

Review Article

Cryoneurolysis is a Safe and Effective Method for Reducing Perioperative Pain in Total Knee Arthroplasty

Taylor J Manes, D.O.^{1a}, Jamison Walker^{2b}, Rileigh Ricken^{3c}, Nithin Gupta^{2d}, Morgan Turnow, D.O.^{1e}, Shaheryar Asad^{4f}, Gabrielle Dykhous^{5g}, James D. Miller, D.O.^{1h}

a Dr. Taylor Manes is a second year orthopedic surgery resident at OhioHealth Doctor's Hospital in Columbus, OH. He attended medical school at A.T. Still University Kirksville College of Osteopathic Medicine. He is passionate about providing mentorship and networking resources for medical students while taking a keen interest in furthering research in the orthopedic world. His current research interests include hand, sports medicine, and shoulder and elbow surgery. Outside of medicine, he enjoys spending time with his family and friends and loves to watch the Kansas City Chiefs win.

[Visit Dr. Taylor Manes](#)

[Connect with Dr. Taylor Manes on LinkedIn](#)

[Conflicts of Interest Statement for Dr. Taylor Manes](#)

b Jamison Walker is currently a fourth year medical student hoping to match into Orthopaedic Surgery.

[Connect with Jamison Walker on LinkedIn](#)

[Conflicts of Interest Statement for Jamison Walker](#)

c Rileigh Ricken is a 4th-year medical student pursuing a career in orthopedic surgery and an officer in the U.S. Navy. Outside of medicine, Ricken is the proud owner of two golden retrievers, enjoys playing golf, crossfit, and softball. A coffee and history enthusiast, Ricken is also an inventor and co-owner of a business that develops innovative medical devices. She is passionate about advancing orthopedic care and balancing her commitment to medicine, service, and entrepreneurship.

[Visit Rileigh Ricken](#)

[Conflicts of Interest Statement for Rileigh Ricken](#)

d Nithin Gupta is a fourth-year medical student at Campbell University School of Osteopathic Medicine in Lillington, NC. He is passionate about providing mentorship and teaching students to grow their network. He also has a strong interest in using research as a tool to advance orthopedic surgery and improve patient outcomes. His current research interests include spine, sports medicine, trauma, and reconstruction.

[Visit Nithin Gupta](#)

[Conflicts of Interest Statement for Nithin Gupta](#)

e Dr. Morgan Turnow is a second year orthopedic surgery resident at OhioHealth Doctor's Hospital in Columbus, OH. She attended medical school at the University of Pikeville Kentucky College of Osteopathic Medicine. She is passionate about enhancing research and educational opportunities for medical students. Her current research interests include shoulder and elbow surgery, sports medicine, and education in orthopedics. Outside of medicine, she enjoys traveling, college football, and spending time with her pets.

[Visit Dr. Morgan Turnow](#)

[Connect with Dr. Morgan Turnow on LinkedIn](#)

[Conflicts of Interest Statement for Dr. Morgan Turnow](#)

f Shaheryar Asad is a second-year medical student at California Northstate University College of Medicine with a strong interest in pursuing a career in orthopedic surgery. In his free time, he enjoys playing soccer and spending quality time with family and friends.

[Conflicts of Interest Statement for Shaheryar Asad](#)

g Gabrielle Dykhous is a third-year medical student with a keen interest in orthopedics and sports medicine. Through her research and rotations at the Hospital for Special Surgery and NewYork-Presbyterian Weill Cornell Medical Center, she has developed a strong commitment to pursuing a career in both academic and clinical medicine.

[Connect with Gabrielle Dykhous on LinkedIn](#)

[Conflicts of Interest Statement for Gabrielle Dykhous](#)

h James D. Miller, D.O. is a fellowship-trained orthopedic surgeon specializing in hip and knee replacement with extensive training in the latest orthopedic technology, techniques and minimally invasive joint replacement surgery. His expertise includes muscle-sparing, direct anterior hip replacement and robotic-assisted joint replacement surgery. Dr. Miller is dedicated to providing his patients with quality care and will work with you to develop a personalized treatment plan for your anterior hip replacement or robotic-assisted total joint replacement. The anterior hip replacement allows Dr. Miller the ability to perform this procedure through a smaller incision without cutting any muscles to give you the best chance for a successful outcome, a shorter hospital stay, less pain and a faster return to normal activity. Dr. Miller graduated with Sigma Sigma Phi honor society standing from the Lake Erie College of Osteopathic Medicine in Erie, Pennsylvania. He went on to complete his Orthopedic Surgery residency at UPMC Pinnacle Health in Harrisburg, where he served as Chief Resident. After residency, he completed an additional year of fellowship training specializing in adult reconstruction and joint replacement at Allegheny Health Network in Pittsburgh. He holds memberships in the Ameri-

¹ Orthopedic Surgery, OhioHealth, ² Campbell University School of Osteopathic Medicine, ³ Oklahoma State University Center for Health Sciences College of Osteopathic Medicine, ⁴ California Northstate University College of Medicine, ⁵ Weill Cornell Medical College, Weill Cornell Medicine

Keywords: Total knee arthroplasty, multimodal pain control, morphine milligram equivalent, opioid, cryoneurolysis, anterior femoral cutaneous nerve, infrapatellar branch of saphenous nerve

<https://doi.org/10.60118/001c.122460>

Journal of Orthopaedic Experience & Innovation

Vol. 5, Issue 2, 2024

Introduction: Pain management following total knee arthroplasty (TKA) is crucial for patient care and recovery. While opioid analgesics have traditionally been used, concerns over their adverse effects and the opioid epidemic have driven exploration of alternative pain management strategies. Multimodal (MM) pain control, targeting multiple pain pathways, has emerged as a promising approach, encompassing various medications and administration routes. Cryoneurolysis, a non-opioid therapy, has garnered attention for its potential in acute pain management, including its use before and after TKA.

Methods: This study is a systematic review aiming to evaluate the efficacy and safety of cryoneurolysis as a method for managing perioperative pain in TKA. Primary outcomes include a reduction in opioid consumption and length of hospital stay, while secondary outcomes encompass functional and pain-related scores.

Results: Seven of 434 studies met inclusion criteria. Published between 2016 and 2023, these included five retrospective studies and two randomized controlled trials, involving a total of 794 patients (38.3% male, 61.7% female). Most studies had a clearly defined control group, and the mean age of participants was approximately 66.6 years. The methodological assessment indicated a moderate to low risk of bias. Results demonstrated that cryoneurolysis reduced opioid consumption and improved pain and functional outcomes compared to control groups, including shorter hospital stays, improved range of motion, and pain score improvements.

Conclusion: Cryoneurolysis presents a promising option, with evidence suggesting its potential to reduce opioid consumption and improve patient outcomes in the face of an opioid epidemic. However, challenges and barriers to its widespread use remain, including technical complexities and the need for further high-quality evidence.

This article, like all JOEI articles, is available for continuing education

Reflect Now!

Click here : <https://joeipub.com/learning>

INTRODUCTION

With an aging population and the high success rate of total joint arthroplasty, total knee arthroplasty (TKA) has be-

come the most common orthopedic procedure in the United States (Shichman, Roof, Askew, et al. 2023). In 2012 alone, approximately 700,000 primary TKA procedures were performed, with projections indicating a 139% increase by

can Association of Hip and Knee Surgeons (A.A.H.K.S.), American Academy of Orthopedic Surgeons (A.A.O.S.) and the American Osteopathic Academy of Orthopedics (A.O.A.O.).

[Visit Dr. James Miller](#)

[Connect with Dr. James Miller on LinkedIn](#)

[Conflicts of Interest Statement for Dr. James Miller](#)

[Visit the Open Payments Data Page for Dr. James Miller](#)

2040 and up to a 460% rise by 2060 (Shichman, Roof, Askew, et al. 2023). This surge underscores the imperative to optimize patient care in perioperative settings.

Effective postoperative pain management is integral to recovery following TKA. Poorly managed pain can lead to adverse effects, including increased sympathetic tone, decreased bowel function, immune system disruption, and heightened susceptibility to chronic pain (Moucha, Weiser, and Levin 2016). Traditionally, opioid analgesics have been the cornerstone of pain control, but their use is associated with numerous adverse reactions, leading to escalated hospital costs and prolonged lengths of stay (Li, Ma, and Xiao 2019).

In recent years, efforts to enhance postoperative pain management following TKA have intensified. Despite advancements in surgical techniques, effective pain relief remains a significant challenge, necessitating innovative interventions. Multimodal (MM) pain control, which includes nerve blocks, local injections, patient-controlled analgesia (PCA), and both opioid and non-opioid medications, has emerged as a widely employed regimen for TKA patients (Moucha, Weiser, and Levin 2016). MM pain regimens target multiple pain pathways simultaneously, mitigating the adverse effects associated with opioid overuse.

Preoperative pain control, by potentially reducing the likelihood of hyperalgesia during surgery, can improve postoperative pain outcomes (Li, Ma, and Xiao 2019). By intervening before tissue injury, preoperative analgesia can prevent central nervous system sensitization and reduce the risk of chronic pain (Moucha, Weiser, and Levin 2016). Intraoperative pain control includes general or neuraxial anesthesia and local tissue infiltration, while postoperative control encompasses opioid and non-opioid medications, neuraxial anesthesia, nerve blocks, and PCA (Li, Ma, and Xiao 2019).

The opioid epidemic in the United States has spurred the increased utilization of MM pain control, driving the exploration of non-opioid therapies (Radnovich, Scott, Patel, et al. 2017). Cryoneurolysis, originally used for chronic pain treatment, has gained traction for acute pain management. This technique involves blocking superficial sensory nerves through the application of cold temperatures, disrupting nerve function while preserving nerve bundle integrity, thus allowing for regeneration and functional recovery (Radnovich, Scott, Patel, et al. 2017).

Although relatively new to TKA, cryoneurolysis has shown promising outcomes for pre- and postoperative administration. Studies have shown significant reductions in overall narcotic consumption and improved pain and function scores during the early postoperative period following TKA (Dasa et al. 2016; Radnovich, Scott, Patel, et al. 2017). Commonly targeted nerves in TKA include the infrapatellar branch of the saphenous nerve (IPSN) and the anterior femoral cutaneous nerve (AFCN) (Dasa et al. 2016). Cryoneurolysis has been commercially utilized for approximately 50 years without permanent nerve damage, with only isolated cases of neuritis reported (Radnovich, Scott, Patel, et al. 2017).

Given the relative novelty of cryoneurolysis in postoperative pain control, there remains a lack of comprehensive synthesis of current evidence on this topic. Therefore, the purpose of this study is to evaluate and consolidate existing evidence regarding the efficacy and safety of cryoneurolysis as a method for managing perioperative pain following TKA.

METHODS

SEARCH AND SCREENING STRATEGY

A literature search of PubMed and Scopus databases was conducted using the boolean search terms, ((“cryoneurolysis” or “Iovera”) AND (“knee”)) and (cryoneurolysis AND (“knee” or “total knee” AND arthroplasty)). Articles were screened by title and abstract by two reviewers (JW and NG) and were included based on the following inclusion criteria: 1) Primary data involving cryoneurolysis in TKA 2) Peer-reviewed full-text manuscript 3) Published in English. Articles were excluded if they were 1) Not primary data involving the use of cryoneurolysis in TKA (literature reviews, case reports, or case series) 2) Not full-text peer-reviewed (abstract, commentary, poster, or letter) 3) Not published in English. After title and abstract screening was finished, the articles remaining were then confirmed to meet inclusion criteria by full-text review. A backward citation search using the references of included articles was also performed.

DATA EXTRACTION AND OUTCOMES OF INTEREST

Articles were subjected to a data extraction process. Demographic and study variables included sex, age, BMI, comorbidities, implant type and cryoneurolysis nerve target. Primary outcomes included reduction in narcotic consumption (reported as MME) and length of hospital stay. Secondary outcomes included preoperative and postoperative WOMAC score, VAS pain score, SF-36 and/or SF-12 scores. Finally, data regarding adverse outcomes related to cryoneurolysis treatment were also collected as reported.

RISK OF BIAS ASSESSMENT

The Newcastle-Ottawa Quality Assessment Scale (NOS) and scoring assessment was used to assess the methodological quality among all studies included in the systematic review by two reviewers. Three key areas were assessed by the NOS for a maximum score of 9 points: “selection of participants” accounted for 4 points, “comparability” accounted for 2 points, and “outcome assessment” accounted for 3 points. Reviewers gathered information based on representativeness of the exposed cohort (cryoneurolysis in TKA), selection of the control, exposure, and the outcome of interest. Comparability assessed the fundamental study design of the cohorts. Finally, outcomes were assessed to determine follow-up length and adequacy (12 weeks of follow up data) in each cohort. Studies receiving a score of 7 – 9 points were classified as “high” quality, 5 – 6 points as “moderate” quality, and a score of 0 – 4 points as “poor” quality.

RESULTS

SEARCH RESULTS, STUDY CHARACTERISTICS AND DEMOGRAPHIC DATA

Initial search results identified 622 total articles. After duplicate removal 434 unique articles remained, of which 7 were identified for inclusion in the study (**Figure PRISMA**). The seven studies included in this review were all published between 2016-2023. Five of the studies had a retrospective design and two were randomized control trials. Two studies had a level of evidence (LOE) of one and five studies had a LOE of three. Additional information of the included studies are further explained in [Table 1](#). Across all seven studies, a total of 794 patients (38.3% male, 61.7% female) were identified. Six out of the seven studies had a clearly defined control group and had a pooled mean age of 66.6 years (range: 66.5 - 66.8 years). Five studies had a single control group that was clearly defined and had a pooled mean age of 66.7 years (range: 66.6 - 66.8 years). Furthermore, six studies used the Iovera method for cryoneurolysis. The study by Swisher et al. used a 14-gauge cryoneurolysis probe that was connected to a console-based cryoneurolysis machine. All seven of the studies assessed the impact of pain management through cryoneurolysis of the anterior femoral cutaneous nerve (AFCN) and the Infra-patellar Branch of the Saphenous Nerve (ISN) in TKA procedures. Demographic characteristics and treatment parameters are further explained in [Table 2](#).

METHODOLOGICAL ASSESSMENT AND RISK OF BIAS

The mean $\pm$ standard deviation of the MINORS score for the seven studies was 17.9 (range, 15.6 to 20.17). 3 studies were deemed to have a low risk of bias, whereas 4 studies were deemed to have a moderate risk of bias. No studies had a high risk of bias.

STUDY DESIGNS

Five studies that were included in this systematic review had a control group in which patients did not receive cryoneurolysis and simply received the current standard of care before undergoing TKA. The study by Swisher et al. had a control group in which patients received a sham procedure. The study by van Deventer et al. had a control group in which the patients did not receive treatment through a multimodal pain protocol.

Six studies that were included in this systematic review had an experimental group in which patients received cryoneurolysis prior to undergoing TKA. The study by van Deventer et al. had an experimental group in which patients received treatment through a multimodal pain protocol after undergoing TKA.

The treatment protocol for the seven studies included varied. In the study by Dasa et al. all patients underwent TKA. The patients in the treatment group received cryoneurolysis and multimodal pain management treatment five days before undergoing TKA. The study by Jennewine et al. had an experimental group in which patients received cry-

oneurolysis treatment, but they were further sub grouped into small, medium, and large categories based on their anterior thigh depth relative to the femur. In the studies by both Jennewine et al. and Mihalko et al., all patients who received cryoneurolysis underwent the procedure three to seven days before their scheduled TKA. In the study by Lung et al., cryoneurolysis was administered one week before patients underwent their scheduled TKA procedure by a fellowship-trained orthopedic surgeon. In the study by Swisher et al, the sham and cryoneurolysis procedures were both performed preoperatively without a specified or standard time frame. All the patients in this study were 18 years or older and underwent a primary unilateral TKA with a planned single injection or a continuous adductor canal block. In the study by Urban et al, all patients received cryoneurolysis treatment preoperatively, after they had received local anesthesia. In the study by van Deventer et al, all patients received cryoneurolysis and were split up into two groups to assess opioid usage. One group was prescribed opioids only upon request, whereas the other group was prescribed opioids automatically at the time of discharge. All patients in this study underwent a primary unilateral TKA by a single fellowship-trained orthopedic surgeon. The study designs for the seven included studies are in [Table 2](#) which summarizes the treatment parameters and the cohort of interest for each study.

OUTCOMES

All seven of the studies included in this systematic review reported a decrease in the MME amongst the cryoneurolysis group compared to the control group. The study by Dasa et. al reported that the treatment group required 45% less opioids during the first 12 weeks after TKA. The morphine equivalents reported for the control group were 3764.42 mg $\pm$ 287.95 mg and 2069.12 mg $\pm$ 132.09 mg for the treatment group ($p < 0.0001$). The study by Jennewine et al. reported that the small cryoneurolysis group showed a decrease in their opioid consumption, as measured by total MME, at the two (54.3 ± 69.6), six (16.8 ± 35.6), and twelve (1.3 ± 3.2) week marks compared to the control group. The MME for the small group was significantly decreased at two weeks compared with the medium group (54.3 vs 142.9 , $p = 0.0097$). The study by Mihalko et al. utilized an intention-to-treat (ITT) protocol with respect to prescribing opioids to patients who underwent TKA. The primary endpoint, however, was not met (4.8 cryoneurolysis vs 6.1 mg standard of care (SOC); $p = 0.0841$). Despite this, the study reports that the per-protocol (PP) endpoint was met (4.2 vs 5.9 mg; $p = 0.0186$). The study by Lung et al. reported that patients treated with cryoneurolysis had fewer MME requirements overall in both the inpatient and outpatient settings. The study by Swisher et al. reported that the treatment group had decreased opioid consumption. The study by Urban et al. reported that during the hospital stay, the cryoneurolysis group had 51% lower daily MMEs (47 vs 97 MMEs; ratio estimate = $0.43 - 0.56$); $p < 0.0001$) compared to the control group. Two weeks postoperatively, the cryoneurolysis group received significantly fewer cumulative MMEs, compared to the control group (855 vs $1,312$ MMEs;

Table 1. Characteristics of Included Studies

Study	Author	Year	Journal	Study Design	Risk of Bias	Quality Analysis
Percutaneous freezing of sensory nerves prior to total knee arthroplasty	Dasa et al.	2016	Knee	Retrospective Cohort	Low	High
Body habitus impact on success of cryoneurolysis for postoperative total knee arthroplasty pain control: a retrospective cohort study	Jennewine et al.	2023	Arthroplasty Today	Retrospective Cohort	Fair	Fair
Cryoneurolysis before total knee arthroplasty in patients with severe osteoarthritis for reduction of postoperative pain and opioid use in a single-center randomized control trial	Mihalko et al.	2021	The Journal of Arthroplasty	Randomized Control Trial	Low	High
Cryoneurolysis is a safe, effective modality to improve rehabilitation after total knee arthroplasty	Lung et al.	2022	Life (Basel)	Retrospective Cohort	Fair	Fair
A randomized controlled pilot study using ultrasound-guided percutaneous cryoneurolysis of the Infrapatellar branch of the saphenous nerve for analgesia following total knee arthroplasty	Swisher et al.	2022	Pain and Therapy	Randomized Control Trial	Fair	Fair
A multimodal pain management protocol including preoperative cryoneurolysis for total knee arthroplasty to reduce pain, opioid consumption, and length of stay	Urban et al.	2021	Arthroplasty Today	Retrospective Cohort	Low	High
A modern multimodal pain protocol eliminates the need for opioids for most patients following total knee arthroplasty: results from a retrospective comparative cohort study	van Deventer et al.	2023	Journal of Experimental Orthopaedics	Retrospective Cohort Study	Fair	Fair

ratio estimate = 0.59 - 0.73); $p < 0.0001$). A similar finding was observed during week six (894 vs 1,406 MMEs; ratio estimate = 0.57 - 0.71; $p < 0.0001$). The study by van Deventer et al. reported that without compromising pain or function, a higher percentage of the “upon request” group was opioid free three months after TKA compared to the “automatic” group (55.6% vs 4.3%; $p < 0.0001$). Furthermore, amongst the opioid-naïve patients, 72% in the “upon request” group were opioid free after 3 months postoperatively compared with 5.4% in the automatic group. However, regardless of the postoperative pain control protocol, opioid prescriptions were not significantly reduced among opioid-tolerant patients.

All seven of the included studies in this systematic review highlight improved patient-reported outcomes amongst patients who underwent cryoneurolysis compared to the control group. The study by Dasa et al. reported that the treatment group (KOOS = 41.80 ± 16.74) reported a statistically significant reduction in symptoms at the six- and 12-week follow-ups compared with the control group (KOOS = 44.11 ± 19.32). However, the control (KOOS = 6.83 ± 2.90 , 65.27 ± 8.23) and treatment groups (KOOS = 6.89 ± 2.16 , 66.13 ± 7.60) reported within-group significant reduc-

tions in pain intensity and pain interference at the two- and six-week follow-ups respectively. The study by Jennewine et al. reported that the rating for pain decreased significantly between small and medium groups (3.4 vs 4.0, $p = 0.012$) and between medium and large groups (4.0 vs 2.4, $p = 0.012$). The range of motion (ROM) also increased at 12 weeks for the small group compared to the medium group (118 vs 112, $p = 0.042$). The study by Mihalko et al. reported that compared with the SOC, the cryoneurolysis group had improved functional and pain scores with significant improvement observed in current pain measured from baseline to the 72-hour and two-week follow-up assessments postoperatively ($p = 0.0023$ and 0.0074 respectively). Pain was also significantly improved from the final week preoperatively to the 12-week follow-up assessment ($p = 0.0256$). The study by Lung et al. reported that patients who received cryoneurolysis demonstrated significantly improved ROM at six weeks and KOOS JR and SF-12 mental scores at one year postoperatively compared to the control group. The study by Swisher et al. reported that the treatment group demonstrated a slight improvement in pain scores postoperatively compared to the sham group. This study also reported a lower incidence of sleep disturbances overall in

Table 2. Demographic Characteristics and Treatment Parameters for Cryoneurolysis

Study	Cohort (N)	M:F	Age (Mean)	Cohort of Interest	Nerve Target	Treatment Parameters	Cryoneurolysis Method
Dasa et al. (2016)	100	30:70	66.4 (9.4)	TKA	AFCN, IPBSN	Cryoneurolysis plus multimodal pain management was performed 5 days before surgery	lovera
Jennewine, Wing, and Mihalko (2023)	114	57:57	68.5 (8.2)	Patients ages 22-79 who underwent primary unilateral TKA due to osteoarthritis and had an anticipated discharge to home following the procedure	AFCN, IPBSN	Cryoneurolysis 3-7 days before TKA	lovera
Mihalko et al. (2021)	96	45:51	66.1 (7.7)	Patients ages 22-79 who were scheduled to undergo primary unilateral TKA as a result of osteoarthritis with anticipated discharge to home	AFCN, IPBSN	Cryoneurolysis 3-7 days before TKA	lovera
Lung, Karasavvidis, Sharma, et al. (2022)	57	20:37	68 ± 7	Patients who underwent TKA by a fellowship-trained orthopaedic surgeon	AFCN, IPBSN	Cryoneurolysis 1 week before TKA	lovera
Swisher et al. (2022)	16	6:10	68 (64-72)	Patients ages 18 years or older presenting for unilateral primary total knee arthroplasty with a planned single-injection or continuous adductor canal block	IPBSN	Single-injection adductor canal nerve block was performed before randomization to the cryoneurolysis group. The patient then immediately underwent TKA following cryoneurolysis	A 14-gauge cryoneurolysis probe connected to a console-based cryoneurolysis machine (PainBlocker, Epimed International, Farmers Branch, TX)
Urban, Dolesh, and Martin (2021)	267	102:165	66 (9)	Optimized preoperative cryoneurolysis to all patients undergoing TKA as part of its standard multimodal perioperative pain protocol	AFCN, IPBSN	Administered to conscious patients after local anesthesia 8-11 days before TKA	lovera
Deventer et al. (2023)	144	44:100		Consecutive patients who underwent primary unilateral TKA by a single fellowship-trained orthopedic surgeon between January 2019 and August 2021 using an enhanced recovery TKA protocol. All patients underwent cryoneurolysis	AFCN, IPBSN	Cryoneurolysis 5 days before TKA	lovera

*The superficial geniculate nerves - Infrapatellar branches of the saphenous nerve (IPBSN) and Anterior femoral cutaneous nerve (AFCN)

the treatment group. The authors explained this reduction in sleep disturbances within the treatment group was most likely attributed to an improvement in acute pain 4-21 days postoperatively. The study by Urban et al. reported that the cryoneurolysis group had a 22% significant reduction in mean pain scores (ratio estimate = 0.70 - 0.88; $p < 0.0001$) compared to the control group.

Three studies reported the impact of cryoneurolysis on the length of stay. The study by Dasa et al. reported a

significantly lower proportion of patients in the treatment group had a length of stay (LOS) greater than or equal to two days, compared with the control group (6% vs 67%, $p < 0.0001$). The study by Lung et al. reported that although it was not found to be statistically significant, patients treated with cryoneurolysis had a shorter length of stay in the hospital (2.5 vs 3.5 days). The study by Urban et al. reported that the cryoneurolysis group had a 44% reduction in the overall LOS which was statistically significant ($p <$

Table 3. Summary of Study Outcomes

Study	Pain Outcomes	Opioid Reduction	PROM Outcomes	Mobility Outcomes	Other
Dasa et al. (2016)	↓ PROMIS pain intensity scores at two and 6 weeks post-surgery	↓ cumulative morphine equivalence during 12 weeks following surgery (45% less narcotics compared to the control group)	Greater reduction in KOOS symptoms subscale score from baseline to six- and 12 week post-operative visits in treatment vs. control	None	↓ Length of hospital stay (≥2 days; 57.3% in control group vs. 6.1% in treatment group) -No local infections, excess bleeding, or local soft tissue necrosis, no persistent numbness reported in the treatment group
Jennewine, Wing, and Mihalko (2023)	↓ NRS-now scores in all 3 treatment groups (small, medium, and large body habitus) compared to control	↓ in morphine equivalence for small body habitus at 2 weeks, 6 weeks, and 12 weeks, medium body habitus at 12 weeks, large body habitus at 72 hours No correlation was noted in morphine equivalents based on body habitus at 72-hour, 6-week, and 12-week	↑ KOOS JR scores at 72 hours for medium and large body habitus. ↑ KOOS JR scores for all 3 groups at 2-weeks	↑ ROM was seen in small body habitus at 72-hour and 12 weeks and in large body habitus at 2 weeks and 6 weeks post-op	None
Mihalko et al. (2021)	↓ NRS scores at 72-hour and 2-week postoperative	↓ opioid usage at 72-hour, 6-week, and 12-week. ↓ 29% total opioids used in the treatment group compared to the control in the 12 weeks	↑ KOOS JR scores in treatment vs control with the most significant improvement at 2-week, 6-week, and 12-week	No difference in ROM at 6 weeks and 12 weeks	No difference in post-operative complications
Lung, Karasavvidis, Sharma, et al. (2022)	No improvement in VAS inpatient pain scores, Interval KOOS JR and SF 12 mental and physical scores	No difference in milligram morphine equivalents during the inpatient stay and at any of the post-operative assessments.	↑ KOOS interval difference from pre-op to 12 months ↑ SF 12 mental score at 12 months	No difference in ROM treatment compared to control.	No difference in the length of hospital stay ↑ estimated blood loss in the treatment group vs. control.
Swisher et al. (2022)	No statistical analysis was performed because of the small sample size	No statistical analysis was performed because of the small sample size	No statistical analysis was performed because of the small sample size	No statistical analysis was performed because of the small sample size	No statistical analysis was performed because of the small sample size
Urban, Dolesh, and Martin (2021)	22% reduction in adjusted mean pain scores during the hospital stay and was 62% less likely to have a mean pain score ≥4.	↓ cumulative MMEs at discharge, 2 weeks and 6 weeks 35% reduction in opioid intake at 2 weeks and 36% reduction at 6 weeks 68% less consumption of total opioids in MMEs during hospital stay (treatment vs control) ↑ proportion of patients in the cryoneurolysis group receiving ≥1 opioid prescription than the control group at 2 weeks (51% vs 26%), but no difference at 6 weeks.	None	↑ Flexion ROM upon discharge ↑ Extension ROM scores at 6 weeks	↓ in overall length of hospital stay (≥2 days 17% vs 99% treatment vs control)
Deventer et al. (2023)	No difference in KOOS pain, KOOS symptoms, KOOS ADL, KOOS QOL, PROMIS-29 pain interference, and pain intensity at 2 weeks and 3 months Both groups showed improvement in all scores after 3 months	↓ number of opioid requests within 3 months after surgery among opioid-naïve patients. (72% did not receive any opioids). No difference in opioid-experience patients. ↑ in MME for initial opioid prescriptions and total MME for all opioid prescriptions in the opioid-experienced group despite cryoneurolysis when obtained from a non-orthopedic provider. No difference in opioid-naïve patients.	None	None	None

PROMIS = Patient-reported Outcomes Measurement Information System, KOOS JR, Knee Injury and Osteoarthritis Outcome Score Joint Replacement; NRS-now, pain numerical rating score now; NRS-7, pain numerical rating score in last 7 days; ROM, range of motion; ADL, Activities of daily living; QOL, quality of life; SF 12, Short Form Survey 12; VAS, Visual Analog Scale

0.0001) and had improved knee flexion at discharge ($p < 0.0001$). The study by Lung et al. was also the only study to comment on complications and reported no difference in rates between the treatment or control group. For a concise summary, each study's measured outcomes are summarized in [Table 3](#).

DISCUSSION

Cryoneurolysis, a relatively novel approach for perioperative pain management in TKA, has garnered attention for its potential to mitigate opioid consumption and improve postoperative outcomes. Our study aimed to comprehensively evaluate its efficacy and safety, revealing significant

reductions in opioid consumption, acute pain levels, and improvements in postoperative functional outcomes (Mihalko et al. 2021; Urban, Dolesh, and Martin 2021). The applications of cryoneurolysis extend beyond TKA to other orthopedic procedures, providing a foundation for its broader adoption (Dasa, Lensing, Parsons, et al. 2014).

The escalating prevalence of TKA procedures underscores the urgent need for effective multimodal pain management strategies (Maradit Kremers, Larson, Crowson, et al. 2015). Cryoneurolysis, amidst the opioid crisis gripping the United States, offers a non-opioid pharmacologic intervention with promising outcomes (Li, Ma, and Xiao 2019). Originating from centuries-old cryotherapy practices, modern advancements have facilitated its adoption in clinical settings, demonstrating efficacy in various surgical contexts (Dasa et al. 2016). Concomitant use of imaging studies such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) have advanced the administration accuracy (Trescot 2003). With the FDA-approved handheld cryoneurolysis device and ultrasound guidance, its use has been promoted in both office and outpatient hospital settings for acute and chronic pain (Trescot 2003; Biel et al. 2023). The cryoneurolysis technique as described by Dasa et al. includes finding either the anterior femoral cutaneous nerve and its branches 7 centimeters (cm) proximal to the superior pole of the patella, or the infrapatellar branch of the saphenous nerve 5 cm medial to the patellar tendon (Dasa et al. 2016). Treatments consist of a series of warming and cooling of the needles and normally last anywhere between 7 to 8 minutes for each nerve (Dasa et al. 2016). Temperatures between -20 degrees and -60 degrees Celsius have been shown to result in Wallerian degeneration of the nerve (Dasa et al. 2016). This occurs distal to the region being treated with disruption of the myelin sheath; however, preservation of the structural anatomy of the nerve including the endoneurium, perineurium, and epineurium is maintained (Dasa et al. 2016). As described, this local mechanism of injury allows for axonal regeneration and remyelination of the sensory axon typically within a few weeks to months following treatment (Dasa et al. 2016).

Interchangeably referred to as cryotherapy or cryoablation, cryoneurolysis has showcased its versatility across medical disciplines. Studies in thoracotomies, mastectomies, and shoulder arthroplasties have underscored its efficacy in providing prolonged postoperative pain relief, setting the stage for its application in TKA (Trescot 2003; Radnovich, Scott, Patel, et al. 2017). Notably, cryoneurolysis targeting specific nerves in TKA, such as the infrapatellar and adductor canal nerves, has yielded notable improvements in functional outcomes and pain scores postoperatively (Mihalko et al. 2021; Urban, Dolesh, and Martin 2021; Lung, Karasavvidis, Sharma, et al. 2022). Studies have demonstrated its effectiveness in reducing postoperative pain and opioid consumption, highlighting its potential in multimodal pain management protocols for TKA (Memtsoudis, Sun, Chiu, et al. 2013; Moucha, Weiser, and Levin 2016).

Despite promising outcomes, integrating cryoneurolysis into routine clinical practice presents challenges. The technical proficiency required for its administration, coupled with transitioning to ultrasound-guided procedures, poses a learning curve for healthcare providers (Biel et al. 2023; Jennewine, Wing, and Mihalko 2023). Cost considerations and patient discomfort, including localized numbness, warrant careful consideration (Trescot 2003; Radnovich, Scott, Patel, et al. 2017). Addressing these challenges necessitates comprehensive training programs and informed patient discussions to ensure optimal outcomes and mitigate potential barriers to adoption (Dasa, Lensing, Parsons, et al. 2014).

While cryoneurolysis offers a safe alternative to pharmacologic interventions, inherent risks, including tissue damage and discomfort, must be acknowledged (Biel et al. 2023; Jennewine, Wing, and Mihalko 2023). Patient selection criteria, contraindications, and thorough pre-procedural assessments are pivotal in minimizing adverse events and optimizing patient outcomes (Trescot 2003; Radnovich, Scott, Patel, et al. 2017). As with any study, there were limitations to this article, one of which being the low number of studies used in the final analysis. The scarcity of studies included was likely related to the strict inclusion criteria and the current paucity in the literature regarding this alternative treatment option in TKA. With a smaller cohort, there is a potential for overestimating results and drawing conclusions from lower-powered studies. Another limitation of this paper was the vast heterogeneity in outcomes measured between the respective studies included and thus did not allow us to include a forest plot for comparison of data between studies. These studies primarily included shorter follow-up data because they wanted to measure acute postoperative pain. Only including shorter follow-up data does not provide insight into long-term results or complications like sensory nerve deficits or pain control years later. Nonetheless, of the 7 studies included in this paper, there has been reasonable data to suggest cryoneurolysis is a safe and effective treatment option for perioperative pain control in patients undergoing TKA. Furthermore, the lack of high-quality evidence, particularly in orthopedic surgery, underscores the need for prospective, randomized studies to validate its safety and efficacy in TKA and other surgical procedures (Trescot 2003; Radnovich, Scott, Patel, et al. 2017).

Future research should focus on large-scale, multicenter randomized controlled trials to establish standardized protocols and long-term outcomes (Mihalko et al. 2021; Shichman, Roof, Askew, et al. 2023). As the prevalence of TKA continues to rise, the integration of cryoneurolysis into multimodal pain management strategies holds promise for enhancing patient care and reducing the reliance on opioids (Maradit Kremers, Larson, Crowson, et al. 2015; Shichman, Roof, Askew, et al. 2023). The applications of cryoneurolysis for acute and chronic pain management, as discussed by Biel et al. (2023), further support its potential role in orthopedic surgery and beyond (Mihalko et al. 2021; Dasa, Lensing, Parsons, et al. 2014). As the use of cryoneurolysis in the literature continues to grow, research

should also focus on other regions of the body and different subspecialties. For example, sports medicine and routine outpatient procedures could benefit from this alternative pain management technique. By embracing innovative pain management techniques such as cryoneurolysis, we can improve postoperative outcomes, reduce opioid consumption, and ultimately enhance the quality of life for patients undergoing TKA (Urban, Dolesh, and Martin 2021; Li, Ma, and Xiao 2019; Lung, Karasavvidis, Sharma, et al. 2022).

CONCLUSION

The current opioid epidemic in the United States has prompted a heightened focus on multimodal pain control in the perioperative setting. Amidst this urgent need, our systematic review examined various non-opioid pharmacologic options aimed at reducing overall narcotic consumption. Specifically, cryoneurolysis emerged as a promising intervention for managing perioperative pain associated with TKA.

Our analysis of the current literature revealed compelling evidence supporting the efficacy and safety of cryoneurolysis in improving patient outcomes post-TKA. By

significantly reducing opioid consumption and acute pain levels while enhancing postoperative functional outcomes, cryoneurolysis offers a valuable alternative to traditional pharmacologic interventions. Furthermore, its demonstrated safety profile underscores its potential to address the pressing challenges posed by the opioid crisis, thereby promoting safer and more effective pain management practices in orthopedic surgery.

As healthcare professionals navigate the complexities of perioperative pain management, cryoneurolysis represents a pivotal advancement in the quest for comprehensive and patient-centered care. Continued research efforts and collaborative initiatives are essential to further elucidate the nuances of cryoneurolysis and optimize its integration into routine clinical practice. By harnessing the collective expertise of clinicians, researchers, and policymakers, we can leverage the full potential of cryoneurolysis to alleviate patient suffering and improve surgical outcomes in TKA and beyond.

Submitted: June 25, 2024 EST, Accepted: August 12, 2024 EST



This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CCBY-NC-ND-4.0). View this license's legal deed at <https://creativecommons.org/licenses/by-nc-nd/4.0> and legal code at <https://creativecommons.org/licenses/by-nc-nd/4.0/legalcode> for more information.

REFERENCES

- Biel, E., E. N. Aroke, J. Maye, and S. J. Zhang. 2023. "The Applications of Cryoneurolysis for Acute and Chronic Pain Management." *Pain Pract* 23 (2): 204–15. <https://doi.org/10.1111/papr.13182>.
- Dasa, V., G. Lensing, M. Parsons, et al. 2014. "An Ancient Treatment for Present-Day Surgery: Percutaneously Freezing Sensory Nerves for Treatment of Postsurgical Knee Pain." *Tech Reg Anesth Pain Manag* 18 (4): 145–49. <https://doi.org/10.1053/j.trap.2015.10.014>.
- Dasa, V., G. Lensing, M. Parsons, J. Harris, J. Volaufova, and R. Bliss. 2016. "Percutaneous Freezing of Sensory Nerves Prior to Total Knee Arthroplasty." *Knee* 23 (3): 523–28. <https://doi.org/10.1016/j.knee.2016.01.011>.
- Jennewine, B. R., C. W. Wing, and W. M. Mihalko. 2023. "Body Habitus Impact on Success of Cryoneurolysis for Postoperative Total Knee Arthroplasty Pain Control: A Retrospective Cohort Study." *Arthroplast Today* 22:101164. <https://doi.org/10.1016/j.artd.2023.101164>.
- Li, J. W., Y. S. Ma, and L. K. Xiao. 2019. "Postoperative Pain Management in Total Knee Arthroplasty." *Orthop Surg* 11 (5): 755–61. <https://doi.org/10.1111/os.12535>.
- Lung, B. E., T. Karasavvidis, A. K. Sharma, et al. 2022. "Cryoneurolysis Is a Safe, Effective Modality to Improve Rehabilitation after Total Knee Arthroplasty." *Life* 12 (9). <https://doi.org/10.3390/life12091344>.
- Maradit Kremers, H., D. R. Larson, C. S. Crowson, et al. 2015. "Prevalence of Total Hip and Knee Replacement in the United States." *J Bone Joint Surg Am* 97 (17): 1386–97. <https://doi.org/10.2106/JBJS.N.01141>.
- Memtsoudis, S.G., X. Sun, Y.L. Chiu, et al. 2013. "Perioperative Comparative Effectiveness of Anesthetic Technique in Orthopedic Patients." *Anesthesiology* 118 (5): 1046–58. <https://doi.org/10.1097/ALN.0b013e318286061d>.
- Mihalko, W. M., A. L. Kerkhof, M. C. Ford, J. R. Jr Crockarell, J. W. Harkess, and J. L. Guyton. 2021. "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." *J Arthroplasty* 36 (5): 1590–98. <https://doi.org/10.1016/j.arth.2020.11.013>.
- Moucha, C. S., M. C. Weiser, and E. J. Levin. 2016. "Current Strategies in Anesthesia and Analgesia for Total Knee Arthroplasty." *J Am Acad Orthop Surg* 24 (2): 60–73. <https://doi.org/10.5435/JAAOS-D-14-00332>.
- Radnovich, R., D. Scott, A.T. Patel, et al. 2017. "Cryoneurolysis to Treat the Pain and Symptoms of Knee Osteoarthritis: A Multicenter, Randomized, Double-Blind, Sham-Controlled Trial." *Osteoarthritis Cartilage* 25 (8): 1247–56. <https://doi.org/10.1016/j.joca.2017.03.006>.
- Shichman, I., M. Roof, N. Askew, et al. 2023. "Projections and Epidemiology of Primary Hip and Knee Arthroplasty in Medicare Patients to 2040-2060." *JB JS Open Access* 8 (1). <https://doi.org/10.2106/JBJS.OA.22.00112>.
- Swisher, M. W., S. T. Ball, F. B. Gonzales, K. R. Cidambi, A. M. Trescot, and B. M. Ilfeld. 2022. "A Randomized Controlled Pilot Study Using Ultrasound-Guided Percutaneous Cryoneurolysis of the Infrapatellar Branch of the Saphenous Nerve for Analgesia Following Total Knee Arthroplasty." *Pain Ther* 11 (4): 1299–1307. <https://doi.org/10.1007/s40122-022-00427-4>.
- Trescot, A. M. 2003. "Cryoanalgesia in Interventional Pain Management." *Pain Physician* 6 (3): 345–60. <https://doi.org/10.36076/ppj.2003/6/345>.
- Urban, J. A., K. Dolesh, and E. Martin. 2021. "A Multimodal Pain Management Protocol Including Preoperative Cryoneurolysis for Total Knee Arthroplasty to Reduce Pain, Opioid Consumption, and Length of Stay." *Arthroplast Today* 10:87–92. <https://doi.org/10.1016/j.artd.2021.06.008>.