Cryoneurolysis Prior to Total Knee Arthroplasty for Postsurgical Pain

LSU Health NEW ORLEANS School of Medicine

Department of Orthopaedics

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ABSTRACT

INTRODUCTION: A prospective, sham-controlled, multi-center study investigating cryoneurolysis in the treatment of pain associated with knee osteoarthritis has shown a statistically significant reduction in knee pain and improved symptoms compared to sham treatment for up to 90 days.[1] A recent retrospective review demonstrated that cryoneurolysis prior to TKA resulted in a statistically significant reduction in the amount of opioids prescribed following discharge.[2] This TKA feasibility study was conducted to investigate cryoneurolysis for the control of postoperative TKA pain.

METHODS: In this multi-center, prospective, sham-controlled, double-blind study 150 subjects were enrolled at either single-surgeon or multi-surgeon sites. Subjects were treated with cryoneurolysis within 1 week prior to TKA surgery and were evaluated at 2, 4, 6 and 12 weeks post-discharge. The primary endpoint was the average morphine equivalent daily dose (MEDD) from discharge to 6-weeks post-TKA.

RESULTS: The primary endpoint, the mean MEDD calculated from hospital discharge to 6 weeks following TKA surgery, was similar for the cryoneurolysis and sham groups over the entire study population. Single surgeon sites with highly standardized practices (perioperative treatment, surgical technique and in-patient pain management) demonstrated a statistically significant difference in cumulative opioid use with respect to the sham group at 4 weeks post-TKA (p=0.0258) (Figure 4). A similar trend was seen at 6 weeks (p=0.0520) and 12 weeks (p=0.0565) post-TKA at these sites. Over the 12 week follow-up period this represents a 36% reduction in average opioids consumed compared to the sham group. There were no differences in the rate or severity of side effects or adverse events between the treatment and control groups.

DISCUSSION: Results of this study suggest that cryoneurolysis treatment prior to a TKA can reduce opioid consumption post-TKA. A strong placebo effect was observed during this study, which is consistent with sham treatments using an interventional device. Also, inclusion of multiple surgeons at study sites increased confounding factors involving perioperative pain protocols. Though the study did not meet its primary endpoint of total DME from the time of hospital discharge to 6-weeks post-TKA surgery, the results do provide insights into the continuing investigation of the clinical benefits of cryoneurolysis in this patient population. A study is now being conducted to further elucidate the potential post-operative benefits of cryoneurolysis treatments prior to TKA.

BACKGROUND

A variety of organizations have recommended multimodal individualized treatment plans for post-operative pain that incorporate non-pharmacological therapies and promote the use of non-opioid pharmacological therapies over opioids.[2-5] Cryoneurolysis, a non-surgical, minimally-invasive, pain-relieving therapy with a well-established mechanism of action,[6] may be an excellent addition to a multimodal regimen for the treatment of post-operative pain from Total Knee Arthroplasty (TKA).

A recently published retrospective study (n=100) compared pre-operative cryoneurolysis to the standard of care and demonstrated a 45% reduction in opioids prescribed post-TKA.[2] The purpose of the prospective study presented here was to evaluate the effect of pre-operative cryoneurolysis on post-operative opioid use and post-operative pain, stiffness and function in a controlled patient population.

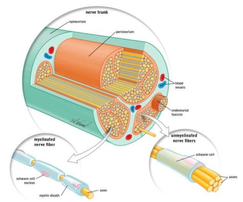

Figure 1. Diagram of nerve anatomy, illustrating the axon and myelin sheath which is degenerated during cryoneurolysis treatment.

Cryoneurolysis is the percutaneous application of low temperatures (-20ºC to -100ºC) to peripheral nerves which leads to Wallerian degeneration, in which the nerve structure and conduction are disrupted while the structural elements of the nerve bundle (endoneurium, perineurium, and epineurium) remain intact (Figure 1), allowing for complete regeneration and functional recovery of the nerve.[7-9] The nerve axon is able to regenerate along the previously established path, at a rate of approximately 1 mm per day, to eventually reinnervate the sensory receptor.[10]

METHODS

Adult men and women ages 22 to 79 in the United States scheduled to undergo primary unilateral TKA under spinal anesthesia for primary diagnosis of osteoarthritis were enrolled in this study. Both subject and physician were blinded to the use of either the cryoneurolysis or sham treatment tip

Cryoneurolysis treatment occurred up to a week prior to TKA. The location of the Infrapatellar Saphenous Nerve (ISN) and the Anterior Femoral Cutaneous Nerve (AFCN) were determined with bony landmarks and palpation.[11] Treatment lines were drawn (Figure 2) and following anesthetizing the cryoneurolysis device (iovera°, Myoscience, Fremont, CA) with a sham or treatment tip was inserted into the skin and an iceball was formed next to the target nerve, exposing it to a temperature below −20°C for 60 seconds (Figure 3). The sham tip appeared and behaved exactly the same as the treatment tip with the exception that no iceball was formed.

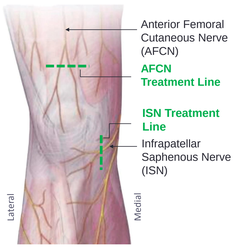

Figure 2. Treatment Lines

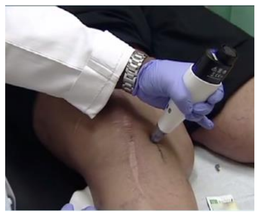

Figure 3. Treatment of the ISN with the Cryoneurolysis device (iovera, Myoscience, Fremont, CA)

The primary efficacy endpoint was the average morphine equivalent daily dose (MEDD) calculated from discharge to the 6-week follow-up visit. Secondary efficacy endpoints included a pain numerical rating scale (NRS), the WOMAC, length of hospital stay, range of motion in active flexion, 40-meter walk test, 30-second chair test, SF-36, and PROMIS-29. Subjects were followed up at 2, 4, 6 and 12 weeks after surgery. Adverse events were also recorded.

RESULTS

The primary endpoint, the mean MEDD calculated from hospital discharge to 6 weeks following TKA surgery, was similar for the cryoneurolysis and sham groups for the total study population. An exploratory analysis examined the primary endpoint separately for the per-protocol subjects who received treatment at the three study sites with a single surgeon versus the five study sites with multiple surgeons. Subjects who received cryoneurolysis at multi-surgeon sites did not demonstrate a difference in the primary endpoint between the cryoneurolysis and sham groups. Subjects who received cryoneurolysis at single surgeon sites with highly standardized practices (perioperative treatment, surgical technique and in-patient pain management) demonstrated a statistically significant difference in cumulative opioid use with respect to the sham group at 4 weeks post-TKA (p=0.0258) (Figure 4). A similar trend was seen at 6 weeks (p=0.0520) and 12 weeks (p=0.0565) post-TKA at these sites. Over the 12 week follow-up period this represents a 36% reduction in average opioids consumed compared to the sham group.

At 12 weeks post TKA, pain intensity was similar between groups (p=0.133). There were no significant differences between groups on the length of hospital stay, WOMAC pain, stiffness, and function subscales and total score at 6- and 12-week follow-up. There were no significant differences between groups in scores for range of motion in active flexion, 40-meter walk test, 30-second chair test, SF-36 subscales, and PROMIS-29 domains.

RESULTS

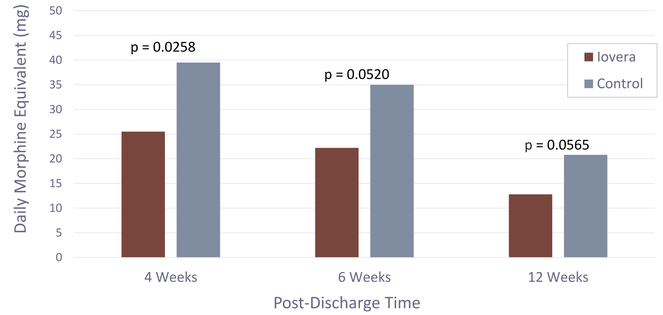

Figure 4. Daily morphine equivalent at single surgeon sites (n=53) for the iovera treatment and sham-controlled groups.

A similar proportion of subjects in both groups experienced at least one AE (51% vs. 48%, p=0.744). A total of 65 AEs were reported by 38 subjects in the cryoneurolysis group. Of these 65 events, 51 were not related to the device, procedure, or opioid use; 11 were related to opioid use and 1 was moderately severe blisters around the TKA surgical site which resolved 28 days after onset.

One subject in the cryoneurolysis group reported severe wound dehiscence along the incision line 11 days post-treatment which became a severe infection 70 days later requiring hospitalization 5 months later as part of a surgical intervention. A post-market formal investigation of this serious adverse event (SAE) by the study Medical Monitor concluded that the cryoneurolysis treatment was not related to the wound dehiscence and subsequent infection.

CONCLUSIONS

At single surgeon sites with controlled perioperative pain protocols and prescribing practices the cryoneurolysis group demonstrated statistically significant reductions in opioid use compared to the sham at 4 weeks post-TKA with similar trends seen at 6 and 12 weeks post-TKA.

An important limitation of this study was the inability to control for differences in perioperative pain management protocols, including opioid prescribing practices, across sites. Pain management protocols are highly variable across settings and associated with a wide range of peri-operative pain levels.[12,13] In addition, there is wide variability in opioid prescription practices following TKA.[14] Differences in perioperative pain management protocols across sites made it difficult to accurately determine the effect of the study intervention on opioid consumption (primary endpoint) and pain. A follow-on study is underway (NCT03327220) that will account for and control these variables.

As the US healthcare system continues to evolve pre-operative cryoneurolysis may play an important role as part of post-TKA multimodal pain regimens that are designed to reduce both patient pain and opioid consumption.

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