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Cryoneurolysis for non-cancer knee pain: A scoping review

Dion Diep [a,*], Nimish Mittal [a,b], Harpreet Sangha [a,b], Jordan Farag [a,b]

[a] Division of Physical Medicine & Rehabilitation, Department of Medicine, University of Toronto, Toronto, ON, Canada
[b] Toronto Rehabilitation Institute, University Health Network, Toronto, ON, Canada

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ABSTRACT

Background and objective: Cryoneurolysis involves percutaneous insertion of a cryoprobe induced to extremely cold temperatures to disrupt peripheral nerve conduction. The primary objective of this scoping review is to summarize and critically appraise the current evidence for the benefits and safety of cryoneurolysis for non-cancer knee pain. The secondary objective is to describe the variations in cryoneurolysis techniques used.

Methods: MEDLINE, EMBASE, PubMed, Cochrane Library, and Web of Science were searched from their inception to February 2023 for any primary literature investigating the use of cryoneurolysis for non-cancer-related knee pain. Data was extracted for study characteristics, intervention characteristics, and clinical outcomes.

Results: Fourteen studies were identified, including three randomized controlled trials, four retrospective cohort studies, and seven case studies/series. Two studies included knee osteoarthritis patients, three studies included non-specific chronic knee pain patients; and nine studies included pre- or post-total knee arthroplasty patients. Ten studies targeted the infrapatellar branch of the saphenous nerve while the remaining four studies did not report the nerve targeted. Studies consistently demonstrated improvements in pain, function, quality of life, and opioid consumption. Most adverse events were mild and self-limiting. Considerable variations in technique parameters were observed.

Conclusions: Cryoneurolysis is a promising intervention to improve outcomes in non-cancer knee pain populations, particularly in mild-to-moderate knee osteoarthritis and pre-total knee arthroplasty populations. However, cryoneurolysis for knee pain remains largely investigational as more high-quality randomized controlled trials are required to further elucidate efficacy as well as optimal nerve selection and technique.

1. Introduction

The local application of cold temperatures—broadly known as cryotherapy—has been applied for thousands of years for its analgesic and anti-inflammatory properties [1]. Modern advancements in cryotherapy have led to innovative and minimally invasive techniques, such as cryoneurolysis. The technique involves percutaneous insertion of a cryoprobe induced to extremely cold temperatures to temporarily disrupt peripheral nerve conduction. Studies suggest that second-degree nerve injury (i.e. axonotmesis as defined by the Sunderland classification) is achieved when the target nerve is exposed to temperatures between −20 °C and −100 °C [2,3]. This results in reversible damage of the axon via Wallerian degeneration, with preservation of its surrounding connective tissue, after which regeneration occurs at a rate of approximately 1–2 mm per day [4]. This translates to pain relief for weeks to months depending on the distance between the cryoneurolysis site and location of pain.

The literature has proposed benefits of cryoneurolysis over conventional thermal radiofrequency, including a reduced risk of damage to nearby structures such as blood vessels and soft tissues [5]. Additionally, some studies suggest that cryoneurolysis results in reduced risk of painful post-procedure neuritis by suppressing the inflammatory cascade [6]. As such, cryoneurolysis presents a potentially attractive option for interventional pain management in patients who fail conservative treatment.

Cryoneurolysis has been increasingly applied to achieve pain-relief in various populations. Multiple systematic reviews of randomized controlled trials (RCTs) suggest that cryoneurolysis of intercostal nerves improves pain and reduces opioid use following thoracotomy [7,8]. There also exists growing literature regarding the use of cryoneurolysis for chronic musculoskeletal pain [9,10].

However, past reviews on cryoneurolysis do not utilize comprehensive and systematic search strategies; do not formally assess study quality; and/or focus on a breadth of conditions such that the implications specific to knee pain are minimally discussed [11,12]. There remains a

* Corresponding author. 550 University Ave, M5G 2A2, Toronto, ON, Canada.
E-mail address: dion.diep@mail.utoronto.ca (D. Diep).

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lack of discussion and consensus for technological, procedural, and methodological considerations on this topic. Studies vary with respect to adjunct modality use, freeze durations, treatment cycles, nerve selection, presence of nerve blocks, use of image-guidance, and outcome measures. As such, an up-to-date and comprehensive review on cryoneurolysis for non-cancer knee pain is warranted.

This scoping review was conducted to answer the following research questions: 1) What is the evidence for cryoneurolysis for non-cancer knee pain with regards to its benefit and safety profile, 2) What are the technical variations of cryoneurolysis for non-cancer knee pain and the considerations required to facilitate a standardized approach to future research? A formal systematic review was not conducted due to the exploratory nature of our research objective, lack of consensus for outcome measures, and anticipated clinical heterogeneity highlighted by previous reviews [5,7,8]. Thus, we performed a scoping review using a systematic approach, as outlined by the PRISMA Extension for Scoping Reviews (PRISMA-ScR) [13].

2. Methods

2.1. Protocol and registration

This review was openly registered with the Open Science Framework on October 23rd, 2022 and is available on https://osf.io/ypxh8.

2.2. Information sources

MEDLINE, EMBASE, PubMed, Cochrane Library, and Web of Science were searched for all primary research in the English language up to February 2023, investigating the effects of cryoneurolysis for any type of non-cancer-related knee pain. Ongoing clinical trials were searched in the following registries: United States (ClinicalTrials.gov), Canada (https://health-products.canada.ca/ctdb-bdec/index-eng.jsp), Europe (https://www.clinicaltrialsregister.eu/), and Australia (https://www.australianclinic altrials.gov.au/).

2.3. Search

Combinations of the following key terms were used: “knee”, “pain”, “cryoneurolysis”, “cryoneurotomy”, “cryoanalgesia”, “cryoablation”, “cryoneuroablation”, and “cryotherapy”. Reference and citation lists of all included studies were manually searched. See Appendix 1 for the search strategy.

2.4. Eligibility criteria

Studies must have included participants with non-cancer knee pain of any age and sex. Duration of knee pain was classified as acute (less than 12 weeks) or chronic (greater than or equal to 12 weeks). Cryoneurolysis was defined as any intervention that involved percutaneous insertion of a cryoprobe induced to temperatures between −20 °C and −100 °C with the purpose of providing pain relief. Control groups consisted of a different therapeutic intervention, sham cryoneurolysis, standard therapy, or no treatment. Relevant outcomes included within-group or between-group changes in pain severity, function, opioid consumption, and adverse events (AEs) measured by any tool. RCTs, non-randomized trials, and observational studies were included. Given the current investigational status of the intervention, conference abstracts, case reports, and case series were included. Animal studies, commentaries, editorials, or review articles were excluded.

2.5. Study selection and data charting

Two authors (D.D. and J.F.) independently screened abstracts and full texts. A data-charting form was jointly created by all authors. The form captured the relevant information on study characteristics, intervention characteristics, and clinical outcomes. Two authors (D.D. and J.F.) independently charted the data, discussed the results, and continuously updated the data-charting form in an iterative process. Disagreements were resolved by consensus.

2.6. Critical appraisal of individual sources of evidence

Given the primary objective of characterizing the benefit and safety profile of cryoneurolysis, all included RCTs and nonrandomized trials were critically appraised to substantiate each outcome. Two authors (D.D. and J.F.) critically appraised studies using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool for RCTs and the Cochrane Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool for non-randomized trials [14,15]. Disagreements were resolved by consensus.

2.7. Data analysis

A narrative approach was used to summarize the evidence. All benefit and safety data were descriptively reported. Benefit data was stratified into chronic knee pain and acute peri-operative pain subgroups. A rating of clinical relevance was determined for each outcome based off its minimally clinically important difference (MCID). MCIDs were determined from a literature search for studies using similar knee pain populations. MCIDs were used as a threshold such that outcomes below the MCID were considered unlikely to be clinically relevant. Outcomes exceeding the MCID were considered likely to be clinically relevant. A rating of unclear clinical relevance was given to outcomes with insufficient information to calculate MCID or if MCID was not established in the literature.

In brief, absolute and relative MCIDs for improvement in visual analogue scale (VAS) scores were −19.9 mm and −40.8%, respectively [16]. The absolute MCIDs for Western Ontario and McMaster Osteoarthritis Index (WOMAC) subscale scores were −4.15 for pain, −2.02 for stiffness, −12.8 for physical function, and −19.68 for total score [17]. The relative MCID for total morphine equivalents (TME) was 40% [18]. Details of additional outcome measures and derivation of MCID is included in Appendix 2.

3. Results

Fig. 1 illustrates the selection of studies depicted in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram. Ultimately, 14 studies met inclusion criteria including: three RCTs, four retrospective cohort studies, and seven case reports/series in all totalling 868 participants. Two studies included knee osteoarthritis (OA) patients, three studies included non-specific chronic knee pain patients; and nine studies included perioperative total knee replacement (TKA) patients. Of the seven total RCTs and cohort studies, five studies received some level of industry funding [9,10,19–21]. Additionally, five ongoing RCTs were found from clinical trial registries [22–26]. Table 1 summarizes the characteristics of included studies.

3.1. Benefit profile of cryoneurolysis

3.1.1. Chronic non-cancer knee pain

Four studies were included featuring patients with chronic non-cancer knee pain, not undergoing arthroplasty [9,27–29]. Radnovich et al. (2017) conducted a double-blind multi-centred RCT, with low risk of bias, investigating cryoneurolysis (n = 121) versus sham (n = 59) for mild-to-moderate knee OA. The cryoneurolysis group demonstrated statistically significant improvements in WOMAC pain subscale score from baseline compared to sham. The between-group mean difference [95% CI] of the least squares change from baseline was −7.12 [−11.01 to −3.22, p = 0.0004] at 30 days, −4.65 [−8.48 to −01.82, p = 0.0176] at 60 days, and −5.67 [−9.69 to −1.64, p = 0.0061] at 90 days of follow-up. Statistically significant differences in favor of the

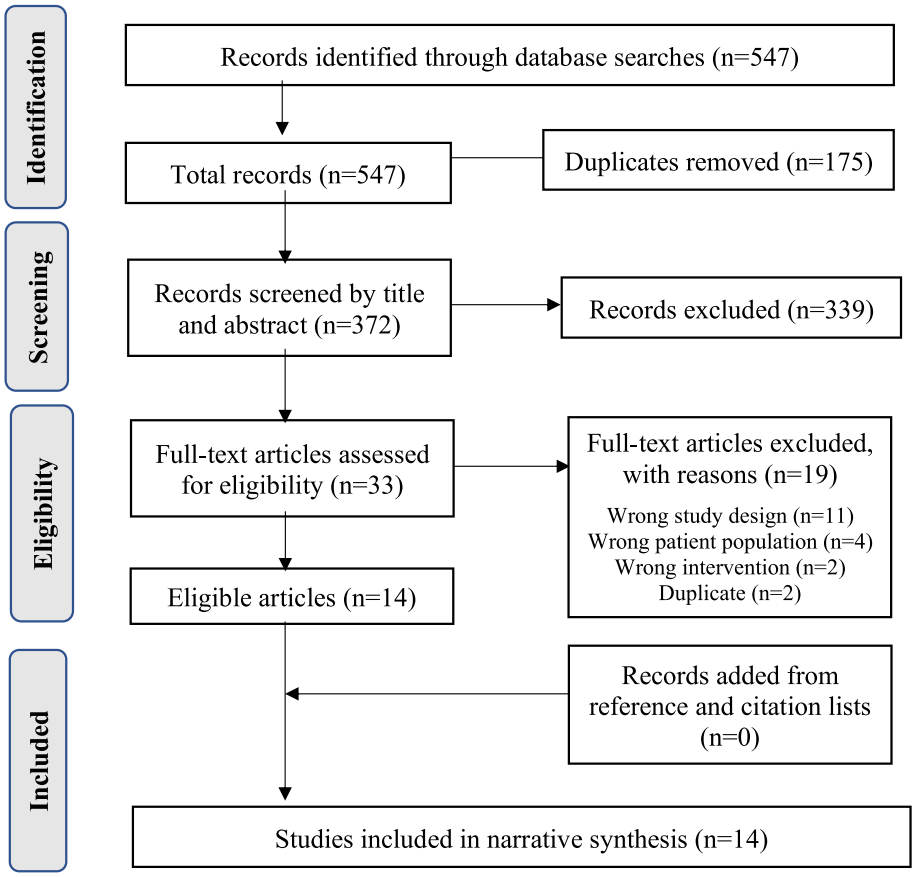

Fig. 1. Diagrammatic illustration of study selection.

cryoneurolysis group were also observed at 30 days follow-up for WOMAC stiffness subscale score (−2.32 [−3.97 to −0.68, p = 0.0060]), WOMAC physical function subscale score (−21.30 [−34.02 to −8.57, p = 0.0012]), WOMAC total score (−30.52 [−48.52 to −12.53, p = 0.0010]), and VAS score (−12.25 [−21.16 to −3.35, p = 0.0073]). All statistically significant between-group improvements exceeded the respective MCID cut-offs [9,16,17]. Statistical findings and clinical relevance are further summarized in Table 2.

Tinnirello (2020) conducted a single-centred retrospective cohort study published as a conference abstract, with serious concerns of bias, comparing the effects of pulsed radiofrequency (n = 8), conventional radiofrequency (n = 36), cooled radiofrequency (n = 11), and cryoneurolysis (n = 10) for chronic non-specific knee pain. For the cryoneurolysis group, a mean reduction of 60% and 50% numeric rating scale (NRS) for pain were observed at 1-month and 6-months follow-up, respectively. No significant between-group differences were observed. Due to numerous reporting deficiencies, further details related to the population studied, interventions used, and statistical analysis were unclear, thus caution is warranted with interpretation of these results.

Moreover, McLean et al. (2020) conducted a single-centred retrospective case series of patients with patellofemoral pain syndrome (PFPS, n = 7), chondromalacia (n = 14), and non-specific chronic knee pain (n = 3) demonstrating within-group improvement in mean (SD) Defence and Veterans Pain Rating Scale (DVPRS) from 5.87 (1.58) to 0.30 (0.56).

Lastly, a case report of chronic knee pain secondary to saphenous nerve neuralgia demonstrated pain relief, functional improvement, and reduction in analgesic medications eight weeks after cryoneurolysis treatment [28].

3.1.2. *Peri-operative TKA*

Nine studies were included featuring patients receiving cryoneurolysis for TKA-related pain [10,19–21,30–34]. Mihalko et al. (2021) conducted an open-label single-centred RCT, with high risk of bias, to investigate the effects of cryoneurolysis and standard therapy (n = 64) versus standard therapy alone (n = 64) prior to TKA. Statistically significant reductions in mean [95% CI] daily TME (in mg) in favor of the cryoneurolysis group were observed at 72-h (−4.0 [−0.5 to 8.4], p = 0.0389), 6-weeks (−1.6 [0.1 to 3.2], p = 0.0186), and 12-weeks (−1.0 [0.0 to 2.0], p = 0.0234) follow-up. However, observed differences did not exceed MCID cut-offs [18]. The remaining outcomes were calculated using area under the curve from baseline analyses, such that MCIDs could not be applied to make judgments of clinical relevance. This is summarized in Table 2. Swisher et al. (2022) conducted a double-blind single-centred RCT, with low risk of bias, to investigate the effects of cryoneurolysis (n = 8) versus sham cryoneurolysis (n = 8) for pre-operative TKA for up to 21 days follow-up. However, this was a pilot study designed to determine feasibility such that within-group and between-group statistical analyses were deferred. Both groups demonstrated comparable improvements in NRS pain scores and reductions in opioid usage over time.

Three single-centred retrospective cohort studies with serious risks of bias investigated the benefit profile of pre-operative cryoneurolysis added to a multi-modal TKA pain protocol versus the protocol alone [10,21,32]. Dasa et al. (2016) enrolled 50 patients into the intervention group and 50 patients into the control group; while Urban et al. (2021) enrolled 169 patients into the intervention group and 98 patients into the control group. Both studies demonstrated statistically significant improvements in favor of the intervention group for length of stay (LOS), cumulative TMEs, and pain score outcomes. Lung et al. (2022) enrolled 29 patients into the intervention group and 28 patients into the control group; however, did not observe statistically significant between-group differences in LOS, TMEs, or most functional outcomes, with the

Table 1
Characteristics of included studies.

Study	Publication Type	Design	Treatment Indication	Sample Size	Intervention	Comparator	Nerve localization	Outcomes Measured
Bellini 2015 *Italy*	Journal publication	Case series	Lumbar facet pain, post-operative TKA-related pain, or SIJ pain for >3 months	18 total; 12 lumbar facet pain patients, 4 TKA patients, 2 SIJ pain patients	Cryoneurolysis (unknown device; variable cycle number of 2–3 min per cycle; unknown temperature)	N/A	Unknown target nerve; localization via direct fluoroscopic guidance; unknown presence of diagnostic nerve block	VAS, PGIC
Dasa 2016 *USA*	Journal publication	Retrospective cohort study	Pre-operative TKA-related pain	100 total; 50 intervention, 50 control	Cryoneurolysis (iovera device®; 6 cycles of 50 s per cycle; −125 °F) and standard therapy	Standard therapy (preoperative, intraoperative, and postoperative multi-modal pain regimen)	IPBSN and AFCN; localization via anatomic landmarks; unknown presence of diagnostic nerve block	TMEs, LOS, WOMAC, KOOS, Oxford Knee Score, SF-12, PROMIS, AEs
Ilfield 2017 *USA*	Journal publication	Case series	Pre-operative TKA-related pain	5 total; 3 RTC repair patients, 2 TKA patients	Cryoneurolysis (iovera device®; 2 cycles of 3 min per cycle; −70 °C)	N/A	IPBSN; localization via ultrasound-guidance; pre-procedure nerve block performed without explicit criteria	TMEs, NRS, AEs
Lung 2022 *USA*	Journal publication	Retrospective cohort study	Pre-operative TKA-related pain	57 total; 29 intervention, 28 control	Cryoneurolysis (iovera device®; 6 cycles of 1 min per cycle; unknown temperature)	Standard therapy (preoperative, intraoperative, and postoperative multi-modal pain regimen)	IPBSN and AFCN; localization via anatomic landmarks; unknown presence of diagnostic nerve block	TMEs, AEs, ROM, PAC, KOOS JR, SF-12, VAS
McLean 2020 *USA*	Journal publication	Case series	Chronic (duration not specified) PFPS, chondromalacia, or non-specific knee pain	23 total; 7 PFPS patients, 14 chondromalacia patients, 3 non-specific knee pain patients	Cryoneurolysis (iovera device®; 4–6 cycles of unknown duration per cycle; unknown temperature)	N/A	IPBSN; localization via peripheral nerve stimulator; pre-procedure nerve block performed with ≥50% pain reduction required	DVPRS
Mihalko 2021 *USA*	Journal publication	Parallel-group RCT	Pre-operative TKA-related pain	124 total; 64 intervention, 64 control	Cryoneurolysis (iovera device®; unknown number of cycles, treatment duration, and temperature) and standard therapy	Standard therapy (preoperative, intraoperative, and postoperative multi-modal pain regimen)	IPBSN and AFCN; localization via anatomic landmarks; unknown presence of diagnostic nerve block	TME, NRS, KOOS JR, TUG, ROM, AEs
Radnovich 2017 *USA*	Journal publication	Parallel-group RCT	Mild-to-moderate knee OA	180 total; 121 intervention, 59 control	Cryoneurolysis (iovera device®; unknown number of cycles, mean (SD) duration of 23±6 min; unknown temperature)	Sham cryoneurolysis	IPBSN; localization via anatomic landmarks; pre-procedure nerve block performed with ≥50% pain reduction required	WOMAC, VAS, SF-36, PGIC, AEs
Roth 2022 *USA*	Journal publication	Case series	Pre-operative TKA-related pain	10 total	Cryoneurolysis (iovera device®; unknown number of cycles of 60 s per cycle; −88 °C)	N/A	IPBSN and AFCN; localization via ultrasound-guidance; pre-procedure nerve block performed without explicit criteria	NRS, TME, ROM

(*continued on next page*)

Table 1 (*continued*)

Study	Publication Type	Design	Treatment Indication	Sample Size	Intervention	Comparator	Nerve localization	Outcomes Measured
Swisher 2022 *USA*	Journal publication	Parallel-group RCT	Pre-operative TKA-related pain	16 total; 8 intervention, 8 control	Cryoneurolysis (iovera device®; 3 cycles of 120 s per cycle; −70 °C)	Sham cryoneurolysis	IPBSN; localization via ultrasound-guidance; unknown presence of diagnostic nerve block	NRS, TME, difficulty sleeping (Y/N), number of awakenings due to pain, and nausea (Likert scale)
Tinnirello 2020 *Italy*	Conference proceeding	Retrospective cohort study	Chronic knee pain (duration and etiology of knee pain not specified)	65 total; 12 PRF patients, 36 CRF patients, 10 cryoneurolysis patients, 11 cooled RF patients	Cryoneurolysis (unknown device, number of cycles, treatment duration, and temperature)	PRF, CRF or cooled RF; unknown device, number of cycles, and treatment duration	Genicular nerves (branches unknown); unknown method of localization and presence of nerve block	NRS
Urban 2021 *USA*	Journal publication	Retrospective cohort study	Pre-operative TKA-related pain	267 total; 169 treatment, 98 control	Cryoneurolysis (iovera device®; 1 cycle of 105 s per cycle; unknown temperature) and standard therapy	Standard therapy (preoperative, intraoperative, and postoperative multi-modal pain regimen)	IPBSN and AFCN; localization via ultrasound-guidance; pre-procedure nerve block performed without explicit criteria	TME, NRS, LOS, ROM, AEs

Abbreviations: TKA, total knee arthroplasty; SIJ, sacroiliac joint; VAS, Visual Analogue Scale; PGIC, Patient Global Impression of Change; AE, adverse event; IPBSN, infrapatellar branch of the saphenous nerve; AFCN, anterior femoral cutaneous nerve; TME, total morphine equivalent; LOS, length of stay; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, Knee Injury and Osteoarthritis Outcome Score; PAC, Post Acute Care; SF-12, Short Form-12; PROMIS, Patient Reported Outcomes Measurement Information System; RTC, rotator cuff; NRS, Numeric Rating Scale; ROM, range of motion; PFPS, patellofemoral pain syndrome; DVPRS, Defense and Veterans Pain Rating Scale; RCT, randomized controlled trial; KOOS JR, Knee Injury and Osteoarthritis Outcome Score for Joint Replacements; TUG, Timed-Up-and-Go test; SF-36, Short Form-36; PRF, pulsed radiofrequency; CRF, conventional radiofrequency; RF, radiofrequency.
Case reports were excluded.

exception of range of motion at 6 weeks as well as Knee Injury and Osteoarthritis Outcome Score for Joint Replacement and 12-Iterm Short Form Survey scores at 1-year follow-up.

Dasa et al. (2016) found that in the intervention group, 44.9% had a LOS of 0 days, 49.0% had a LOS of 1 day, and 6.1% had a LOS of 2 days; compared to 14.3%, 18.4%, and 67.3% in the control group, respectively ($p < 0.0001$). Additionally, statistically significant between-group differences in favor of the intervention group were found for cumulative mean (SE) TME (in mg) at 12-weeks follow-up (intervention: 2069.12 (132.09); control: 3764.42 (287.95); $p < 0.0001$), which exceeded the MCID cut-off [10,18]. Meanwhile, Urban et al. (2021) found that in the intervention group, 17% of patients had an LOS greater than or equal to 2 days compared to 99% in the control group ($p < 0.0001$). Additionally, statistically significant between-group differences in favor of the intervention group were found for mean [95% CI] cumulative TMEs (in mg) at discharge (intervention: 660 [593 to 736]; control: 1154 [1044–1277]; $p < 0.0001$), which exceeded the MCID cut-off [18,21]. Statistically significant between-group differences were also observed at 2-weeks follow-up (intervention: 855 [765 to 957]; control: 1312 [1182–1457]; $p < 0.0001$) and 6-weeks follow-up (intervention: 894 [795 to 1004]; control: 1406 [1260–1570]; $p < 0.0001$); however, did not exceed MCID cut-offs [18,21]. Statistical findings and clinical relevance for remaining outcomes are summarized in Table 2.

A case series of ten patients who received cryoneurolysis prior to TKA demonstrated immediate post-treatment reductions in pain, post anesthesia care unit pain scores of zero (with exception of two patients), and satisfactory post-operative knee flexion measurements up to twelve weeks follow-up [34]. A case-series of three patients who received cryoneurolysis prior to TKA demonstrated reductions in pain and peri-operative opioid use [31]. A case-series of four patients who received cryoneurolysis post TKA demonstrated improvements in VAS and patient global impression of change scores up to 3-months follow-up [30]. A case report of a patient with 3-months of postoperative pain following TKA secondary to saphenous nerve neuritis demonstrated pain relief, improvement of function, and avoidance of further surgery 10-weeks after cryoneurolysis treatment [33].

3.2. Safety profile

Seven studies reported data on AEs (n = 465) [9,10,19,21,31,32,35]. Most intervention-related AEs were mild and self-limiting. Most common AEs (in the order of most frequent) were bruising, numbness, redness, swelling, local pain, altered sensation, tenderness on palpation, tingling, crusting, itching, and hyperpigmentation [9,10,31]. Radnovich et al. (2017) found similar incidence of AEs between cryoneurolysis versus sham groups at 180-days follow-up. In peri-operative TKA populations, Mihalko et al. (2021) and Dasa et al. (2016) also found similar incidence of AEs between groups up to 12-weeks follow-up. Most AEs were related to the arthroplasty itself with no severe intervention-related AEs observed [10,19,32]. Overall, there were three reported severe intervention-related AEs [21,35]. Urban et al. (2021) reported two patients with dysesthesia that did not resolve by the end of their 6-week follow-up period. Cahani et al. (2019) reported one patient with non-specific chronic knee pain who required hospital admission for myonecrosis, believed secondary to an infectious process following infiltration of deep tissues from the cryoneurolysis probe 10-days prior.

3.3. Technical and procedural considerations

Studies varied considerably with respect to technical and procedural specifications and often reported insufficient information to ensure reproducibility. Device type, number of cycles, duration of treatment,

Table 2
Summary of findings and clinical relevance.

Study	Results	Clinical Relevance[a]
Population: chronic mild-to-moderate knee OA **Intervention:** cryoneurolysis **Comparison:** sham cryoneurolysis		
Radnovich 2017	**30-day follow-up:**	Likely
	Reduction in least squares mean [SD] WOMAC pain score (−7.12 [-11.01 to −3.22, p = 0.0004]), physical function score (−21.30 [-34.02 to −8.57, p = 0.0012]), stiffness score (−2.32 [-3.97 to −0.68, p = 0.0060]), and total score (−30.52 [-48.52 to −12.53, p = 0.0010]) in favor of intervention group over comparison group.	
	Reduction in mean [SD] VAS (−12.25 [-21.16 to −3.35, 0.0073]) in favor of intervention group over comparison group.	Likely
	60-day follow-up:	Likely
	Reduction in least squares mean [SD] WOMAC pain score (−4.65 [-8.48 to −01.82, p = 0.0176]) in favor of intervention group over comparison group.	
	90-day follow-up:	Likely
	Reduction in least squares mean [SD] WOMAC physical function score (−15.89 [-28.93 to −2.86, p = 0.0172]), pain score (−5.67 [-9.69 to −1.64, p = 0.0061]), and total score (−23.80 [-42.02 to −5.57, p = 0.0108]) in favor of intervention group over comparison group.	
	150-day follow-up:	Likely
	Reduction in least squares mean [SD] WOMAC pain score (−6.40 [-10.28 to −2.51, p = 0.0015]), physical function score (−19.91 [-32.98 to −6.83, p = 0.0031]), stiffness score (−2.72 [-4.39 to −1.05, p = 0.0016]), and total score (−28.58 [-47.03 to −10.13, p = 0.0027]) in favor of intervention group over comparison group.	
	Reduction in mean [SD] VAS (−14.60 [-23.20 to −6.00, p = 0.0010]) in favor of intervention group over comparison group.	Likely
Population: perioperative-TKA **Intervention:** cryoneurolysis and standard therapy **Comparison:** standard therapy alone		
Mihalko 2021	**3-day follow-up:**	Unlikely
	Reduction in mean [95% CI] daily TMEs (−4.0 [-0.5 to 8.4], p = 0.0389) in favor of intervention group over comparison group.	
	14-day follow-up:	Unclear[b]
	Reduction in mean change in AUC/time from baseline KOOS JR scores (intervention: −2.3, comparator: 1.0, p < 0.0001) in favor of intervention group over comparison group.	
	42-day follow-up:	Unlikely
	Reduction in mean [95% CI] daily TMEs (−1.6 [0.1 to 3.2], p = 0.0186) in favor of intervention group over comparison group.	
	Reduction in mean change in AUC/time from baseline KOOS JR scores (intervention: −9.7, comparator: −7.7, p < 0.0001) in favor of intervention group over comparison group.	Unclear[b]
	84-day follow-up:	Unlikely
	Reduction in mean [95% CI] daily TMEs (−1.0 [0.0 to 2.0], p = 0.0234) in favor of intervention group over comparison group.	
	Reduction in mean change in AUC/time from baseline KOOS JR scores (intervention: -16.0, comparator: 14.1, p < 0.0001) in favor of intervention group over comparison group.	Unclear[b]
Dasa 2016	**Discharge follow-up:**	Unclear[c]
	Reduction in length of stay in favor of intervention group (44.9% had a LOS of 0 days, 49.0% had a LOS of 1 day, and 6.1% had a LOS of 2 days) over comparison group (14.3% had a LOS of 0 days, 18.4% had a LOS of 1 day, and 67.3% had a LOS of 2 days, p < 0.0001)	
	42-day follow-up:	Likely
	Reduction in mean daily KOOS score from baseline in favor of intervention group (63.8 ± 18.7) over comparison group (55.6 ± 15.3, p = 0.0037).	
	84-day follow-up:	Likely
	Reduction in cumulative mean (±SE) TMEs (intervention: 2069.12±132.09; control: 3764.42±287.95; p < 0.0001) in favor of intervention group over comparison group.	
	Reduction in mean daily KOOS score from baseline in favor of intervention group (69.9 ± 18.0) over comparison group (57.7 ± 16.6, p = 0.0011).	Likely
Lung 2022	**Discharge follow-up:**	Unclear[c]
	No statistically significant between group differences in LOS.	
	42-day follow-up:	
	No statistically significant between group differences in TMEs.	
	Improvement in knee ROM in favor of the intervention group (12° ± 9°, n = 29) over the comparison group (3° ± 12°, n = 28, p = 0.0420).	
	84-day follow-up:	
	No statistically significant between group differences for KOOS JR and SF-12 scores.	
	365-day follow-up:	Likely
	Improvement in KOOS JR in favor of the intervention group (38.2 ± 11.2, n = 29) over the comparison group (11.1 ± 9.6, n = 28, p = 0.007).	
	Improvement in SF-12 mental scores in favor of the intervention group (60.4 ± 5.1, n = 29) over the comparison group (50.4 ± 6.7, n = 28, p = 0.01).	Likely
Urban 2021	**Discharge follow-up:**	Likely
	Reduction in mean [95% CI] cumulative TMEs (intervention: 660 [593 to 736]; control: 1154 [1044–1277]; p < 0.0001) in favor of intervention group over comparison group.	
	Reduction in LOS in favor of intervention group (n = 29 (17%) for LOS≥2 days) over comparison group (n = 97 (99%) for LOS≥2 days, p < 0.0001).	Unclear[b, c]
	Lower NRS pain score in favor of the intervention group (3.06 [2.71 to 3.46]) over comparison group (3.92 [3.49 to 4.40], p < 0.0001).	Unlikely
	Improvement in ROM in favor of the intervention group (n = 165 (98%) for knee flexion ≥90°; n = 164 (97%) for knee extension ≤5°) over the comparison group (n = 78 (80%) for knee flexion ≥90°; n = 77 (79%) for knee extension ≤5°; p < 0.0001).	Unclear[b, c]
	14-day follow-up:	Unlikely
	Reduction in mean [95% CI] cumulative TMEs (intervention: 855 [765 to 957]; control: 1312 [1182–1457]; p < 0.0001) in favor of intervention group over comparison group.	
	42-day follow-up:	Unlikely
	Reduction in mean [95% CI] cumulative TMEs (intervention: 894 [795 to 1004]; control: 1406 [1260–1570]; p < 0.0001) in favor of intervention group over comparison group.	

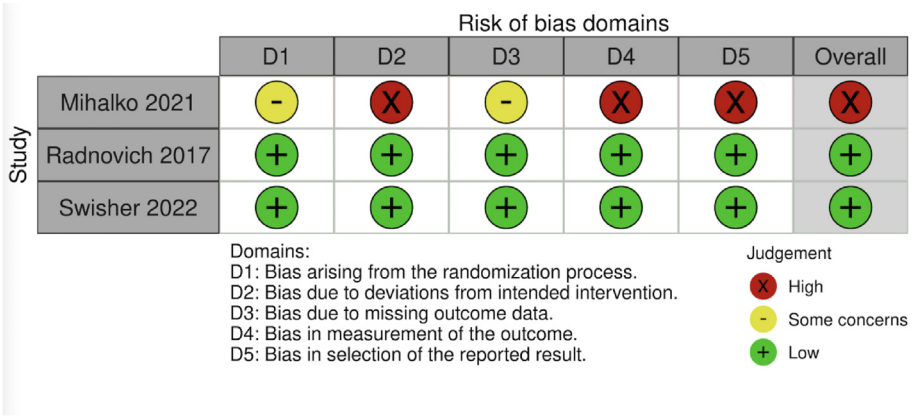

Fig. 2. Risk of bias summary of all included randomized controlled trials using the Risk of Bias 2.0 tool.

probe temperature, target nerve, method of localization, and presence of diagnostic nerve block are outlined in Table 1.

4. Discussion

4.1. Findings

The studies included in this review provide evidence to support cryoneurolysis in providing clinically meaningful improvements in WOMAC scores in chronic OA populations compared to sham; as well as clinically meaningful reductions in opioid use when added to perioperative multimodal pain regimens for TKA. Improvements in pain, function, quality of life, and opioid consumption were consistently seen in favor of cryoneurolysis for non-cancer knee pain, although many studies had at least some risk of bias. Most adverse events were mild and self-limiting. Considerable variations in technique parameters were observed.

4.2. Methodological considerations

The present evidence on cryoneurolysis for chronic non-cancer knee pain is supported by one RCT with low risk of bias [9] and one retrospective cohort study with serious risk of bias [29]. Meanwhile, evidence for peri-operative TKA populations is supported by one RCT with low risk of bias [20], one RCT with high risk of bias [19], and three retrospective cohort studies with serious risks of bias [10,21,32] (see Figs. 2 and 3). All included observational studies were at risk of bias due to lack of controlling for relevant confounding domains, for example, baseline opioid tolerance for TMEs [10,21,32] and baseline clinical data for pain scores [21,29]. With the exception of two RCTs, consistent concerns of bias warrant additional caution when interpreting results.

Among studies, there was considerable clinical heterogeneity with respect to patient population, intervention, control, and outcome parameters. This precluded quantitative analyses or further appropriate subgrouping of studies beyond chronic knee pain and acute perioperative populations. Acute and chronic pain populations may respond differently to cryoneurolysis due to different peripheral and central pain processing pathways involved [36]. Cryoneurolysis temporarily disrupts the peripheral nociceptive afferent pathways that contribute to acute pain. However, central sensitization observed in chronic pain is characterized by increased neuronal membrane excitability and reduced descending inhibition of pain pathways [37]. The efficacy of cryoneurolysis may be decreased in chronic pain populations as its primary mechanism does not target the aforementioned pathological processes unique to central sensitization [36,37].

4.3. Implications for practice

There is no consensus among studies for parameters related to the intervention, control, and outcome measures. Interventions vary considerably with respect to number of cycles, duration of treatment, probe temperature, nerve selection, method of nerve localization, and presence of nerve blocks. All but one study used conventional therapy consisting of multimodal pain regimens as a control group [9]. Unique to the single centre in which each study was conducted, definitions of conventional therapy varied among studies with respect to pain medication allowance and exercise therapy. Finally, outcome measures varied with respect to multiple outcome measurements within the same domain (e.g. using WOMAC, VAS, NRS, or DVPRS to measure pain domain). Only one study interpreted their results using MCID thresholds to demonstrate clinical importance [9].

The majority of included studies targeted either the infrapatellar branch of the saphenous nerve (IPBSN) [9,20,27,31,33] or both the IPBSN and anterior femoral cutaneous nerve (AFCN) [10,19,21,32,34]. Both nerve targets primarily provide cutaneous innervation to the knee. However, cadaveric studies demonstrate that the knee joint receives sensory innervation from multiple nerves including the superolateral genicular nerve (SLGN), superomedial genicular nerve (SMGN), inferolateral genicular nerve (ILGN), inferomedial genicular nerve (IMGN), recurrent fibular nerve, posterior genicular nerve (PGN) as well as nerves arising from the vastus medialis, intermedius, and lateralis [38–43]. The current nerve targets described in the knee cryoneurolysis literature do not address the deep sensory supply of the knee joint, but rather the

Abbreviations: OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; VAS, Visual Analogue Scale; TKA, total knee arthroplasty; TME, total morphine equivalent; AUC, area under the curve; KOOS JR, Knee Injury and Osteoarthritis Outcome Score for Joint Replacements; LOS, length of stay; KOOS, Knee Injury and Osteoarthritis Outcome Score; NRS, Numeric Rating Scale; SIJ, ROM, range of motion.

[a] A judgement of clinical relevance was determined for any statistically significant between-group differences. The minimally clinically important difference (MCID) for each outcome measure was determined from a literature search (Appendix 2). The MCID was used as a threshold such that results below the MCID were considered unlikely to be clinically relevant and results exceeding the MCID were considered likely to be clinically relevant. Based on the method of derivation, MCIDs for VAS and WOMAC were used as a threshold for within-group differences observed in the intervention group, while the MCID for opioid consumption was used as a threshold for between-group differences.

[b] Insufficent information provided in the analysis (e.g. unreported mean difference). Therefore, a rating of unclear clinical relevance was made.

[c] MCID is not clearly established in the literature. Therefore, a rating of unclear clinical relevance was made.

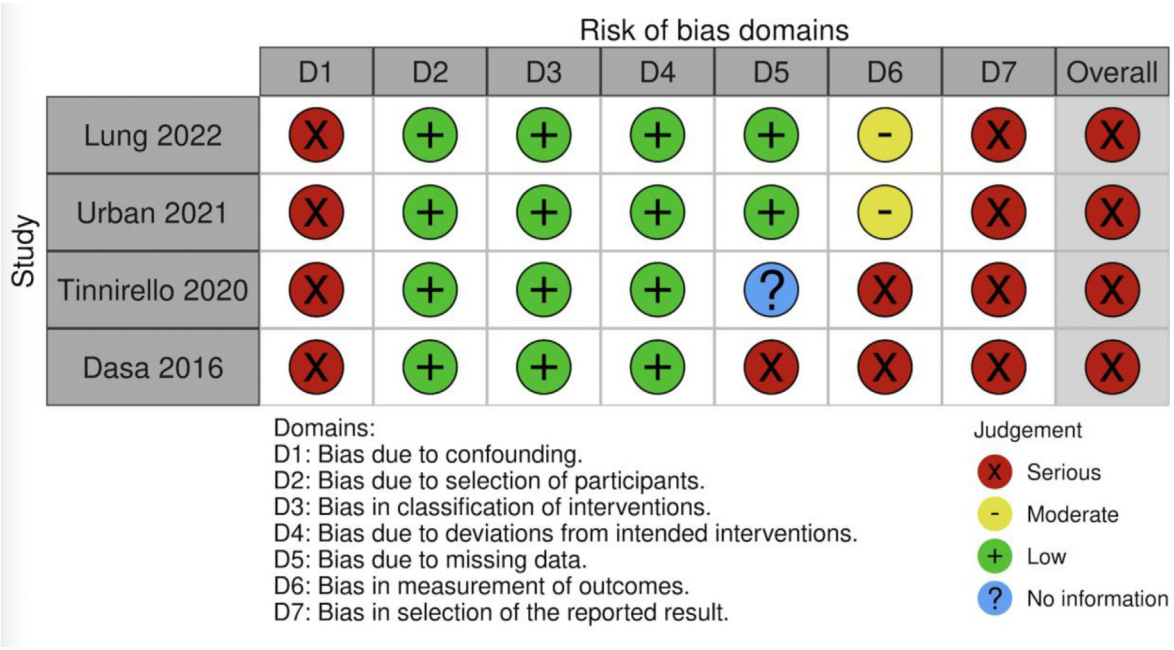

Fig. 3. Risk of bias summary of all included non-randomized trials using the Risk of Bias In Non-Randomized Studies of Interventions tool.

anterior superficial cutaneous distribution [38,40]. While knee pain can be cutaneous (e.g. neuropathic pain post-TKA, incisional pains, etc.), it stems more commonly from intra-articular processes including OA- or TKA-related pain. Therefore, the IPBSN and/or the AFCN may not be sufficient targets for patients presenting with intra-articular knee pathology, in which case the genicular branches supplying the joint itself should be targeted. The same may be true for more diffuse knee pain presentations, in which targeting additional cutaneous nerves might be considered.

Traditionally, the SLGN, SMGN, and IMGN have been proposed as the target nerves for RFA in knee pain populations, based a prior landmark RCT [44]. However, numerous RFA studies have produced mixed results for chronic knee OA [30,45–53] or post-TKA pain [54–56]. Subsequently, other experts in the field have suggested adding additional nerve targets [53,57]. On the basis of the current available literature, there is no consensus for which nerve to target for the treatment of chronic knee OA or TKA-related pain. Consideration might also be given to targeting only the nerves which appear to be involved clinically based on the location of pain [58,59]. However, increasing the number of nerve targets may increase risk of adverse events; for instance, targeting of the ILGN may risk injury to the motor branches of the common fibular nerve causing weakness, while targeting the PGN may risk injury to vital neurovascular structures, although both potential complications resulting from interventional procedures have not been reported. Despite this, future studies should aim to identify optimal nerve targets taking into consideration cutaneous and intracapsular sources of pain. Intra-articular knee pain is likely undertreated in current cryoneurolysis literature targeting only IPBSN and/or AFCN distributions. A careful balance between maximizing analgesia through multiple nerve targets while minimizing adverse events should be sought through comparisons of cryoneurolysis targeting IPBSN/AFCN versus genicular nerves versus both.

Moreover, the cryoneurolysis literature is limited in its use of and reporting of pre-procedure blocks. Six of 14 studies [9,21,27,28,31,34] reported using a pre-procedure diagnostic block, and only two studies [9,27] indicated specific block criteria requiring ≥50% pain reduction. Indeed, a previous RCT of patients with knee OA undergoing cooled RFA demonstrated that a single block using ≥50% pain reduction thresholds did not predict treatment success [60]. However, future directions include further research into defining inclusion criteria for cryoneurolysis, where higher pain reduction thresholds may improve specificity [61]. Validation of specific diagnostic blocks has yet to be explored and has the potential to enhance treatment outcomes.

4.4. Implications for research

Despite the seemingly favorable safety profile of cryoneurolysis, it is unclear how it compares to other common interventional procedures for non-cancer knee pain. There were no direct comparisons of safety between cryoneurolysis versus radiofrequency ablation (RFA) or chemical neurolysis. There exist case reports of pes anserine tendon injury [62], periarticular hematoma [63], third-degree skin burn [64], and septic arthritis secondary to RFA [65]; however, a systematic review of 29 studies (10 RCT's, 19 nonrandomized studies) on RFA for symptomatic knee OA demonstrated no serious knee-related AEs pertaining to RFA modalities [66]. Meanwhile, a systematic review of 9 studies (5 RCTs, 4 nonrandomized studies) on chemical neurolysis using local anesthetics, corticosteroids, or alcohol for chronic knee OA also demonstrated no serious treatment-related AEs [67]. Unlike RFA and chemical neurolysis, cryoneurolysis preserves the outer connective tissue nerve architecture such that theoretical risk of reinnervation dysesthesias and neuroma formation is decreased [6]. Surrounding structures including major blood vessels have also been shown to withstand 10 min of direct contact to a cryogenic probe cooled to −180 °C [68]. Despite these theoretical reductions of risk, further research with larger sample sizes and direct comparison is required for confirmation.

Furthermore, the number of cycles, duration of treatment, and probe temperature varies within the peri-operative literature, such that optimal cryoneurolysis parameters are yet to be determined [5,7,8]. Degree of analgesia is dependent on the extent of freezing. Freezing is achieved through manipulation of proximity of the cryoprobe to the nerve, size of the cryoprobe, size of the ice ball formed, rate and duration of freezing, and local temperature of tissues [6]. Optimal selection of such parameters has yet to be elucidated for knee pain. A proposed percutaneous technique involves a freeze of 30–120 s followed by a thaw of 30–60 s, with the freeze-thaw cycle repeated 1 to 2 times [6]. However, optimization of cycle number and duration may depend on the final probe temperature and the size of the target nerve.

Control conditions also require further optimization. Despite three

ongoing RCTs featuring sham comparison groups, the technical and procedural specifications of what constitutes adequate sham therapy is unclear [23–25]. Two RCTs cite using a sham Iovera device® [23,25], while one RCT cites using local anesthesia as sham therapy [24]. Further refinement and validation of sham therapy would provide more accurate estimates of treatment efficacy. Moreover, multiple studies utilize standard therapy as a control group; however, definitions of standard therapy vary across sites. Site-specific variations are difficult to avoid, such that future RCTs should be multi-centred to increase external validity of the findings.

While there are multiple ongoing RCTs, there will continue to exist multiple technical, procedural, and methodological gaps in the literature. For instance, only one ongoing RCT [22] compares between cryoneurolysis of the IPBSN versus genicular nerves for pre-TKA populations, while the remaining RCTs continue to only target the IPBSN and/or the AFCN. Diagnostic nerve block criteria, number of cryoneurolysis cycles, and duration of each cycle are not defined in any of the ongoing trials. Additionally, outcome measures continue to vary widely with respect to specific measurement tools and outcome domains, such that further work to establish consensus is warranted.

Finally, future studies should further explore the utility of cryoneurolysis in real-world settings. Cryoneurolysis has been proposed as a perioperative intervention with promise superior to nerve blocks given its longer lasting analgesic effects as well as its decreased risk of infection without the requirement of in-situ catheters [36]. However, treatment can be more time-consuming, which may pose as a barrier for applications in acute pain centres where time is limited. Alternatively, less time restrictions may apply in outpatient settings for treatment of chronic knee pain. Cost-effectiveness analyses are warranted to explore its utility in such settings among anesthetists and other interventional pain clinicians.

4.5. Strengths and limitations

This review was mainly limited by clinical heterogeneity and small sample sizes. Studies varied considerably with respect to treatment indication, nerve targets, cryoneurolysis parameters, comparator groups, and outcome measures. Limited sample sizes and clinical heterogeneity should be overcome with future high-powered, bias appropriately designed RCTs. Further, only one study interpreted their results using MCID thresholds to demonstrate clinical importance [9]. Future trials should prioritize reporting the clinical significance of their results. Moreover, despite searching five databases, repeating the search, and hand-searching reference and citations lists, it is possible that some relevant non-English studies may have been missed.

5. Conclusions

Cryoneurolysis holds promise as an adjunct modality to existing multimodal pain regimens for treatment of non-cancer knee pain. However, considerable risk of bias and clinical heterogeneity precludes the ability to reliably quantify any measures of effect, limits scientific reproducibility, and warrants caution with interpretation of results. Further, only one study interpreted their results using MCID thresholds to demonstrate clinical importance [9]. Future trials should explore differences in effect based on nerve selection as well as ensure transparent reporting of treatment and procedural parameters to improve scientific reproducibility.

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Authorship statement

All authors were responsible for the study conception and design. DD and JF were responsible for data extraction and validation, and data analysis and interpretation. All authors drafted the manuscript, provided critical review, and approved the final manuscript. JF is the guarantor.

Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inpm.2023.100247.

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