Accepted Manuscript online: 2023-09-26 Article published online: 2023-12-13

Cryoanalgesia: Review with Respect to Peripheral Nerve

Benjamin R. Slavin, MD[1,*] Moses I. Markowitz, BS[1,*] Kevin M. Klifto, DO, PharmD[2] Frank J. Prologo[3] Susan M. Taghioff, MD[1] A. Lee Dellon, MD, PhD[4]

[1] Division of Plastic Surgery, University of Miami Miller School of Medicine, Miami, Florida
[2] Division of Plastic Surgery, University of Missouri School of Medicine, Columbia, Missouri
[3] Department of Biological Sciences, University of Georgia, Athens, Georgia
[4] Department of Neurosurgery and Plastic Surgery, Johns Hopkins School of Medicine, Baltimore, Maryland

Address for correspondence Benjamin R. Slavin, MD, Division of Plastic and Reconstructive Surgery, University of Miami Miller School of Medicine, 4th Floor, 1120 NW 14th Street, Miami, FL 33136 (e-mail: b.slavin@umiami.edu).

J Reconstr Microsurg 2024;40:302–310.

Abstract

Background Cryoanalgesia is a tool being used by interventional radiology to treat chronic pain. Within a certain cold temperature range, peripheral nerve function is interrupted and recovers, without neuroma formation. Cryoanalgesia has most often been applied to the intercostal nerve. Cryoanalgesia has applications to peripheral nerve surgery, yet is poorly understood by reconstructive microsurgeons.

Methods Histopathology of nerve injury was reviewed to understand cold applied to peripheral nerve. Literature review was performed utilizing the PubMed and MEDLINE databases to identify comparative studies of the efficacy of intraoperative cryoanalgesia versus thoracic epidural anesthesia following thoracotomy. Data were analyzed using Fisher's exact and analysis of variance tests. A similar approach was used for pudendal cryoanalgesia.

Results Application of inclusion and exclusion criteria resulted in 16 comparative clinical studies of intercostal nerve for this review. For thoracotomy, nine studies compared cryoanalgesia with pharmaceutical analgesia, with seven demonstrating significant reduction in postoperative opioid use or postoperative acute pain scores. In these nine studies, there was no association between the number of nerves treated and the reduction in acute postoperative pain. One study compared cryoanalgesia with local anesthetic and demonstrated a significant reduction in acute pain with cryoanalgesia. Three studies compared cryoanalgesia with epidural analgesia and demonstrated no significant difference in postoperative pain or postoperative opioid use. Interventional radiology targets pudendal nerves using computed tomography imaging with positive outcomes for the patient with pain of pudendal nerve origin.

Conclusion Cryoanalgesia is a term used for the treatment of peripheral nerve problems that would benefit from a proverbial reset of peripheral nerve function. It does not ablate the nerve. Intraoperative cryoanalgesia to intercostal nerves is a safe and effective means of postoperative analgesia following thoracotomy. For pudendal nerve injury, where an intrapelvic surgical approach may be difficult, cryoanalgesia may provide sufficient clinical relief, thereby preserving pudendal nerve function.

Keywords
- cryoanalgesia
- peripheral nerve
- peripheral nerve surgery

[*] *These authors contributed equally as co-first authors.*

received
May 24, 2023
accepted after revision
September 18, 2023
accepted manuscript online
September 26, 2023
article published online
December 13, 2023

DOI https://doi.org/10.1055/a-2182-1198.
ISSN 0743-684X.

Cryosurgery has been utilized in various modalities for more than 60 years. Beginning in the mid-20th century, cryoablation, via targeted application of −196°C liquid nitrogen, had become a widely accepted option to treat tumors with well-defined borders, with up to a 99% 5-year cure rate for some cancers.[1,2] Subsequently, in 1962, the first modern use of cryoanalgesia began to take shape with Cooper and Dawber using a targeted approach to introduce liquid nitrogen at −196°C to peripheral nerves.[2] Additional refinements have been made to the duration of application, delivery, and optimal temperature of cryoanalgesia, many of which evolved following a deeper understanding of the pathophysiology of peripheral nerve injury and repair: specifically, the delineation of Sunderland second-degree injury as desirable, with predictable subsequent events that allow for the management of patient expectations as well as the specific design of cryonanalgesia devices.

Thoracotomy is a commonly performed procedure which can result in significant postoperative pain and opioid use.[3–5] Intraoperative cryoanalgesia of intercostal nerves has become a favored method of mitigating postoperative pain, despite increasing operative time.[3–6] With the development of modern cryoprobes, which reach temperatures of −60°C, multiple randomized controlled trials and prospective cohort studies have assessed intraoperative intercostal cryoanalgesia in comparison with the present gold standard of thoracic epidural anesthesia.[3–5,7]

The pudendal nerve presents a surgical challenge, as it may be injured within the pelvis. Therefore, percutaneous image-guided cryoanalgesia has been used to treat pain syndromes related to the pudendal nerve.[8–10] Application of cold to the pudendal nerve illustrates the ability to superimpose a deliberate specific lesion to a peripheral neural target and induce Wallerian degeneration while maintaining the connective tissue scaffold employed for predictable subsequent axonal regeneration. This may correct the underlying structural changes associated with the original injury.[11–14]

The purpose of this review was to understand the effect of cold upon peripheral nerve tissues, learn about the preemptive effectives of cyroanalgesia of the intercostal nerve, and appreciate the potential efficacy of cryoanalgesia for pelvic pain of neural origin due to the pudendal nerve.

Classifications of Nerve Injury and Cryoanalgesia

To understand the effect of cryoprobe temperatures applied to the peripheral nerve, a review of the histopathology of nerve injury is necessary. In 1943, Seddon et al described three distinct types of nerve injury: neurapraxia, axonotmesis, and neurotmesis.[15] Neurapraxia most commonly results from blunt trauma, which causes a temporary conduction block, with recovery ranging from a few days to 12 weeks. The second degree of nerve injury, axonotmesis, is characterized by axonal loss with preservation of the surrounding connective tissue layers. With this injury, chemotactic factors are released from distal targets to guide proximal axonal growth to the appropriate target.[16–18] Neurotmesis, Seddon et al's third and most severe degrees of nerve injury, involves the complete transection of a nerve with no expectation of recovery expected without surgical repair. Given that nerve conduction is disrupted in both axonotmesis and neurotmesis, electrophysiologic studies are unable to differentiate Seddon et al's second and third degrees from one another.[19] In 1951, Sunderland published his five grades of nerve injury.[20] Similar to Seddon et al, Sunderland's Grades I and II of nerve injury are defined as neurapraxia and axonotmesis. However, Sunderland expanded upon Seddon et al's definitions by stratifying neurotmesis into his Grades III, IV, and V of injury which specify damage to include the endoneurium, perineurium, and epineurium, respectively.[13]

Guided by the principle that risk of neuroma formation would outweigh the intended benefit of decreased postoperative pain, it was found that temperatures below −25°C create a desired conduction block in peripheral nerves via disruption of cell membrane, sodium and potassium channel pumps. By gradually decreasing temperatures, it was discovered that a range between −20 and −100°C was cold enough to induce axonotmesis with a long-lasting conduction block with Wallerian degeneration, without disrupting the epineurial and perineurial layers of the peripheral nerve.[21] By inducing conduction block and Wallerian degeneration, the desired long-lasting analgesia could be achieved with eventual sensory recovery weeks to months later.[22] The preservation of epineurial and perineurial layers meant that the regenerating axons of the proximal nerve stump would have a preexisting scaffold to guide them to their distal targets, as described by Seddon et al and Sunderland, thereby mitigating the risk of neuroma formation.[20,23]

For terminology then, as currently employed, *cryoablation* is somewhat of a misnomer given that the neural structure is not damaged, and thus nerve function is not actually ablated. Further, the term *cryoneurolysis* also does not seem appropriate as nothing is physically done to the nerve itself to separate it from its adjacent anatomic structures. That being said, the volume of the treated nerve segment may shrink or decreases during Wallerian degeneration, thereby decreasing the degree of nerve compression. More appropriately, *cryoanalgesia* does describe temporary loss of function that can subsequently recover.

Intercostal Nerve

Cryoanalgesia of intercostal nerves has been studied extensively. Green et al described its efficacy as a treatment modality for chronic postthoracotomy pain, with 50% of their 43-patient cohort reporting significant pain relief 3 months after treatment.[24] This finding is comparable to other treatments for intercostal neuralgia such as topical or invasive nerve blocks,[25,26] radioablation,[27] or neurectomy.[28] It was appropriate then to evaluate cyroanalgesia to prevent postthoracotomy pain. To best understand this pre-emptive approach to pain management, a comprehensive review of the literature was conducted using the PubMed, MEDLINE, Embase, CENTRAL, and ClinicalTrials.gov databases (►**Fig. 1**).

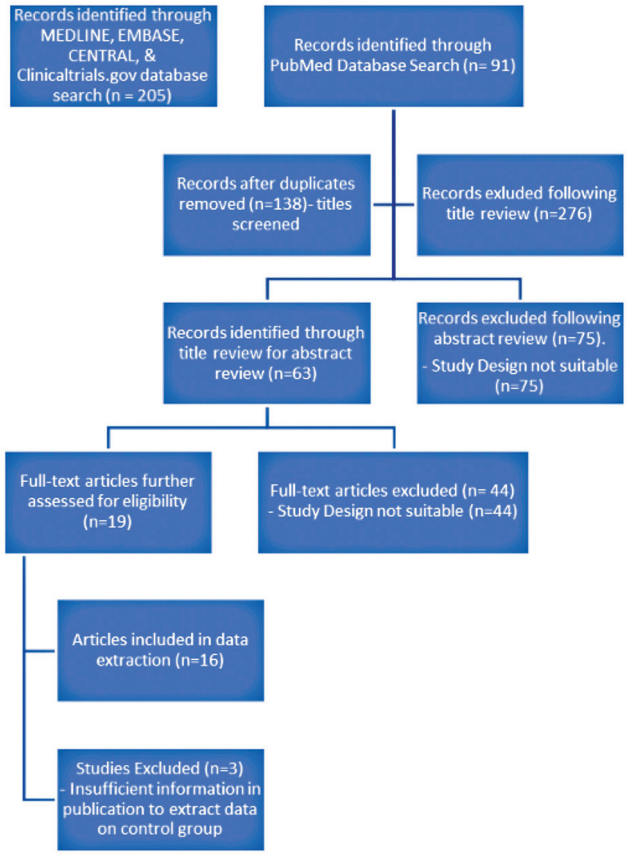

Fig. 1 Comprehensive review inclusion and exclusion methodology.

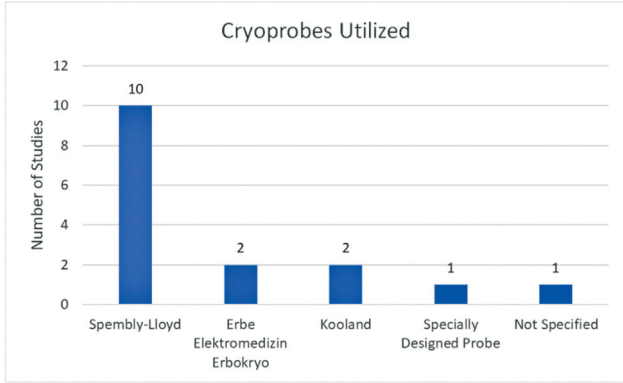

Fig. 2 Distribution of types of cryoprobes employed for intercostal nerve studies.

Search terms included "Cryoanesthesia," "Cryoanalgesia," "Cryosurgery," and "Thoracotomy." Inclusion criteria were that each study specifies a cryotechnique, aims to address postthoracotomy pain, specifies peripheral nerve of interest, and was prospective in nature. Studies were excluded if the following variables were not explicitly defined: number of patients starting the study, number of patients treated with cryoanalgesia, the number of patients who finished the study, the use of any local anesthetics, length of follow-up, hospital length of stay, and quantification of postoperative pain control. All statistical analysis was performed with SPSS Version 28.0.0. Data were analyzed using Fisher's exact and analysis of variance tests. A p-value of < 0.05 was considered significant.

Sixteen articles on the intercostal nerve were included in the final analysis. Nine studies assessed intraoperative cryotherapy compared with a control group receiving only postoperative pharmaceutical analgesia, two compared intraoperative cryotherapy to the intraoperative administration of local anesthetic, three compared intraoperative cryotherapy to various intraoperative pain management modalities such as epidural analgesia, and three studies compared a combination treatment of epidural analgesia and intraoperative cryoanalgesia with epidural analgesia alone. The majority of these studies utilized the Spembly Cryoprobe (Spembly Medical Ltd., Andover, UK) ($n = 10$), followed by the Erbokryo probe (Erbe Elektromedizin Marietta, GA) ($n = 2$), and K300 Cryosurgery Equipment (Beijing Kooland Technology, Co., Ltd., Beijing, China) ($n = 2$) (►**Fig. 2**).

All studies treated various intercostal nerves between the third and ninth intercostal spaces. The number of intercostal nerves treated in each thoracotomy procedure varied greatly across the included studies, with some studies only treating the intercostal nerve at the level of the incision plus one intercostal nerve above and below, while other studies treated up to three intercostal nerves above and below the level of the incision (►**Table 1**). All studies reported direct visualization of the thoracic wall upon cryoablation treatment. In terms of study protocols, there was a great deal of variability in application of intraoperative cryotherapy in terms of both the number of cycles as well as the duration of those cycles. More specifically, some studies utilized a single cycle with others utilizing up to three cycles, while durations ranged from 30 to 120 seconds per cycle. In each of the included studies, the probe temperature was set to a value ranging from −80 to −20°C (►**Table 2**).

When assessing studies comparing intraoperative cryotherapy with pharmaceutical analgesia modalities, the majority of studies demonstrated a significant reduction in acute postoperative pain using a 10-point visual analog scale (VAS) (5/9 studies, $p < 0.05$) (►**Table 1**).

Of the studies that compared intraoperative cryotherapy to pharmaceutical analgesia modalities, six assessed reductions in postoperative opioid use with four of six studies demonstrating a significant reduction in postoperative opioid use ($p < 0.05$). A total of seven of nine studies noted a decrease in pain or postoperative opioid use. Of the three studies that assessed the effect of cryotherapy compared to pharmaceutical analgesia on postoperative spirometry, two studies demonstrated increased forced vital capacity and one study demonstrated an increase in forced expiratory volume ($p < 0.05$)(►**Table 3**).

Of the nine studies that compared intraoperative intercostal nerve cryotherapy to pharmaceutical analgesia, eight specified the number of nerves treated. The number of nerves treated ranged from three to six nerves. Two of the studies treated three nerves, four studies treated four nerves, and two studies treated five or six nerves. Across these eight

Table 1 Number of intercostal nerves treated intraoperatively

	Authors	Number of nerves treated	Location of nerves treated
1	Glynn et al.[57]	3	1 cranial, 1 caudal
2	Katz et al.[29]	5 or 6	1 at the incision level, 2 cranial, 2 or 3 caudal
3	Keenan et al.[58]	5 to 6	2 above, 2 below, 1 at the interspace, 1 at the drainage site (if not already included)
4	Roxburgh et al.[33]	5 or 6	5 or 6 centered around incision
5	Müller et al.[41]	4	1 at the incision level, 1 cranial, 2 caudal
6	Miguel and Hubbell[31]	3	1 at the incision level, 1 cranial, 1 caudal
7	Brichon et al.[32]	5	5 centered around incision
8	Ju et al.[30]	3	1 at the incision level, 1 cranial, 1 caudal
9	Yang et al.[34]	3	1 at the incision level, 1 cranial, 1 caudal
10	Mustola et al.[35]	3	1 at the incision level, 1 cranial, 1 caudal
11	Momenzadeh et al.[59]	3	1 at the incision level, 1 cranial, 1 caudal
12	Moorjani et al.[60]	4	1 at the incision level, 1 cranial, 2 caudal
13	Ba et al.[38]	4	1 at the incision level, 1 cranial, 2 caudal
14	Pastor et al.[53]	6	3 cranial, 3 caudal (including at the incision)
15	Gwak et al.[37]	3	1 at the incision level, 1 cranial, 1 caudal
16	Sepsas et al.[39]	4	1 at the incision level, 1 cranial, 2 caudal

Table 2 Temperature/duration of intercostal cryoanalgesia

Author (year)	Cycles	Duration (s)	Temperature (°C)
Glynn et al.[57]	2	60	−60
Keenan et al.[58]	1	45	−60
Müller et al.[41]	1	Not specified	Not specified
Momenzadeh et al.[59]	1	90	−70
Moorjani et al.[60]	1	60	−50
Ba et al.[38]	1	90	−60
Gwak et al.[37]	1	90	−20
Sepsas et al.[39]	1	60	−40
Pastor et al.[53]	2	30	Not specified
Katz et al.[29]	2	30	−60
Ju et al.[30]	1	90	−70
Miguel and Hubbell[31]	1	30	−70
Brichon et al.[32]	1	30	−20
Roxburgh et al.[33]	1	60	−60
Yang et al.[34]	1	90	−20
Mustola et al.[35]	1	60	−70

studies, there was no association between the number of nerves treated and reduction in acute postoperative pain scores on the VAS ($p = 0.714$) or postoperative opioid use ($p = 0.400$).

Additionally, for the nine studies that compared cryotherapy to pharmaceutical analgesia, no significant association was found between the number of cycles, duration of treatment, or probe temperature utilized and reduction in postoperative pain on the VAS scale ($p = 1.000$, $p = 0.679$, $p = 0.629$). There was also no significant association found between the number of cycles or duration of treatment and postoperative opioid use ($p = 1.000$, $p = 0.272$). One study comparing cryotherapy to intraoperative administration of local anesthetic, using 3 to 5 mL of 0.5% bupivacaine per

Table 3 Outcomes of intercostal cryoanalgesia

	Cohorts	Author (year)	Difference in acute postoperative pain on the VAS pain score ($p < 0.05$)	Decreased postoperative opioid usage ($p < 0.05$)	Improved spirometry ($p < 0.05$)	Reduction in complications ($p < 0.05$)
Cryoanalgesia compared with no intraoperative analgesia						
1	Cryoanalgesia vs. no intraoperative analgesia	Glynn et al.[57]	Not significant	Decreased opiates	–	No significant difference
2	Rectal indomethacin and cryoanalgesia vs. rectal indomethacin	Keenan et al.[58]	Reduced pain	–	–	No significant difference
3	Cryoanalgesia vs. no intraoperative analgesia	Müller et al.[41]	Not significant	Not significant difference	Not significant difference	Some patients treated with cryoanalgesia noted neuralgias at 6 wk postoperatively. *Statistical analysis was not performed*
4	Cryoanalgesia vs. no intraoperative analgesia	Momenzadeh et al.[59]	Reduced pain	–	–	Hypoesthesia less than 3 mo in some patients treated with cryotherapy
5	Cryoanalgesia vs. no intraoperative analgesia	Moorjani et al.[60]	Not significant	Decreased opiates	Increased FEV, FVC	Hypoesthesia less than 6 mo in some patients treated with cryotherapy
6	Cryoanalgesia vs. parecoxib	Ba et al.[38]	Reduced pain	Decreased opiates	–	Significantly reduced complications
7	IV continuous analgesia and cryoanalgesia vs. IV continuous analgesia	Gwak et al.[37]	Not significant	Not significant difference	Increased FVC	No significant difference
8	IV continuous analgesia and cryoanalgesia vs. IV continuous analgesia	Sepsas et al.[39]	Reduced pain	Decreased opiates	Increased FEV, FVC at 30 d postoperatively	Significantly reduced complications
9	Cryoanalgesia vs. no intraoperative analgesia	Pastor et al.[53]	Reduced pain	–	–	No significant difference
Cryoanalgesia compared with local anesthetic						
10	Cryoanalgesia vs. local anesthetic	Katz et al.[29]	Reduced pain	–	–	No significant difference
Cryoanalgesia compared with different pain management modalities						
11	Cryoanalgesia vs. epidural anesthesia	Ju et al.[30]	Not significant	Not significant difference	–	No significant difference
12	Postoperative analgesia, epidural analgesia, cryoanalgesia	Miguel and Hubbell [31]	Not significant	Not significant difference	No significant difference between groups	No significant difference
13	Postoperative analgesia, epidural analgesia, cryoanalgesia	Brichon et al.[32]	Not significant	No significant difference between epidural and cryoanalgesia groups	–	No significant difference

Journal of Reconstructive Microsurgery Vol. 40 No. 4/2024

Table 3 *(Continued)*

	Cohorts	Author (year)	Difference in acute postoperative pain on the VAS pain score ($p < 0.05$)	Decreased postoperative opioid usage ($p < 0.05$)	Improved spirometry ($p < 0.05$)	Reduction in complications ($p < 0.05$)
Cryoanalgesia and epidural compared with epidural alone						
14	Epidural anesthesia and cryoanalgesia vs. epidural anesthesia	Roxburgh et al.[33]	Not significant	Not significant difference	–	Increased neuropathic pain at 6 wk in the combination treatment group. *Statistical analysis was not performed*
15	Epidural anesthesia and cryoanalgesia vs. epidural anesthesia	Yang et al.[34]	Reduced pain	Decreased opiates	Increased FVC, normal FEV	Increased pain at rest during the third postoperative month in the combination treatment group
16	Epidural anesthesia and cryoanalgesia vs. epidural anesthesia	Mustola et al.[35]	Increased pain	Not significant difference	–	Significant allodynia and hypoesthesia up until 6 mo postoperatively

Abbreviations: FEV, forced expiratory volume; FVC, forced vital capacity; IV, intravenous; VAS, visual analog scale.

nerve, demonstrated a significant reduction in postoperative pain when treated with cryotherapy ($p < 0.05$).[29]

All three studies that compared cryotherapy to epidural analgesia demonstrated no significant difference in postoperative pain or in postoperative opioid analgesic use ($p < 0.05$)[30–35] (►**Table 3**). All three studies found that in patients treated with both cryotherapy and epidural analgesia, at 6 weeks to 3 months postoperatively, there was a significantly increased incidence of neuropathic pain and numbness at the incision site compared with the cohort treated with epidural analgesia alone.[33–35] This pain was reported to have completely resolved by 6 months in all the three studies. None of the included studies demonstrated significantly increased risk of postoperative complications including pruritus, nausea and vomiting, atelectasis, pneumonia, and pleural effusion with the introduction of cryoanalgesia to control regimens of either no intraoperative analgesia, local anesthetic, or epidural analgesia.[34,37]

In cohorts comparing cryoanalgesia to postoperative opioids alone, Ba et al demonstrated significantly decreased risk of pneumonia, atelectasis, and intestinal disturbance in those patients treated with cryoanalgesia.[38] The study by Sepsas et al demonstrated significantly decreased nausea, numbness, epigastric distension, and back pain at days 5, 6, 7, 14, 30, and 60 following surgeries in patients treated with cryoanalgesia versus only postoperative opioids.[39] No significant differences in postoperative pulmonary function tests, pulmonary physiotherapy compliance, or time to mobilization were observed comparing cryotherapy to pharmaceutical analgesia alone. No studies reported emergence of chronic pain conditions, defined as those lasting longer than 6 months, such as neuroma or neuropathy, in their cryoanalgesia cohorts.

Pudendal Nerve

With regard to the pudendal nerve, review of the publicly available Medicare standard analytical files reveals that the number of cryoanalgesia cases performed since 2018 ($n \approx$ 1,500) has increased by nearly an order of magnitude through 2022 ($n \approx 11{,}000$), determined by combining the tracking code for cryotherapy devices with Current Procedural Terminology codes that reflect nerve targets.[40] The pudendal nerve is an illustrative target beyond the intercostal nerves because it requires imaging guidance and reflects the proposed mechanism of relief via Sunderland II injury. Two structured studies are found in the literature, both prospective reviews of structured clinical practices.[8,9] The first article describes 11 patients treated percutaneously with computed tomography (CT) guidance who presented with symptoms of pudendal neuralgia and underwent CT-guided diagnostic block for confirmation (►**Fig. 3**). All patients were administered the Brief Pain Inventory as part of their clinical follow-up and records existed for clinic visits to a mean of 204 days postprocedure. The distal pudendal nerve was targeted. The technique employed a Boston Scientific cryoprobe with an alternating freeze-thaw protocol that is tailored to the individual nerve target. In the case of pudendal nerves, the typical protocol involved an 8-

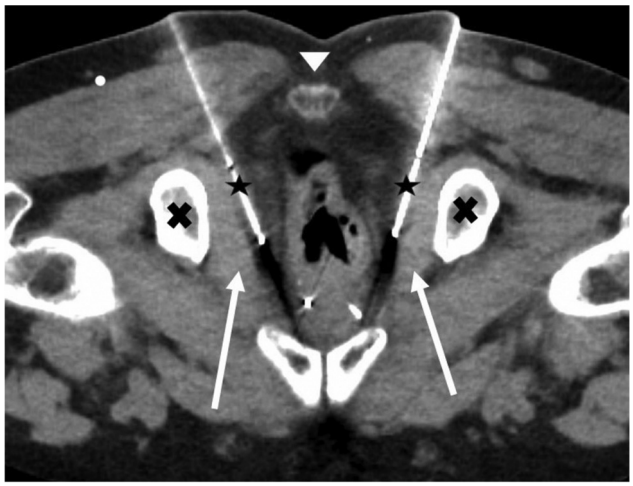

Fig. 3 Single axial intraprocedural computed tomography image demonstrating placement of 17-gauge cryoprobes (stars) bilaterally in the pudendal canal superficial and medial to the obturator internus muscles (arrows) at the level of the ischium ("X") and coccyx (arrowhead).

minute freeze to −20 to −40°C, followed by a 3-minute passive thaw, a second 3-minute freeze, and a final 3-minute passive thaw. Patients reported an overall decrease in average pain according to VAS of 4.5, with no procedure-related complications or adverse events.

The second population of patients suffered from intractable pain related to pelvic neoplasm. Patients were admitted for pain control, and interventional radiology was consulted at some point during their stay. Each patient underwent bilateral pudendal nerve cryoanalgesia procedures. There were no procedure-related complications or adverse events and the cohort mean values of VAS pain scores decreased by 5.20. Of note, the mean time from procedure to discharge for this cohort was 2.3 days, suggesting potential impact on length of stay worthy of further investigation. None of the patients in either study required a repeat procedure.

Discussion

Analysis of the included studies suggests that intraoperative cryoanalgesia may allow for significantly lower dosage and duration of postoperative opioid analgesia in addition to significantly decreased acute postoperative pain scores in patients undergoing thoracotomy. This finding is in line with the recent review study performed by Park et al, which also demonstrated that cryoanalgesia is associated with better pain relief and opioid reduction than intercostal nerve blocks but not superior to epidural analgesia.[6] The premise of decreased need for opioid analgesia even after discharge is particularly exciting given the advent of increasingly strict prescribing regulations in response to the opioid crisis.[41]

Across the included studies comparing the efficacy of cryotherapy to regimens of conventional pharmaceuticals, there was a great deal of variability among cryoanalgesia protocols. In these studies, the number of cycles utilized varied from one to three cycles, the length of the cycles varied from 30 to 90 seconds, and the probe temperature varied from −70 to −20°C; however, there was no significant association between any of these variables and either acute postoperative pain or postoperative opioid analgesia usage. Thus, despite the wide variance in probe temperature, cycle duration, and number of cycles, no specific intraoperative cryotherapy protocol appears to be superior to others when compared against epidural analgesia or pharmaceutical regimens alone (►**Table 2**).

The fact that all included studies that assessed a combined protocol of cryotherapy with epidural analgesia found a significant increase in temporary neuropathic pain appearing at 6 weeks to 3 months postoperatively, and resolving by 6 months, requires further consideration.[33–35] This observed pain may be attributable to the pain associated with the neural regeneration and should be explained to the patient during preoperative consent.

Percutaneous cryoanalgesia as applied to pudendal nerves has been performed under CT guidance with increasing frequency during recent years, by our interventional radiology colleagues. Paired pudendal nerves are primarily responsible for sensory activity in the perineum, pelvic musculature, and external genitalia with only minimal motor function to the same areas.[42] Various sources of pain can arise related to pudendal nerve damage or transmitted via the pudendal nerves.[8,9,11] Operators may safely target cryoanalgesia of the pudendal nerve with existing equipment either at bedside using imaging guidance or intraoperatively (►**Fig. 3**). When the temperature is lowered throughout the nerve to −20°C or below (but not colder than −100°C), signal transduction is interrupted and Wallerian degeneration is induced, followed by predictable axonal regeneration over a period of 6 to 8 months.[12,43,44] Patients with nonneoplastic pathology are selected for improved relative success using diagnostic injections prior to any cryoanalgesia procedure.[45] Patients who have undergone cryoanalgesia of the pudendal nerve consistently report decreases in pelvic pain regardless of cause.[8,9,11] Success rates when targeting the pudendal nerves for cryoanalgesia, as defined by a $\geq$ 50% improvement in pain, were 67 and 81%, respectively, in the studies described earlier.[8,9]

The finding of a transient increase in intercostal neuropathic pain may be better understood based on previous clinical and basic science investigations of cryotherapy. Notably, the observed temporary period of increased pain several weeks after treatment followed by reduction and resolution by 6 months follows a similar timeline to that demonstrated after targeted muscle reinnervation in which sensory and/or mixed nerves are transferred or coapted to motor nerve branches, to promote organized nerve growth and also to improve prosthetic control.[46,47] In terms of basic science, Willenbring et al treated a rodent model with two cryotherapy cycles lasting 30 seconds each, in which sciatic nerves were treated to −60°C.[36] In the study, rats treated with sciatic cryoneurolysis exhibited significant allodynia that persisted for more than 10 weeks after treatment. DeLeo et al utilized the same methodology in performing sciatic cryoneurolysis; however, utilized immunohistochemistry to examine the localization of cytokines and growth factors

after treatment.[48] This study found that in nerves treated with sciatic cryoneurolysis, there are increases in interleukin-1β-, tumor necrosis factor-α-, and transforming growth factor-β-like immunoreactivity. Considering the postoperative increases in the inflammatory cytokines, combined with the transient hypoesthesia and allodynia followed by return of sensation, it is likely that the nociceptive process following cryoanalgesia is multiphasic. Another point of consideration is that the accuracy and degree of the temporary nerve injury induced by the cryoprobe is paramount to a successful ablation. Specifically, too little can result in neuropraxia with worsening of underlying symptoms, while overtreatment can cause deafferentation pain.[10,49–53] This observation has spurred the ongoing development of next-generation devices with directional capability.[54–56]

Though this review focuses mainly on the open approach to intercostal cryoanalgesia, as well as the percutaneous approach to pudendal neuralgia, it is also worth noting that percutaneous intercostal cryoneurolysis for the management of postthoracotomy syndrome remains one of the most common applications of cryoanalgesia.[54–56] That being said, many other indications outside of the scope of this discussion, such as fibrothorax, trauma, and herpetic neuralgia have also been reported under a variety of imaging guidance modalities percutaneously.[11]

Conclusion

Intraoperative cryoanalgesia represents a relatively safe and effective means of intra- and postoperative analgesia following thoracotomy. An awareness of the increased operating time required to complete this procedure via careful patient selection is paramount. Taken as a whole, the studies included in this review suggest that cryoanalgesia is a promising pain management modality in addition to pharmaceutical pain management and local anesthetics. However, there remains an increased risk of transient neuropathic pain and incision site numbness in patients treated with a combination of epidural analgesia and cryotherapy. Further prospective investigations with more standardized study designs to better characterize and guide the application of intraoperative cryotherapy for patients undergoing thoracotomy would be beneficial. Additionally, as the body of literature regarding intraoperative and percutaneous cryotherapy continues to expand, a future aim of our group will be to describe a new stratified care pathway for these patient populations, along with the integration of cryoanalgesia with surgical ablative options.

Conflict of Interest
None declared.

References

1 Gage AA, Baust JG. Cryosurgery for tumors - a clinical overview. Technol Cancer Res Treat 2004;3(02):187–199
2 Cooper SM, Dawber RP. The history of cryosurgery. J R Soc Med 2001;94(04):196–201
3 Graves CE, Moyer J, Zobel MJ, et al. Intraoperative intercostal nerve cryoablation during the Nuss procedure reduces length of stay and opioid requirement: a randomized clinical trial. J Pediatr Surg 2019;54(11):2250–2256
4 Clemence J Jr, Malik A, Farhat L, et al. Cryoablation of intercostal nerves decreased narcotic usage after thoracic or thoracoabdominal aortic aneurysm repair. Semin Thorac Cardiovasc Surg 2020;32(03):404–412
5 Hsu M, Stevenson FF. Wallerian degeneration and recovery of motor nerves after multiple focused cold therapies. Muscle Nerve 2015;51(02):268–275
6 Park R, Coomber M, Gilron I, Shanthanna H. Cryoanalgesia for postsurgical pain relief in adults: a systematic review and meta-analysis. Ann Med Surg (Lond) 2021;69:102689
7 Harbaugh CM, Johnson KN, Kein CE, et al. Comparing outcomes with thoracic epidural and intercostal nerve cryoablation after Nuss procedure. J Surg Res 2018;231:217–223
8 Prologo JD, Lin RC, Williams R, Corn D. Percutaneous CT-guided cryoablation for the treatment of refractory pudendal neuralgia. Skeletal Radiol 2015;44(05):709–714
9 Prologo JD, Manyapu S, Bercu ZL, Mittal A, Mitchell JW. Percutaneous CT-guided cryoablation of the bilateral pudendal nerves for palliation of intractable pain related to pelvic neoplasms. Am J Hosp Palliat Care 2020;37(08):619–623
10 Filippiadis D, Efthymiou E, Tsochatzis A, Kelekis A, Prologo JD. Percutaneous cryoanalgesia for pain palliation: current status and future trends. Diagn Interv Imaging 2021;102(05):273–278
11 Sag AA, Bittman R, Prologo F, et al. Percutaneous image-guided cryoneurolysis: applications and techniques. Radiographics 2022; 42(06):1776–1794
12 Shah SB, Bremner S, Esparza M, et al. Does cryoneurolysis result in persistent motor deficits? A controlled study using a rat peroneal nerve injury model. Reg Anesth Pain Med 2020;45(04):287–292
13 Gilron I, Baron R, Jensen T. Neuropathic pain: principles of diagnosis and treatment. Mayo Clin Proc 2015;90(04):532–545
14 Trescot AM. Cryoanalgesia in interventional pain management. Pain Physician 2003;6(03):345–360
15 Seddon HJ, Medawar PB, Smith H. Rate of regeneration of peripheral nerves in man. J Physiol 1943;102(02):191–215
16 Filler AG, Maravilla KR, Tsuruda JS. MR neurography and muscle MR imaging for image diagnosis of disorders affecting the peripheral nerves and musculature. Neurol Clin 2004;22(03):643–682, vi–vii
17 Glaus SW, Johnson PJ, Mackinnon SE. Clinical strategies to enhance nerve regeneration in composite tissue allotransplantation. Hand Clin 2011;27(04):495–509, ix
18 Yan Y, Johnson PJ, Glaus SW, Hunter DA, Mackinnon SE, Tung TH. A novel model for evaluating nerve regeneration in the composite tissue transplant: the murine heterotopic limb transplant. Hand (N Y) 2011;6(03):304–312
19 Chhabra A, Ahlawat S, Belzberg A, Andreseik G. Peripheral nerve injury grading simplified on MR neurography: as referenced to Seddon and Sunderland classifications. Indian J Radiol Imaging 2014;24(03):217–224
20 Sunderland S. A classification of peripheral nerve injuries producing loss of function. Brain 1951;74(04):491–516
21 Evans PJ, Lloyd JW, Green CJ. Cryoanalgesia: the response to alterations in freeze cycle and temperature. Br J Anaesth 1981; 53(11):1121–1127
22 Keller BA, Kabagambe SK, Becker JC, et al. Intercostal nerve cryoablation versus thoracic epidural catheters for postoperative analgesia following pectus excavatum repair: preliminary outcomes in twenty-six cryoablation patients. J Pediatr Surg 2016;51 (12):2033–2038
23 Maxwell DJ, Christie WM, Short AD, Storm-Mathisen J, Ottersen OP. Central boutons of glomeruli in the spinal cord of the cat are enriched with L-glutamate-like immunoreactivity. Neuroscience 1990;36(01):83–104
24 Green CR, de Rosayro AM, Tait AR. The role of cryoanalgesia for chronic thoracic pain: results of a long-term follow up. J Natl Med Assoc 2002;94(08):716–720

25 Devers A, Galer BS. Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study. Clin J Pain 2000;16(03):205–208
26 Doi K, Nikai T, Sakura S, Saito Y. Intercostal nerve block with 5% tetracaine for chronic pain syndromes. J Clin Anesth 2002;14(01): 39–41
27 Stolker RJ, Vervest AC, Groen GJ. The treatment of chronic thoracic segmental pain by radiofrequency percutaneous partial rhizotomy. J Neurosurg 1994;80(06):986–992
28 Williams EH, Williams CG, Rosson GD, Heitmiller RF, Dellon AL. Neurectomy for treatment of intercostal neuralgia. Ann Thorac Surg 2008;85(05):1766–1770
29 Katz J, Nelson W, Forest R, Bruce DL. Cryoanalgesia for postthoracotomy pain. Lancet 1980;1(8167):512–513
30 Ju H, Feng Y, Yang BX, Wang J. Comparison of epidural analgesia and intercostal nerve cryoanalgesia for post-thoracotomy pain control. Eur J Pain 2008;12(03):378–384
31 Miguel R, Hubbell D. Pain management and spirometry following thoracotomy: a prospective, randomized study of four techniques. J Cardiothorac Vasc Anesth 1993;7(05):529–534
32 Brichon PY, Pison C, Chaffanjon P, et al. Comparison of epidural analgesia and cryoanalgesia in thoracic surgery. Eur J Cardiothorac Surg 1994;8(09):482–486
33 Roxburgh JC, Markland CG, Ross BA, Kerr WF. Role of cryoanalgesia in the control of pain after thoracotomy. Thorax 1987;42(04): 292–295
34 Yang MK, Cho CH, Kim YC. The effects of cryoanalgesia combined with thoracic epidural analgesia in patients undergoing thoracotomy. Anaesthesia 2004;59(11):1073–1077
35 Mustola ST, Lempinen J, Saimanen E, Vilkko P. Efficacy of thoracic epidural analgesia with or without intercostal nerve cryoanalgesia for postthoracotomy pain. Ann Thorac Surg 2011;91(03): 869–873
36 Willenbring S, DeLeo JA, Coombs DW. Differential behavioral outcomes in the sciatic cryoneurolysis model of neuropathic pain in rats. Pain 1994;58(02):135–140
37 Gwak MS, Yang M, Hahm TS, Cho HS, Cho CH, Song JG. Effect of cryoanalgesia combined with intravenous continuous analgesia in thoracotomy patients. J Korean Med Sci 2004;19(01):74–78
38 Ba YF, Li XD, Zhang X, et al. Comparison of the analgesic effects of cryoanalgesia vs. parecoxib for lung cancer patients after lobectomy. Surg Today 2015;45(10):1250–1254
39 Sepsas E, Misthos P, Anagnostopulu M, Toparlaki O, Voyagis G, Kakaris S. The role of intercostal cryoanalgesia in post-thoracotomy analgesia. Interact Cardiovasc Thorac Surg 2013;16(06):814–818
40 Theisen K, Jacobs B, Macleod L, Davies B. The United States opioid epidemic: a review of the surgeon's contribution to it and health policy initiatives. BJU Int 2018;122(05):754–759
41 Müller LC, Salzer GM, Ransmayr G, Neiss A. Intraoperative cryoanalgesia for postthoracotomy pain relief. Ann Thorac Surg 1989;48(01):15–18
42 Schraffordt SE, Tjandra JJ, Eizenberg N, Dwyer PL. Anatomy of the pudendal nerve and its terminal branches: a cadaver study. ANZ J Surg 2004;74(1-2):23–26
43 Finneran Iv JJ, Ilfeld BM. Percutaneous cryoneurolysis for acute pain management: current status and future prospects. Expert Rev Med Devices 2021;18(06):533–543
44 Prologo JD, Johnson C, Hawkins CM, et al. Natural history of mixed and motor nerve cryoablation in humans-a cohort analysis. J Vasc Interv Radiol 2020;31(06):912–916.e1
45 Prologo JD, Edalat F, Moussa M. Interventional cryoneurolysis: an illustrative approach. Tech Vasc Interv Radiol 2020;23(04): 100698
46 Dumanian GA, Potter BK, Mioton LM, et al. Targeted muscle reinnervation treats neuroma and phantom pain in major limb amputees: a randomized clinical trial. Ann Surg 2019;270(02): 238–246
47 Kuiken TA, Dumanian GA, Lipschutz RD, Miller LA, Stubblefield KA. The use of targeted muscle reinnervation for improved myoelectric prosthesis control in a bilateral shoulder disarticulation amputee. Prosthet Orthot Int 2004;28(03):245–253
48 DeLeo JA, Colburn RW, Rickman AJ. Cytokine and growth factor immunohistochemical spinal profiles in two animal models of mononeuropathy. Brain Res 1997;759(01):50–57
49 Said ET, Marsh-Armstrong BP, Fischer SJ, et al. Relative effects of various factors on ice ball formation and ablation zone size during ultrasound-guided percutaneous cryoneurolysis: a laboratory investigation to inform clinical practice and future research. Pain Ther 2023;12(03):771–783
50 Ilfeld BM, Smith CR, Turan A, et al; PAINfRE Investigators. Ultrasound-guided percutaneous cryoneurolysis to treat chronic postamputation phantom limb pain: a multicenter randomized controlled trial. Anesthesiology 2023;138(01):82–97
51 Bittman RW, Behbahani K, Gonzalez F, Prologo JD. Interventional cryoneurolysis: what is the same, what is different, what is new? Semin Intervent Radiol 2019;36(05):374–380
52 Gabriel RA, Finneran JJ, Asokan D, Trescot AM, Sandhu NS, Ilfeld BM. Ultrasound-guided percutaneous cryoneurolysis for acute pain management: a case report. A A Case Rep 2017;9(05): 129–132
53 Pastor J, Morales P, Cases E, et al. Evaluation of intercostal cryoanalgesia versus conventional analgesia in postthoracotomy pain. Respiration 1996;63(04):241–245
54 Huang J, Delijani K, El Khudari H, Gunn AJ. Intercostal cryoneurolysis. Semin Intervent Radiol 2022;39(02):167–171
55 Hashemi M, Mahmood SMJ, Fernandez J, Oswald J. Cryoneurolysis of intercostal nerve for rib trauma and intercostal neuralgia in the emergency department: a multidisciplinary approach. J Emerg Med 2022;63(03):376–381
56 Delijani K, Wei B, Huang J. Percutaneous intercostal cryoneurolysis in the management of symptomatic fibrothorax. J Vasc Interv Radiol 2023;34(02):305–307
57 Glynn CJ, Lloyd JW, Barnard JD. Cryoanalgesia in the management of pain after thoracotomy. Thorax 1980;35(05):325–327
58 Keenan DJ, Cave K, Langdon L, Lea RE. Comparative trial of rectal indomethacin and cryoanalgesia for control of early postthoracotomy pain. BMJ 1983;287(6402):1335–1337
59 Momenzadeh S, Elyasi H, Valaie N, et al. Effect of cryoanalgesia on post-thoracotomy pain. Acta Med Iran 2011;49(04):241–245
60 Moorjani N, Zhao F, Tian Y, Liang C, Kaluba J, Maiwand MO. Effects of cryoanalgesia on post-thoracotomy pain and on the structure of intercostal nerves: A human prospective randomized trial and a histological study. European Journal of Cardio-Thoracic Surgery 2001;20(03):502–507