatment group received cryoneurolysis of the AFCN and ISN five days prior to surgery in addition to the standard preoperative multimodal pain management program.

Table 1
Patient demographics.

	Control (N = 50)	Treatment (N = 50)	p value
Gender			0.66
Male, N (%)	14 (46.7)	16 (53.3)	
Female, N (%)	36 (51.4)	34 (48.6)	
Age (years), mean (SD)	66.4 (9.4)	68.5 (8.2)	0.24
Body mass index (kg/m^2), mean (SD)	30.9 (5.7)	32.1 (5.3)	0.26

Table 2
Baseline clinical characteristics.

Variable		Control	Treatment	p value
KOOS				
Activities of daily living	N	46	49	0.82
	Mean (SD)	41.07 (21.97)	40.14 (17.51)	
Pain	N	46	49	0.57
	Mean (SD)	36.04 (20.82)	38.18 (15.38)	
Quality of life	N	44	49	0.29
	Mean (SD)	22.16 (23.42)	17.86 (15.34)	
Sports and rec	N	31	37	0.70
	Mean (SD)	25.58 (31.54)	22.68 (29.62)	
Symptoms	N	46	49	0.53
	Mean (SD)	44.11 (19.32)	41.80 (16.74)	
Oxford Knee Score	N	46	46	0.97
	Mean (SD)	18.72 (10.30)	18.78 (8.45)	
PROMIS				
Anxiety	N	18	41	0.32
	Mean (SD)	58.78 (12.88)	55.45 (11.11)	
Depression	N	19	45	0.5
	Mean (SD)	51.03 (11.17)	49.14 (9.71)	
Fatigue	N	18	44	0.85
	Mean (SD)	53.23 (8.74)	52.73 (10.07)	
Pain interference	N	18	46	0.69
	Mean (SD)	65.27 (8.23)	66.13 (7.60)	
Pain intensity	N	18	46	0.93
	Mean (SD)	6.83 (2.90)	6.89 (2.16)	
Sleep disturbances	N	17	41	0.16
	Mean (SD)	54.45 (9.41)	51.14 (7.48)	
Social satisfaction	N	18	43	0.86
	Mean (SD)	39.83 (10.63)	40.42 (12.10)	
Physical function	N	19	43	0.12
	Mean (SD)	35.49 (6.49)	33.05 (5.17)	
SF-12 mental component	N	30	41	0.01
	Mean (SD)	42.77 (12.28)	50.00 (10.43)	
SF-12 physical component	N	30	41	0.22
	Mean (SD)	30.76 (7.12)	28.77 (6.41)	
WOMAC				
Function	N	50	49	0.99
	Mean (SD)	41.92 (22.10)	41.90 (17.00)	
Pain	N	50	49	0.74
	Mean (SD)	41.20 (22.69)	42.55 (17.74)	
Stiffness	N	50	49	0.39
	Mean (SD)	40.82 (26.19)	36.94 (17.03)	

KOOS = Knee Injury and Osteoarthritis Outcome Score; PROMIS = Patient-reported Outcomes Measurement Information System; SD = standard deviation; SF-12 = **12**-item Short Form Health Survey; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

Cryoneurolysis was administered using a novel handheld device, iovera (Myoscience, Fremont California, Figure 1), which was FDA approved (K100447 and K133453) in 2012 to produce "lesions in peripheral nervous tissue by the application of cold to the selected site for the blocking of pain." This device converts liquid nitrous oxide into a gas, creating temperatures of −125 °F along three hollow closed tip short needles (27 gauge, 6 mm long), introduced percutaneously at a target site, to produce a five millimeter cold zone (ice ball) under the skin. Ice ball contact with the target nerve causes Wallerian degeneration, creating axonotmesis while maintaining the original surrounding anatomy (maintaining the scaffold) to allow predictable regrowth of the axon along the original epineurium and endoneurium. The maximum cold temperature produced by the device has no known permanent risks because the original structural scaffold of the nerve is preserved. There are limited transient side effects, such as bruising and tenderness where the needles are inserted.

Treatments were done in the office five days before planned TKA. The AFCN and ISN and their branches were targeted along two treatment lines. The AFCN was targeted approximately 70 mm above the superior pole of the patella along a horizontal line the width of the patella. The AFCN lies within the fascia overlying the quadriceps tendon deep to the subcutaneous fat (Figure 2). The ISN was targeted approximately 50 mm medial to the patella tendon (Figure 3) along a longitudinal line from the inferior pole of the patella and tibial tubercle. The ISN

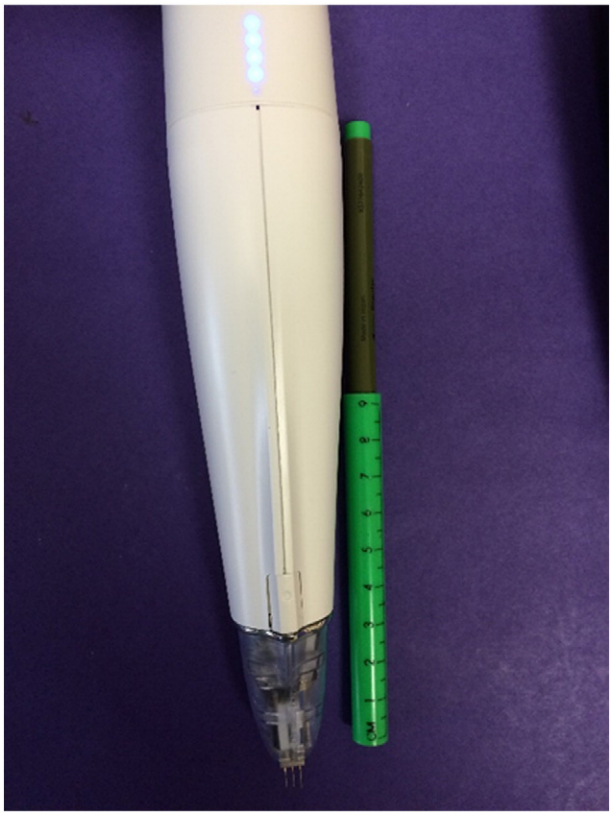

Figure 1. Iovera cryoneurolysis device.

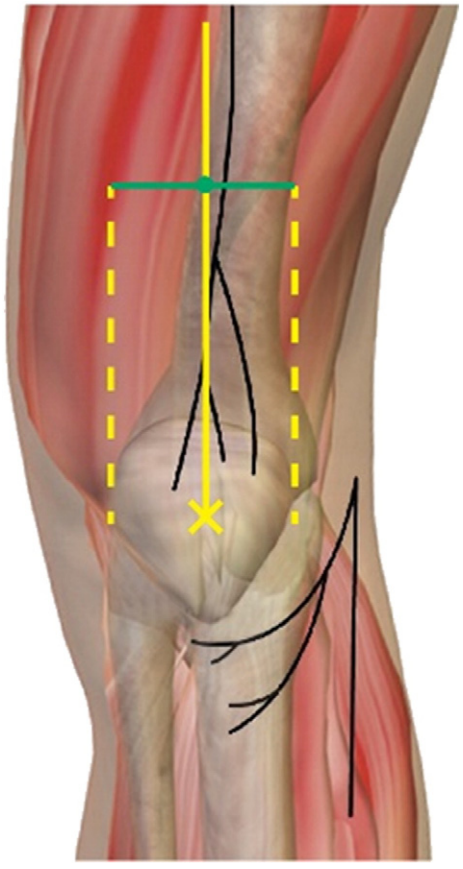

Figure 2. Anterior femoral cutaneous nerve (AFCN) treatment line (published with permission from Myoscience, Inc.).

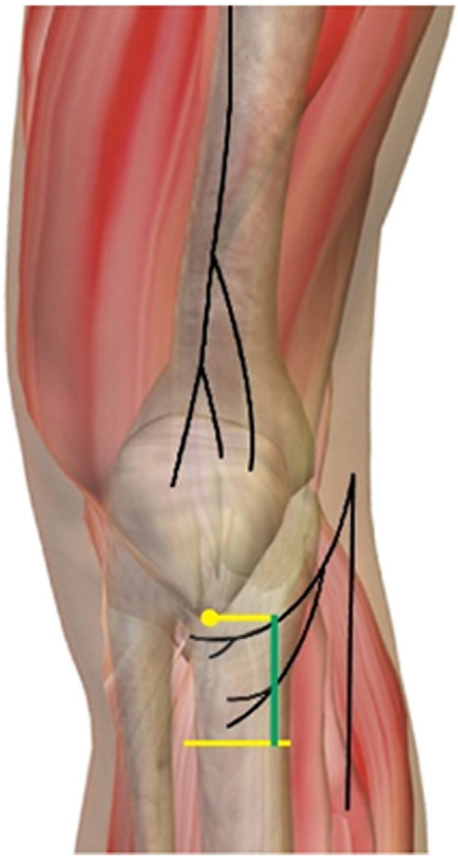

Figure 3. Infrapatellar branch of saphenous nerve (ISN) treatment line (published with permission from Myoscience, Inc.).

lies along the joint capsule deep to the subcutaneous fat. Using these anatomical landmarks, treatment lines were drawn on the patient's knee. Approximately five cubic centimeters of one percent of lidocaine using a 25 gauge needle was injected subcutaneously along the treatment lines to provide cutaneous analgesia.

A treatment cycle consists of a period of cooling then warming of the needles, lasting approximately 50 s. Once a treatment cycle was complete, the needles were then introduced along the next section of the treatment line. Each line required approximately six treatment cycles to cover the length of the treatment line. When the ice ball encountered the target nerve, most patients provided sensory feedback (e.g., burning or tingling sensations) as Wallerian degeneration was induced; this feedback confirmed that the treatment was being applied to the area in which the target nerve traverses. This subjective sensation was difficult to record or quantify. Total time to freeze both nerves and their branches was approximately 15 min. The technique is fairly straightforward and intuitive. Although there may be a limited learning curve of one or two treatments, the authors did not notice any appreciable difficulty in conducting the first few treatments compared with later in the course of the study.

Both groups received the same preoperative, intraoperative, and post-operative care with exception of the additional perioperative cryoneurolysis treatment received by the treatment group. The multimodal pain regimen was administered as follows. Preoperatively during the admission process, patients received one dose of acetaminophen 650 mg, pregabalin 300 mg, and celecoxib 200 mg. Intraoperatively, patients received decadron of 10 mg and a periarticular injection of bupivacaine with epinephrine administered in two phases. Approximately 30 min before the surgery, all patients received spinal anesthesia and a single-injection femoral nerve or adductor block (20 ml ropivicaine 0.2%, decadron one milligram, clonidine 25 mcg,

and epinephrine 1:200,000). No patient received general anesthesia. Prior to incision, bupivacaine with epinephrine was injected along the anterior and medial knee targeting the AFCN and ISN nerves within the deep fascia. During the surgery, after bony cuts were complete, lamina spreaders were used in flexion to expose the posterior capsule, and two 10 cm^3 syringes of bupivacaine with epinephrine were injected into the posterior, medial, and lateral capsules. Post-operatively in the hospital, patients received acetaminophen of 650 mg every eight hours, celecoxib 200 mg twice daily, pregabalin 150 mg twice daily, and oxycodone 10 mg every six hours as needed.

All patients underwent navigated posterior stabilized TKA using an anterior midline incision and medial parapatellar arthrotomy. No quadriceps-sparing procedures were performed. Patients aged <65 years received a Zimmer® NexGen® Complete Knee Solution (Zimmer, Inc., Warsaw, IN) implant with a monolithic uncemented tibial component; those aged ≥65 years received either a Zimmer® NexGen® Complete Knee Solution or U2 Knee™ System (United Orthopedic Corporation, Irvine, CA) implant with traditional cemented components. All surgeries were performed by the senior author (VD), a board-certified orthopedic surgeon who had completed a fellowship in adult reconstruction.

Narcotics were prescribed in the hospital with a prn dosing regimen. The treating surgeon used a standard opioid prescription protocol for all patients. Patients received a prescription for 84 pills (two weeks) of oxycodone-acetaminophen 10/325 mg at discharge. All patients were seen at two, six, and 12 weeks following surgery. Only if requested, patients could receive a prescription for 120 pills (one-month supply) of oxycodone-acetaminophen 10/325 at the two-week follow-up visit and 90 pills (one-month supply) of oxycodone-acetaminophen 10/325 at the six-week visit. No narcotics were given at the 12-week visit. All prescribed narcotics were converted into morphine equivalents using an opioid dose calculator where one milligram of hydrocodone and one milligram of oxycodone were equal to one milligram and 1.5 mg of morphine, respectively.

Patient-reported outcome measures, including the WOMAC, Knee injury and Osteoarthritis Outcome Score (KOOS), Oxford Knee Score, 12-item Short Form Health Survey (SF-12) and Patient-reported Outcomes Measurement Information System (PROMIS), were completed at baseline (precryoneurolysis) and at the two-, six- and 12-week post-operative visits. In 2013, the clinic switched from using the WOMAC to the KOOS questionnaire; WOMAC scores were calculated for patients who completed the KOOS questionnaire based on their responses to the KOOS survey. Hospital discharge criteria included the ability to walk 50 ft with a walker or crutches, get in and out of bed and on and off a toilet independently, and pain adequately controlled with oral medications. Patient medical records were reviewed to determine the incidence of any complications or side effects associated with cryoneurolysis. Patients were discharged directly to home with outpatient physical therapy beginning the following day. An Institutional Review Board approved the study protocol.

3. Statistical analysis

Statistical analyses were conducted using SAS software (version 9.4, SAS Institute, Inc., Cary, NC). Differences between groups on demographics and baseline characteristics were examined using chi-square tests (categorical variables) or Wilks' F test (continuous patient-reported outcomes). Efficacy endpoints were length of hospital stay (LOS), mean cumulative narcotic use in morphine equivalent units, and mean scores on the KOOS, WOMAC, Oxford Knee Score, SF-12 and PROMIS. LOS was categorized into three levels as follows: 0 (0 days), one (one day), and two (≥2 days). Pearson's chi-square test examined differences between the control and treatment groups on LOS. A general linear model, with age and gender, and BMI as covariates and allowing for different variances in the two groups, was used to compare differences in mean cumulative narcotic use between the groups using the Satterthwaite adjusted F-test. Mean change from baseline to two-, six- and 12- week follow-up on the KOOS, WOMAC, Oxford Knee Score, SF-12 and PROMIS were compared using a repeated measures analysis that allowed for modeling dependencies between observations within subjects with age, gender, and BMI as covariates, the Kenward–Roger adjusted F-test as the test for statistical significance, and the Tukey–Kramer adjustment for multiple comparisons.

4. Results

A significantly greater proportion of patients in the control group had a longer LOS than the treatment group (Figure 4). Specifically, 67.3% (33/49) of patients in the control group had a LOS of ≥2 days compared with 6.1% (3/49) in the treatment group ($p < 0.0001$). Similarly, a higher proportion of patients in the treatment group had a LOS of 0 days (44.9% vs. 14.3%) or one day (49.0% vs. 18.4%). The mean ± SD (range) for LOS was 1.7 ± 1.01 (0 to seven) days for the control group, and 0.8 ± 1.14 (0 to five) days for the treatment group. Statistical analysis was based on median values. The mean ± SE cumulative morphine use during the 12 weeks following surgery was significantly lower for the treatment versus control group (2069.12 ± 132.09 mg vs. 3764.42 ± 287.95 mg, $p < 0.0001$). As shown in Figure 5, the treatment group used 45% less morphine equivalent narcotics than the control group during the 12 weeks following surgery after adjusting for age, gender, and BMI.

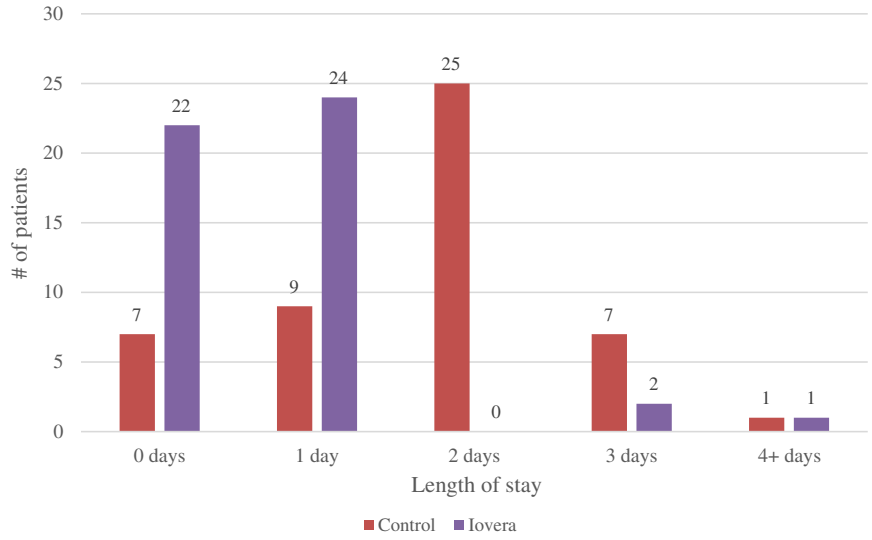

Figure 4. Length of hospital stay in treatment and control groups.

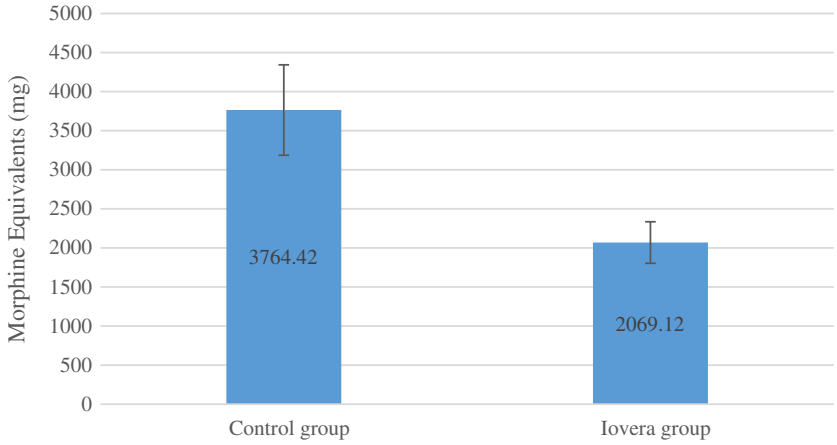

Figure 5. Average cumulative morphine equivalent prescribed at 12 weeks post-TKA in the control and treatment groups. ($p < 0.0001$). Error bars are at 95% CI.

Table 3 (see Supplemental online Appendix) shows the patient-reported outcomes at the two-, six-, and 12-week post-operative visits. The treatment group achieved statistically significantly greater reductions in the KOOS symptoms subscale score from baseline to the six- and 12-week post-operative visits than control group ($p = 0.0037$ at six weeks and 0.0011 at 12 weeks). These differences were attenuated but remained statistically significant after adjusting for age, gender, and BMI. Results also indicated that the treatment group experienced less pain.

When comparing differences within groups to baseline at two weeks post-surgery, the treatment group had significantly reduced PROMIS pain intensity scores ($p < 0.0001$) whereas the control group showed no significant change ($p = 0.176$) from baseline. PROMIS pain interference, a scale that quantifies the extent to which pain interferes with daily activities, was significantly decreased from baseline to six weeks in the treatment group ($p = <0.0001$), but not in the control group ($p = 0.067$).

No complications were noted related to cryoneurolysis treatment. There were no local infections, excess bleeding, or local soft tissue necrosis encountered within the surgical field. Patients did not complain of persistent numbness or other neurologic effects at their three-month post-operative visit. The most common side effect was local bruising at the site of treatment, which had no clinical impact.

5. Discussion

The use of traditional nerve blocks has been proven effective in reducing post-operative pain and producing better long-term knee scores [14]. To our knowledge, this is the first study to show that cryoneurolysis administered prior to TKA in combination with a standard multimodal pain management regimen improves outcomes compared with standard multimodal pain management alone. Patients who received perioperative cryoneurolysis targeting the AFCN and ISN had a significantly shorter LOS, were prescribed significantly less opioids during the first 12 weeks post-operatively, and had significantly less knee symptoms than patients who did not receive perioperative cryoneurolysis. The means did show improved scores across all categories; however, given the natural amount of variation between patients, these results only achieved statistically significant between-group differences in KOOS symptoms and PROMIS pain intensity and pain interference when compared with baseline in the treatment group but not the control group. These results are consistent anecdotal reports by our hospital and outpatient physical therapists, who noticed greater patient satisfaction and more productive physical rehabilitation sessions after preoperative cryoneurolysis was instituted as part of the multimodal pain regimen.

The ability to decrease hospital LOS following TKA should substantially reduce costs for hospitals and payers. In the present study, only six percent of patients treated with cryoneurolysis prior to surgery stayed in the hospital for two or more days compared with 67% of patients who did not receive this treatment. Similarly, almost half of patients treated with cryoneurolysis were discharged on the same day of surgery compared with only 14% in the control group. The shorter LOS for patients who received adjunctive perioperative cryoneurolysis may be due to 1) better local control of pain and a reduced need for proximal nerve blocks that can impair motor function and delay discharge and 2) reduced use of opioids to control pain during the immediate post-operative period, which allows for earlier ambulation and achievement of function required for discharge. Earlier ambulation following TKA has been associated with a shorter LOS and lower hospitalization costs [15]. Shortening the patient's hospital stay may also help lower costs by reducing the risk of developing hospital-acquired infections, which are strongly correlated with LOS [16,17], and add to the cost of hospitalization.

Patients who received cryoneurolysis in addition to standard multimodal pain management were prescribed 45% less opioids during the first 12 weeks of recovery following TKA than those who did not receive cryoneurolysis. Reduced opioid requirements to manage pain has important benefits, including decreased health care utilization (ER visits and office phone calls) and a lower risk of opioid-related side effects (e.g., nausea, constipation/ileus, sedation, dizziness, vomiting, physical dependence, tolerance, and respiratory depression) [2,18]. The significant reduction in narcotic use observed in the present study confirms that the innervation and pain generators surrounding the incision and anterior knee targeted in the present study are a major source of pain following TKA, and suggests that soft tissue innervation originating from the femoral nerve, rather than bony and posterior pain innervated by the geniculate nerves originating from the tibial nerve, is the major source of post-operative pain. However, future studies should evaluate whether targeting the geniculate nerves in addition to the AFCN and ISN provides further reduction in pain.

This study had several limitations, including its retrospective, nonrandomized nature, and lack of blinding of patients and investigators, which may have biased results and limits the generalizability of findings. Selection bias may have influenced results as the control group was comprised of the first 50 patients with complete WOMAC responses treated prior to the initiation of preoperative cryoneurolysis. These patients may have been different from less compliant patients who did not complete the questionnaire and were excluded from the control group. In addition, differences between the control and treatment groups may be attributable to history or other confounding factors, rather than the study intervention. Because the treatment group underwent TKA more recently than the control group, and there has been a trend towards reducing post-operative LOS in the U.S. [19], it is possible that the shorter LOS observed in the treatment group may be an artifact of history. However, the U.S. hospital mean LOS decreased by just 0.2 days from 2003 to 2012 [19]. Thus, it seems unlikely that historical trends can explain the dramatically lower LOS observed in the treatment group compared with the control group (mean of 0.8 days vs. 1.7 days).

Patients' and surgeons' awareness of which patients received cryoneurolysis may have contributed to some of the improved

outcomes in the treatment group, including self-reported measures and LOS. Although the surgeon made the ultimate determination for discharge, this decision was based on the patient's ability to meet certain objectively-measured physical therapy metrics, which reduces the likelihood that discharge decisions were biased. Further, while patients' and surgeons' expectations may have favorably influenced outcomes in the treatment group, it is unlikely that these expectations were solely responsible for the dramatic reduction in LOS and post-operative opioid requirements observed in this group. There were missing data on PROMS for both study groups, due to inconsistent completion of questionnaires, although missing PROM data was more commonly seen in the control group as the office improved its efforts to encourage patient completion of surveys over time. The lack of significant differences between the treatment and control groups on PROM's may be due in part to unequal and small sample sizes for these measures.

In conclusion, adding cryoneurolysis to a multimodal perioperative pain management protocol in patients undergoing TKA may help decrease hospital LOS, reduce post-operative opioid requirements, and improve knee symptoms and pain. Adequately powered prospective randomized studies are needed to validate the findings of this preliminary report.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.knee.2016.01.011.

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