Cryoneurolysis

Dossier

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The iovera° System: Clinical Evidence of Effective Pain Management via Cryoanalgesia

Approved by the FDA in 2009, the iovera° system is a cryoneurolytic device used to destroy tissue during surgical procedures by applying freezing cold. It can also be used to produce lesions in peripheral nervous tissue by the application of cold to the selected site for the blocking of pain. It is also indicated for the relief of pain and symptoms associated with osteoarthritis of the knee for up to 90 days. The iovera° system is not indicated for treatment of central nervous system tissue.[1]

iovera° is a handheld device which applies freezing temperatures to targeted nerve sites. The iovera° handheld device delivers a controlled amount of liquid nitrous oxide to closed-end probes, which is then applied to specific target nerves. As this highly pressurized liquid travels from the handpiece to the probe, it undergoes a phase change and becomes very cold by drawing in heat energy from the surrounding tissue, forming an ice ball at the targeted nerve. The gaseous nitrous oxide returns to the handpiece to be expelled; leaving nothing behind in the body.

Cryoneurolysis for Peripheral Sensory Nerve Blockade

Cryoneurolysis (also referred to as cryoanalgesia, cryotherapy, and cryoneuroablation) is a form of thermal neurolysis, specifically the application of cold temperature to peripheral sensory nerves. This freezes the nerves at or near the source of pain which results in a nerve block. Similar to the effect of a local anesthetic, cryoneurolysis interrupts signal conduction and/or inflicts injury to the nerve; depending on the temperature applied (Table 1).[2,3]

Table 1. Sunderland Nerve Injury Classification[4-6]

Description of Injury	Temperature	Coolants
REVERSIBLE		
1st Degree Neuropraxia – Interruption of conduction; short recovery time	+10 to -20°C	Ice water Freon
2nd Degree **Axonotmesis – Loss of continuity of the axon; preservation of the endo-, peri-, and epineurium; Wallerian degeneration**	**-20 to -100°C** ***Coldest iovera° temperature -88°C***	**Carbon dioxide** ***Nitrous oxide***
NON-REVERSIBLE		
3rd/4th Degree Neurotmesis – Loss of axon continuity; endoneurium damage; perineurium damage; (4th degree); epineurial sheath may be intact; Wallerian degeneration	-140°C and colder	Nitrogen, Argon *Not possible with iovera°*
5th Degree Transection (Severe Neurotmesis) – Gross loss of continuity	*NA*	*Not possible with iovera°*

Mechanism of Cryoanalgesia

In 1976, Lloyd et al. coined the term "cryoanalgesia" in their study published in the Lancet describing outcomes of 64 patients treated with a cryoprobe cooled with nitrous oxide for a variety of painful conditions. He proposed that this technique was more advantageous to other methods of peripheral nerve destruction, e.g. chemical neurolysis, or surgical lesions, because it is not followed by neuritis or neuralgia.[7]

Similar to the probe used by Llyod, the iovera° system uses liquid nitrous oxide to apply freezing temperatures which reaches as low as -88°C to peripheral sensory nerves, causing a second-degree nerve injury which results in Wallerian degeneration.[4,5,8] In Wallerian degeneration, the nerve's axon and myelin sheath degenerate, resulting in a blockade of nerve signals lasting from weeks to months.[9,10] Because the integrity of the endoneurium, perineurium, and epineurium remain, the nerve regenerates for complete restoration of function.[9,10] Pain is relieved as the treated sensory nerves cannot conduct a signal until the axon is regenerated. The nerve axon regenerates at the rate of about 1-2 mm per day, which provides a predictable indicator for restoration of nerve function.[10] Only cryoanalgesia reliably produces a second-degree nerve injury via coolants which achieve moderately freezing temperatures, such as liquid nitrous oxide.

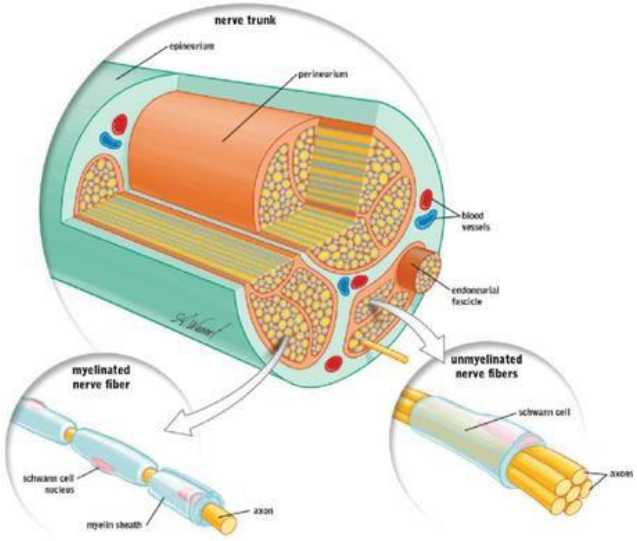


Figure 1. Key structures of nerves.[6] The nerve is an enclosed bundle of axons, which transmit electrochemical nerve impulses. In myelinated nerves, axons are surrounded by a myelin sheath composed of layers of Schwann cells which increase neuronal signaling speed. Axons are surrounded by the endoneurium, a layer of connective tissue. The axons are bundled together into groups called fascicles. Each fascicle is wrapped in connective tissue, the perineurium. The entire nerve is wrapped in a dense layer of connective tissue, called the epineurium. By applying moderately freezing temperatures, the iovera° system selectively targets axons, causing Wallerian degeneration, and preserving the sheath structures of the endo-, peri- and epineurium, which allows for regeneration of axons within existing nerve sheaths.

Comparison of Nerve Treatments

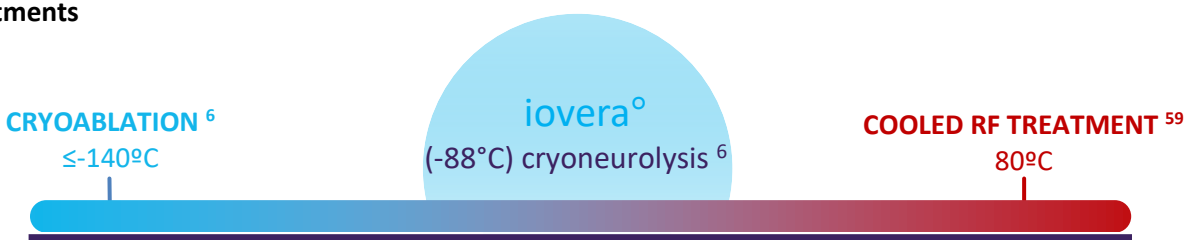
Cryoanalgesia with iovera° (cryoneurolysis) uses liquid nitrous oxide to reach -88°C at peripheral nerves, causing Wallerian degeneration and temporarily blocking nerve signals from weeks to months.[4-6, 8-10] The effect on the nerve is temporary, providing pain relief until the nerve regenerates and function is restored. Cryoablation uses extreme cold, below -140°C, but causes irreversible nerve degeneration and destruction of nearby tissues.[57, 58] Cooled or conventional RF uses heat, around 80°C, to ablate the nerve structure, but risks neuroma formation, neuritis, and injury to nearby tissue and vessels (Figure 2).[57, 59]

The advantages of cryoanalgesia via a cryoprobe over hyperthermal modalities (neurolysis via high heat e.g. radiofrequency ablation), are increased visibility of ice ball on imaging, and less damage to tissue architecture and adjacent tissues.[3,11] Radiofrequency ablation (including "cooled" radiofrequency), which has a different mechanism of action, produces a third- or -fourth degree nerve injury.[12]

Rationale for Use: Professional Guidelines

In use for over 50 years, cryoanalgesia has a well-documented mechanism of action and substantial and growing body of literature demonstrating clinically meaningful pain relief, as well as a strong safety profile, particularly when applying freezing temperatures via a nitrous oxide coolant. It has been recommended by professional organizations including American Society of Regional Anesthesia and Pain Medicine, the American Society of Anesthesiologists, and the US Department of Health and Human Services as a viable treatment for long term pain (Table 2).[13-15]

Figure 2. Comparison of Nerve Treatments



	CRYOABLATION [57, 58]	iovera° CRYONEUROLYSIS [6]	COOLED/CONVENTIONAL RF [57, 59]
Conversational synonyms	Cryosurgery	Cryoanalgesia	RF ablation
Clinical application	Tumor destruction	Pain relief	Pain relief
Mechanism of action	Process that uses extreme cold to permanently destroy nerves or abnormal tissues	Treatment that temporarily blocks nerve conduction along peripheral nerve pathways	Heat-based ablation
Duration of effect	Permanent	Temporary	Temporary
Temperature	≤-140°C	-88°C	80°C
Safety	Complete destruction of nearby tissues	Risk of local bruising; no effect on nearby tissues	Potential damage to nearby tissues and blood vessels

Table 2. Cryoanalgesia in Professional Guidelines

Year	Authority	Recommendation
2002	US Veterans Affairs (VA)/ Department of Defense (DoD)[13]	Recommends cryoneurolysis for post-thoracotomy pain: "more prolonged relief can be obtained by performing cryoanalgesic blocks of the intercostal nerves." (Grade IB recommendation)[13] *Note: This guideline has been retired and updated via the 2019 HHS*
2010	American Society of Regional Anesthesia and Pain Medicine (ASRA), and American Society of Anesthesiologists (ASA)[14]	"Cryoablation may be used in the care of selected patients (e.g., postthoracotomy pain syndrome, low back pain [medial branch], and peripheral nerve pain)." Noting "studies with observational findings for cryoablation report pain relief for assessment periods ranging from 1 to 12 months among patients with lumbar facet joint pain, postthoracotomy neuralgia, or peripheral nerve pain" (Category B2 evidence).[14]
2019	US Department of Health and Human Services (HHS)[15]	Pain Management Best Practices Inter-Agency Task Force recognizes cryoanalgesia as "a specialized interventional pain management technique" that "is indicated for numerous persistent and intractable painful conditions, including paroxysmal trigeminal neuralgia, chest wall pain, phantom limb pain, neuroma, peripheral neuropathy, knee osteoarthritis, and neuropathic pain caused by herpes zoster." [15]
2021	American Academy of Orthopaedic Surgeons (AAOS)[17]	"Denervation therapy may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee…One high quality study (Radnovich et al. 2017) specifically evaluated the efficacy of cryoneurolysis to placebo control in patients with knee OA. It was found that the group receiving cryoneurolysis had improved total WOMAC, WOMAC stiffness, WOMAC pain, WOMAC physical function, and in VAS pain compared to placebo control group."

Clinical Evidence for Cryoneurolysis via Wallerian Degeneration

Knee Osteoarthritis

Study	Design	Results	Safety/Tolerability
Radnovich et al. (2017)[16] N=180	Randomized, double-blind, sham-controlled, multicentered trial in patients experiencing pain from mild to moderate knee osteoarthritis (OA) • Treatment group: Cryoneurolysis treatment to the infrapatellar branch of the saphenous nerve (IPBSN) • Control group: sham treatment Primary endpoint: Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain subscale score at Day 30	• Greater reduction in WOMAC pain compared to sham on Days 30, 60, and 90 (P=0.0004, P=0.0176, P=0.0061 respectively) • Patients who reported continued effect at Day 120 also showed greater reduction in WOMAC scores at day 150.16 (-20.58 vs -14.19, P=0.0015) • Greater proportion of responders to WOMAC pain at day 30 (P=0.0015) and responders to WOMAC total at day 30 and 90 (P=0.0003, P=0.0069) • Greater change from baseline to Day 30 for WOMAC stiffness (-6.70 vs -4.38, P=0.0060) and Day 90 (-6.79 vs -4.97, P=0.0325) • Greater change from baseline to Day 30 for WOMAC physical function (-55.48 vs -34.18, P=0.0012) and Day 90 (-56.00 vs -40.11, P=0.0172) • Greater change from baseline to Day 30 for WOMAC total (-78.78 vs -48.26, P=0.0010), Day 60 (-75.75 vs -56.28, P=0.0359), and Day 90 (-80.31 vs -56.51, P=0.0108) • Greater change in VAS score from baseline to Day 30 (-40.09 vs -12.25, P=0.0073)	The most common side effects were bruising, numbness, redness, tenderness upon palpitation, and swelling

Total Knee Arthroplasty

Study	Design	Results	Safety/Tolerability

Urban et al. (2021)[18]
 	
N=267
	Retrospective chart review of patients who underwent inpatient primary Total Knee Arthroplasty (TKA)
	
	• Treatment group: Cryoanalgesia treatment to the IPBSN and anterior femoral cutaneous nerve (AFCN) 8-11 days prior to TKA (N=169)
	• Historical control group (N=98)
	
	Primary endpoint: Opioid intake in morphine milligram equivalents (MME) from hospital stay to 6 weeks after discharge
		<u>Opioid intake</u>
		• Lower opioid use during hospital stay
		  • 51% lower daily use (47 vs 97 MME, P<0.0001)
		  • 68% lower total use (104 vs 324 MME, P<0.0001)
		• Lower cumulative MME at discharge (660 vs 1154, P<0.0001)
		• Lower cumulative MME at week 2 (855 vs 1312, P<0.0001)
		• Lower cumulative MME at week 6 (894 vs 1406, P<0.0001)
		<u>Other endpoints</u>
		• 22% lower mean pain score during hospital stay (P<0.0001)
		  • 62% less likely to have pain score ≥4 (P=0.0031)
		• 44% shorter length of stay (1.42 vs 2.52 days, P<0.0001)
		• Higher proportion of patients achieving flexion ≥90° (165 vs 78, P<0.0001) and extension ≤5° (164 vs 77, P<0.0001) at discharge
		• Greater adjusted mean extension scores (2.11 vs 4.14, P<0.0001) and higher proportion of patients achieving extension ≤2° (141 vs 67, P=0.0094) at week 6
			Dysesthesia – consistent with mechanism of cryoanalgesia

Plessl et al. (2020)[19]
 	
N=323
	Retrospective chart review of patients who underwent primary TKA, comparing cryoneurolysis as part of rapid recovery protocol (RRP) to standard recovery protocol (SRP)
	
	• RRP group: Cryoanalgesia treatment to the IPBSN and AFCN 7 days prior to TKA; multimodal pain management (N=194)
	• SRP group (N=129)
	
	Endpoints included knee range of motion (ROM): flexion ≥120° and having a flexion contracture ≥10°. Flexion contracture ≥10° is associated with higher pain and lower function and satisfaction scores. Other endpoints included length of stay.
		<u>Range of motion</u>
		• RRP patients achieved greater flexion at:
		  • 2 weeks (96.3° vs 92.9°, P=0.008)
		  • 6 weeks (108.5 vs 104.7, P=0.002)
		  • 12 weeks (112.5 vs 108.5, P=0.003)
		• Higher probability of attaining flexion ≥120° at 6 and 12 weeks (P<0.05)
		• Less severe flexion contracture at 2, 6, and 12 weeks (P<0.0001, P=0.0004, P=0.0006)
		• Lower probability of flexion contracture ≥10° at 2, 6, and 12 weeks (P=0.001, P=0.035, P=0.044)
		<u>Length of stay</u>
		• 68% shorter length of stay (0.8 vs 2.5 days, P<0.0001)
			N/A

Mihalko et al. (2019)[20]
 	
N=124
	Prospective, randomized controlled trial in patients who underwent primary total knee arthroplasty
	
	• Treatment group: Cryoanalgesia treatment to the IPBSN and AFCN 3-7 days prior to TKA (N=62)
	• Control group (N=62)
	
	Primary endpoint: cumulative opioid consumption from discharge to week 6.
		<u>Per-protocol analysis, opioid</u>
		• Patients treated with cryoanalgesia required significantly fewer daily opioids at: 72 h, 6 weeks, and 12 weeks (P=0.0389, P=0.0186, and P=0.0234 respectively)
		• More opioid-free patients at 6 weeks (93% vs 81%, P=0.0059)
		
		<u>Per-protocol analysis, symptoms</u>
		• Greater improvement in KOOS Jr scores at all timepoints
		  • 72 h (-0.80 vs -0.140, P<0.0001)
		  • 2 weeks (2.30 vs 1.00, P<0.0001)
		  • 6 weeks (9.70 vs 7.70, P<0.0001)
		  • 12 weeks (16.00 vs 14.10, P<0.0001)
		• Greater change in pain AUC baseline-current pain at 72 h and 2 weeks (P=0.0023, P=0.0074 respectively)
		• Greater change in pain AUC baseline-past week at 12 weeks (P=0.0256)
		
		<u>Intention to treat analysis</u>
		• Did not meet primary endpoint
			AE rate similar across groups; most surgery related and mild or moderate severity
			
			No AE's due to cryoneurolysis

Dasa et al. (2016)[21] N=100	Retrospective chart review in patients who underwent total knee arthroplasty • Treatment group: Cryoanalgesia treatment to the IPBSN and AFCN 5 days prior to TKA (N=50) • Control group (N=50) Endpoints included length of stay, opioid use, and patient-reported pain and function.	• Patients in the cryoanalgesia group had a shorter length of stay; LOS ≥2 days (6.1% vs 67.3%, P<0.0001) • 45% lower cumulative opioid requirement during 12 weeks after surgery (2069.12 vs 3764.42 mg, P<0.0001) • Greater improvement in KOOS symptom scores at 6 weeks (P=0.0037) and 12 weeks (P=0.0011) • Lower pain intensity and interference via reduced PROMIS scores at 6 weeks (P<0.0001)	No complications related to cryoneurolysis Most common side effect was local bruising at the site of treatment

Bronstone et al. (2022) conducted a retrospective case series of 40 consecutive patients who underwent primary unilateral TKA receiving a multimodal analgesia regimen that consisted of preoperative cryoneurolysis; perioperative oral and intravenous analgesics, a neuraxial (spinal) and regional adductor canal block, and local infiltration of liposomal bupivacaine (Exparel); intraoperative periarticular infiltration of bupivacaine hydrochloride (Marcaine); and postoperative oral non-opioid analgesics. Two thirds (67.5%; 27/40) of patients recovered from TKA without using opioids. Whereas 100% of the experienced opioid users required opioids after TKA, only 15.6% of opioid-naïve patients required postoperative opioids. Opioid-experienced patients had a higher mean number of post-TKA opioid prescriptions (3.1 vs. 1.6) and total morphine milligram equivalent (985 vs. 265) than opioid-naïve patients. Patients who used opioids after TKA reported higher levels of pain at each time point than those who had opioid-free TKA.[22]

Foot and Ankle

Perry et al. (2022)[51]
 	
N=40
	Single center, open label trial in patients with evidence of unilateral symptomatic ankle OA pain, comparing post-cryoanalgesia treatment results with baseline.
	
	• Treatment: Cryoanalgesia treatment to superficial nerves or deep fibular nerve depending on location of pain
	
	The primary endpoint was change in Foot and Ankle Outcome Score (FAOS)-pain subscale at 12 weeks.
		<u>Compared to baseline</u>
		• Cryoanalgesia group experienced improved FAOS-pain score
		  • 12 weeks (+20.8, P<0.0001)
		  • 24 weeks (+21.7, P<0.0001)
		• Improved FAOS-quality of life score and FOAS-activities of daily living score at 12 and 24 weeks (P<0.0001)
		• Less average 7-day pain
		  • 12 weeks (3.7 vs 6.3, P<0.0001)
		  • 24 weeks (3.5 vs 6.3, P<0.0001)
		• No difference in 40-meter fast-paced walking test
			No serious AE's
			
			Most frequent AE's were index ankle arthralgia and paresthesia

Mastectomy

Ilfeld et al.* (2022)[52] N=60	Randomized controlled pilot study in patients who underwent unilateral or bilateral mastectomy • Treatment group: Cryoanalgesia treatment at the 2nd-5th intercostal nerves on the ipsilateral surgical side (N=31) • Control group: Sham treatment (N=29) The primary endpoint was the average pain on the afternoon of POD2. Participants were followed for 1 year.	<u>Pain (NRS)</u> • Lower median pain on POD2 (0 vs 3, P<0.001) • Lower median pain at each timepoint POD1-21 (P<0.001) • Lower max pain at each timepoint POD1-21 (P<0.001) and over entire first year (4 vs 7, P<0.001) • 48% of cryoanalgesia group experienced only mild pain (<4) compared with 10% of sham group in post-hoc analysis • Less phantom pain at Months 3, 6, and 12 (P<0.04), no difference on Month 1 • Less sleep difficulty or awakenings due to pain over 3 weeks <u>Opioid Use</u> • 98% less total opioids use at 3 weeks (0.3 vs 15 mg, P<0.001) • More opioid-free patients (50% vs 14%, P<0.001)	No AE's deemed related to study participation

Gabriel et al. (2019) reported outcomes of 3 patients who received preoperative ultrasound-guided percutaneous intercostal nerve cryoanalgesia post-mastectomy.[27] Patients reported an NRS pain score of 0, and no patients required supplemental opioid, through postoperative day 28. In addition, none of the patients reported insomnia or awakenings due to pain. This was in contrast to historic controls who reported sleep disturbances, as well as pain, and opioid consumption, particularly after continuous paravertebral blocks were removed.[27]

Occipital Neuralgia

Grigsby et al. (2021)[55] N=26	Prospective, non-randomized, interventional study in patients who received cryoanalgesia for the treatment of occipital neuralgia. • Treatment: Cryoanalgesia treatment administered in a linear fashion across the predicated nerve path of the greater occipital nerve and/or the lesser occipital nerve The primary endpoint was an improvement in Visual Analog Scale (VAS) pain at day 7 compared to baseline.	<u>Pain (VAS)</u> • Lower mean pain post-treatment (2.8 vs 6.3, P<0.0001) • Lower mean pain on Day 7 (3.8 vs 6.3, P<0.0001) • Lower mean pain on Day 30 (3.6 vs 6.3, P<0.0001) • <u>Opioid Use</u> • 98% less total opioids use at 3 weeks (0.3 vs 15 mg, P<0.001) • More opioid-free patients (50% vs 14%, P<0.001)	Vast majority noted as mild and resolved by Day 30 AE's included crusting at insertion site, redness/inflammation, Local pain, swelling, hyperpigmentation, and itching

Kim et al. (2015)[†] reported outcomes of 38 patients who received local anesthetics in addition to cryoanalgesa to the occipital nerve (ON) to treat occipital neuralgia (20 were treated for unilateral greater ON, 10 for unilateral greater and lesser ON, and 8 for bilateral greater ON) who experienced ≥50% benefit following local anesthetic injections.[44] The average improvement of pain relief with cryoanalgesia was 57.9% with an average duration of 6.1 months. The percentage (*P*=0.007) and duration of pain relief (*P*=0.0006) were significantly greater in patients reporting at least 75% relief of pain with local anesthetic injections (Group 2) versus those who experienced 50-74% relief with local anesthetic injections (Group 1). Group 2 reported an average of 70.5% pain relief for 8.1 months compared with an average of 45.2% for an average of 4.1 months in Group 1. Of the 38 treated patients, 3 (7.8%) adverse effects were seen. Two patients reported post-procedure neuritis and one was monitored for procedure-related hematoma.[44]

Stogicza et al. (2019)[†] reported on the safety of an ultrasound-guided technique to target the greater ON with cryoanalgesia.[44] The authors had performed this procedure on more than 50 patients in their clinic and reported no major complications and rare minor complications (post-procedure soreness), which resolved spontaneously in 1 to 3 weeks.[45]

Rib Fracture

Finneran et al. (2020) reported outcomes of an 80-year-old patient who was admitted to the ICU with left-sided rib fractures (4th through 8th) and deteriorating pulmonary status requiring intubation. Single-injection anesthetic-based intercostal nerve blocks and cryoanalgesia were administered, under ultrasound guidance, to each intercostal nerve associated with a fractured rib. Over the following 12 hours, the patient's opioid requirement decreased precipitously. After extubation, the patient remained in the ICU for two additional days and the pain was well-controlled without opioids.[53]

Kwater et al. (2022) reported outcomes of a polytrauma patient with sternal and multiple rib fractures. The patient received ultrasound-guided cryoanalgesia at each intercostal space associated with the fractures. The following day, the patient reported static pain (NRS) of 0 and dynamic pain of 2 with deep inspiration. 10 days after cryoanalgesia, the patient reported static pain of 0 and dynamic pain of 1-2, with continued pain relief through 30 days.[54]

Hashemi et al. (2022)† reported outcomes of a 47 year old man with a history of multiple healed left-sided rib fractures and recent left-sided rib fracture secondary to sports-related trauma. Patient presented to ED with severe left lower chest wall pain. A multilevel intercostal nerve block followed by ultrasound-guided cryoanalgesia of the same intercostal nerves was administered. At a 2 week follow up, he required no further prescription analgesia and remained completely pain free for more than 6 months post treatment and resumed athletic activities.[63]

Lumbar Facet Joint

Three prospective observational studies[23-25] and one retrospective study[26] described outcomes of cryoanalgesia for the treatment of lumbar facet joint pain. No patient reported any side effect of cryoanalgesia in any of these studies aside from an occasional incidence of local pain attributable to the procedure which resolved within a few days.

Berlocher et al. (2003)† conducted a prospective study of patients with chronic low back pain to evaluate percutaneous lumbar medial branch cryoanalgesia of the facet joints before and after the procedure (N=50). Results showed that 62% (31/50) experienced ≥50% reduction of pain after 1 year. Patients who had not undergone previous spine therapy were more likely to experience at least a 50% reduction in pain than patients who had undergone spine surgery (85% vs. 47%, $P<0.01$). [23]

Berkenmaier et al. (2007)† conducted a prospective study of patients with chronic low back pain who underwent percutaneous medial branch cryoanalgesia of the facet joints (N=46). After cryoanalgesia treatment, 72% were pain free or had major improvement of low back pain at 6 weeks and mean VAS low back pain decreased significantly from 7.7 preoperatively to 3.2 at 6 weeks, 3.3 at 3 months, 3.0 at 6 months, and 4.2 at 12 months ($P<0.0001$).[24]

Staender et al. (2005)† conducted a prospective study of 76 patients who underwent percutaneous medial branch cryoanalgesia of the facet joints and were followed for a median of 22.5 months (range 6- 43 months). The mean VAS pain score decreased from 6.7 pre-procedure to 2.9, 3.2, and 3.4 at 3 days, 3 months, and 6 months post-procedure, respectively. In 40% of patients, pain was reduced for 12 months or longer. Patients who had no prior surgical treatment of the relevant spinal segment had a significantly longer duration of pain relief than patients who had previously undergone surgery ($P<0.03$).[25]

Wolter et al. (2011)† conducted a retrospective study of 165 patients who underwent 222 cryoanalgesia procedures to treat painful lumbar facet joints. Follow-up survey data were available for 91 of the 165 patients. Of the 91 patients with follow-up data, 69 had one cryoanalgesia procedure, 18 had two procedures on different dates, and four had three procedures. The mean pain VAS score before therapy (7.7) decreased to 3.7 immediately after treatment and 4.2 at 3-month follow-up. At final follow-up (mean 1.7 years, range 6-52 months), the mean pain VAS score was 5.0. Among patients who had a second cryoanalgesia, the mean pain rating was 6.9 pre-intervention, 3.2 directly after the intervention, and 5.0 at 3 months.[26]

Thoracotomy

Thirteen RCTs have evaluated the efficacy of cryoanalgesia of the intercostal nerves for the management of post-thoracotomy pain.[28-40] Seven of 13 RCTs showed that cryoanalgesia was superior to other pain relief methods.[29,30,32,34,36-38] Studies varied in the comparator group, number of intercostal nerves treated, chest drain location, number of treatment cycles, duration of treatment, and cryoanalgesia temperature.[41]

RCTs conducted by **Mustola et al. (2011)†,[33]** and **Ju et al. (2008)†,[29]** in N=42 and N=107 respectively showed a statistically significant increase in the incidence of neuropathic pain following cryoanalgesia administered via the surgical incision in patients at 8 weeks (resolving by 6 months)[33] and at 6 months and 1 year following open thoracotomy.[29] In contrast, the majority of RCTs of cryoanalgesia via the surgical incision did not report any increased risk of persistent postoperative pain, although a few small studies did note a possible association that did not reach statistical significance.[41]

Ba et al. (2015)† conducted an RCT which compared the analgesic and adverse effects in 178 lung cancer patients awaiting large-sized lobectomy who were randomized to intercostal nerve cryoanalgesia or parecoxib.[38] During the first postoperative week, the pain scores in the cryoanalgesia group were significantly lower than those of the parecoxib group on days 1, 2, 3, and 7 (P<0.05). One month after the surgery, the cryoanalgesia group felt no apparent pain and had local numbness around the incisions, whereas the parecoxib group reported persistent pain around the incisions and in the upper abdomen, with a significant difference in pain scores (P<0.05). The cryoanalgesia group used significantly less morphine than the parecoxib group (P<0.05). Patients treated with cryoanalgesia were significantly less likely to experience postoperative complications, including pneumonia, atelectasis, intestinal disturbance, and somnolence (P<0.05 for each), than patents treated with parecoxib.[38]

Pectus Excavatum Nuss Procedure

Graves et al. (2019)† conducted a prospective RCT which compared intraoperative intercostal nerve cryoanalgesia with thoracic epidural analgesia in patients undergoing repair of pectus excavatum by the Nuss procedure (N=20; age 13 – 31 yrs).[43] Patients who received cryoanalgesia showed a median 2-day reduction in hospital stay (P=0.0001), and required significantly less opioids during their hospital stay, showing a mean decrease of 416 mg oral morphine equivalent per patient (P=0.0001). Patients consumed 52%-82% fewer milligrams on postoperative days 1-3 (P<0.01 each day) with comparable and adequate pain control. No complications were noted in the cryoanalgesia group; among patients receiving epidurals, one experienced a symptomatic pneumothorax, and another had urinary retention.[43]

Tonsillectomy

Robinson et al. (2000)† conducted a prospective double-blinded RCT in patients undergoing tonsillectomy with bipolar electrocautery, for recurrent tonsillitis. Patients were randomized to cryoanalgesia of the glossopharyngeal nerve or a control group (N=47; age 9- 36 yrs).[42] Treatment resulted in a mean pain VAS difference of 1.70 cm (95% confidence interval [CI], 0.78-2.62; *P*=0.0005) over the first 10 postoperative days, which represents a 13% to 45% relative reduction in mean VAS values. The patients treated with cryoanalgesia had significantly less time off work than the controls (10 vs. 14 days, *P*=0.007). There was no significant difference in the proportion of patients who had postoperative bleeding or in the rate of wound healing 1 month after tonsillectomy.[42]Temporomandibular Joint Pain

Sidebottom et al. (2011)† reported outcomes of patients who underwent cryoanalgesia for severe temporomandibular joint pain who had failed to respond to all forms of conventional conservative treatment and were not appropriate for simple open operation (N=17).[45] Patients were followed up to one year after treatment. There was a significant (*P*<0.0001) improvement in pain VAS from 6.8 (range 4-10) to 2.0 (range 0-7). Two patients had no change in their pain scores, and 2 had complete resolution of their pain. The mean number of pain-free months after treatment was 7 (interquartile range, 3-15). Three patients had long-term pain relief, and 12 temporary relief. Of the 17 patients treated, 2 had predictable temporary complications (numbness of the temple, partial palsy of the temporal branch of the facial nerve) after cryoanalgesia.[46]

Trigeminal Neuralgia

Nally et al. (1984)† reported outcomes of 211 patients with paroxysmal trigeminal neuralgia.[47] The report included 42 patients who were treated with open nerve cryoanalgesia and followed for 3 years. This cohort showed no return of pain in the distribution of the 54 (out of 55) nerves treated with cryoanalgesia. In 16 patients, the pain migrated from its original source 3 to 9 months after the initial treatment. [47]

Zakrzewska and Nally (1988)† reported outcomes of a series of 145 patients with paroxysmal trigeminal neuralgia who were treated with cryoanalgesia and followed from 1 month to 6 years.[48] Most patients had immediate pain relief following treatment. The mean time to recurrence of pain was 10 months. A second treatment session was required by 38% of patients due to migration of their pain to another nerve. Of the 89 patients whose infra-orbital nerve was treated, 58% were pain free at 1 year and the mean time to recurrence was 20 months. Of the 66 long buccal nerves treated, 45% were pain free at 1 year and the mean recurrence time was at 13 months. Only 4% of patients developed local infections which necessitated antibiotic treatment. Forty percent (n=58) described some form of facial pain which had no characteristics of paroxysmal trigeminal neuralgia or anesthesia dolorosa and were labelled as mild atypical facial pain.[48]

Phantom Limb Pain

Moesker et al. (2014)† reported a case series of five patients who had suffered from phantom limb pain (2 arms, 3 legs) from 3 months to 7 years before receiving cryoanalgesia.[49] The peripheral sensory nerve(s) identified as a source of pain were identified with a nerve stimulator prior to treatment. Patients were followed for a minimum of 3 months and every 6 months thereafter. Three of the five patients had excellent outcomes, with a 90-100% reduction in pain, one patient had an acceptable outcome (40% reduction in pain), and one patient had a suboptimal response (20% reduction in pain)

but was able to reduce opioid use by half. Of the three patients with an excellent outcome, one was pain free after 2.5 years, and the other two patients reported 90-95% improvement after 5 years. The two patients with an acceptable or poor response were last assessed at 5 months when both died. [49]

Peripheral Neuropathic Pain

Yoon et al. (2016)† reported outcomes in 22 patients with chronic peripheral neuropathic pain who were treated with cryoanalgesia after failure of first- and second-line therapy.[50] Three plantar neuromas and three ilioinguinal, four posterior tibial, seven saphenous, one gluteal, one sural, one geniculate, and two digital nerves were treated in the study. Mean VAS pain scores were 8.3 before the intervention and 2.3 at 1 month, 3.2 at 3 months, 4.7 at 6 months, and 5.1 at 12 months after treatment (P<0.05 versus baseline at each time point). Eleven of the 22 patients had repeat treatments within 12 months of the initial procedure. There were no complications from these procedures. [50]

Shoulder Pain

MacRae et al. (2023) reported outcomes of a patient with severe pain from bilateral glenohumeral osteoarthritis, complicated by several concurrent diagnoses leaving them ineligible for surgical intervention; pharmacological treatments were insufficient for pain management.[60] The patient received ultrasound-guided bilateral cryoanalgesia to the suprascapular nerve at the suprascapular notch. Shoulder pain and range of motion were improved in the minutes after the procedure. At 6 weeks and 7 months, the patients showed significant improvement in range of motion, function, and pain scores.[60]

Stogicza, Peng et al. (2022)† reported outcomes in four patients with histories of rotator cuff disease refractory to conservative therapy and not amenable to surgery.[56] The patients previously tried pharmacological management, physical therapy, hyaluronidase, and steroid injections without sustained benefit. The patients received ultrasound-guided cryoanalgesia to the acromial, superior, and inferior branches of the suprascapular nerve; the anterior branch of the axillary nerve; the nerve to the subscapularis; and lateral pectoral nerve. All patients experienced at least 60% pain relief and improved shoulder function and sleep at month 3. Two patients experienced sustained pain relief through month 12, one patient through month 6, while one patient (who had the most advanced disease) returned to baseline level at month 6. No supraspinatus or infraspinatus weakness was clinically evident in any of the patients.[56]

Matelich et al. (2022) reported outcomes in three patients with chronic shoulder pain. All patients had diagnostic lidocaine injections at the suprascapular nerve that resulted in pain relief. The patients received ultrasound-guided cryoanalgesia with iovera to the suprascapular nerve at the suprascapular notch. All patients experienced immediate pain relief with pain reduction to 0. Motor weakness lasted 14-18 days. Follow up phone calls showed a duration of pain relief of 3-6 months. No adverse events were observed.[61]

Pudendal Neuralgia

Hampton and Kavala (2023) reported outcomes in two patients with histories of chronic pelvic pain. Both patients received cryoanalgesia with iovera to bilateral pudendal nerves. Diagnostic nerve block with lidocaine, fluoroscopic imaging guidance, and nerve stimulation were used to indicate correct positioning.[62]

Patient A presented with a 10-year history of penile pain, burning micturition, and baseline NRS pain score of 6-8. After iovera treatment, Patient A reported 85% burning micturition pain relief and 25% distal penile pain relief for 3 months. The only side effect reported was minor inferior scrotal discomfort which shortly resolved. At 4 months, iovera treatment was repeated for returning pain, providing 80% pain relief and no adverse events.[62]

Patient B presented with a 10-year history of constant vaginal and vulvar pain radiating along the groin following rectocele repair procedure 9 years prior. After iovera treatment, Patient B reported no pain relief at 3 weeks, but > 40% pain relief of deep vaginal pain at 4 weeks through 2 months. Patient reported lingering vulvodynia and radiating groin which resolved after subsequent thermal treatment. At 4 months, iovera treatment was repeated for returning deep vaginal pain, providing > 50% pain relief with no anal sphincter dysfunction.[62]

* = cryoanalgesia with both iovera and non-iovera device
† = cryoanalgesia with non-iovera device

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Indication

The iovera° system is used to destroy tissue during surgical procedures by applying freezing cold. It can also be used to produce lesions in peripheral nervous tissue by the application of cold to the selected site for the blocking of pain. It is also indicated for the relief of pain and symptoms associated with osteoarthritis of the knee for up to 90 days. The iovera° system is not indicated for treatment of central nervous system tissue.

When stimulation compatible components are used, the iovera° system can also facilitate target nerve location by conducting electrical nerve stimulation from a compatible 3rd party nerve stimulator.

IMPORTANT SAFETY INFORMATION

Contraindications
The iovera° system is contraindicated for use in patients with the following:

- Cryoglobulinemia, paroxysmal cold hemoglobinuria, cold urticaria, Raynaud's disease, and open and/or infected wounds at or near the treatment site

Potential Complications
As with any surgical treatment that uses needle-based therapy and local anesthesia, there is a potential for site-specific reactions, including, but not limited to:

- Ecchymosis, edema, erythema, local pain and/or tenderness, and localized dysesthesia

Proper use of the device as described in the User Guide can help reduce or prevent the following complications:

- At the treatment site(s): injury to the skin related to application of cold or heat, hyper- or hypopigmentation, and skin dimpling
- Outside the treatment site(s): loss of motor function