Cryoanalgesia for refractory neuralgia

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Abstract

Analgesia by cryoneurolysis is a technique by which controlled lesions of the peripheral nerve are produced to manage refractory pain. The technique is particularly useful in situations where persistent pain is associated with pathologies of small and superficial nerves. Common targets of cryoneurolysis include the intercostal nerves for pain of the chest wall and abdominal wall, the iliohypogastric nerves and the ilioinguinal nerves for pain in the inguinal area, the genitofemoral nerves for pain in scrotum and inner thigh, the lateral femoral cutaneous nerves for lateral thigh pain (meralgia paresthetica), the pudendal nerves for vaginal, penoscrotal, perianal, and rectal pain, and sacral nerve roots (S4 and S5) for perineal pain and coccydynia. The procedure is usually performed after a diagnostic nerve block with local anesthetic has been successful with at least 50% pain reduction. The efficacy of cryoneurolysis has been supported by multiple clinical studies in a period of over several decades even though randomized controlled trials are scarce for practical reasons. The safety is acceptable when caution is exercised to avoid complications such as pneumothorax, bleeding, infection, unintended nerve injury, and damage to adjacent structures. When utilized appropriately with careful case selection, neurolysis appears to be a cost effective treatment.

Keywords: Neurolysis; neuropathic pain; diagnostic nerve block; neuroma; cryoneuroablative; cryoanalgesia; cryoneurolysis; electrical stimulation.

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Introduction

Neuropathic pain from peripheral nerve disease or injury consequent to trauma, surgery, infection, cancer or other causes is often referred to as neuralgia. It is common and often difficult to treat. For instance, the incidences of chronic post-surgical pain (CPSP) are reported to range between 25 to 50% in patients underwent thoracic surgeries[1,2], mastectomies[3,4] or abdominal surgeries[5]. A significant number of patients with CPSP is accompanied with a neuropathic component[1,2]. Neuralgia is typically described by patients as burning or "electric-shock" pain sensation. In many patients, neuropathic pain is debilitating and interferes with many aspects of their lives and significantly degrades quality of life. It is often refractory to pharmacological therapy as well as surgical exploration and decompression[6,7]. Targeted nerve blocks usually provide short-term pain relief. With positive responses to nerve blocks, clinicians often consider neuromodulatory or neurodestructive therapies for longer term pain relief. Neuromodulation is typically achieved by peripheral nerve stimulation, spinal cord stimulation, cortical stimulation, or deep brain stimulation[8]. Neurodestruction can be achieved by controlled thermal lesion using radiofrequency ablation or by cryoneurolysis[9,10].

Cryoneurolysis, the use of cold to provide anesthesia or analgesia, is the oldest anesthetic and analgesic technique that is still in current clinical use. Hippocrates (460-377 BC) has been credited with providing the first written record of the use of ice and snow packs as a local preoperative analgesic technique[11]. In 1962 Irvine Cooper et al. constructed the first cryoprobe used for cryoanalgesia[12]. It was based on the phase change of liquid nitrogen to produce temperatures of -196°C. In 1967, Amoils developed a less complex hand held unit that used either carbon dioxide (CO₂)
or nitrous oxide (N₂O), the early prototype for modern devices[13]. Lloyd et al. (1976) first reported clinical use of cryoanalgesia that achieved days to months of pain relief in fifty-two out of sixty-four patients with intractable pain from the intercostal nerve and other sources[14]. Cryoablation of peripheral nerve or nerves has been used in interventional pain medicine to relieve refractory and debilitating pain[15].

**Principles of Cryoanalgesia**

The principle of the cryoanalgesia technique is the formation of an ice-ball (temperature = -60°C) at the tip of a cryoprobe that is produced by rapid expansion of a gas (N₂O or CO₂) through a micropore outlet or by phase changes of liquid nitrogen. Direct application of the ice-ball to the nerve disrupts nerve function for 2-3 weeks[16]. The axons and myelin sheaths degenerate after cryolesion (Wallerian degeneration). However, the basal lamina, as well as the epineurium and perineurium are maintained intact, thus, leaving a “tube” which may serve as tracks to guide nerve regeneration and allowing for a precise return of pre-existing structure. As there is minimal inflammatory reaction and no external nerve damage, regenerating axons are unlikely to form neuromas. The rate of axonal regeneration after cryolesioning has been reported to be between 1 and 3 mm per day[17]. Since the rate of axonal regeneration is essentially constant, the return of baseline sensorimotor function (a major determinant of block duration) is dependent on the distance between the cryolesion and the end organ[18].

Theories as to how cryoneurolysis works include ischemic necrosis, physical destruction through large ice crystals, damage to proteins, alterations in cell volume, production of autoimmune antibodies, and membrane disruption caused by rapid water loss[14,19]. The temperature is important in the long-term success of cryoneurolysis. In rabbit studies, nerve fibers cryolesioned at -60°C lost conduction ability and degenerated but completely recovered. At -100°C, nerves also showed degeneration, but also recovered completely albeit at a slower rate. At -140 and -180°C, nerves immediately necrosed and scar tissue replaced the nerve rather than complete recovery thereby providing long-term analgesia[19]. Successful analgesia is also affected by the duration of application of the cryoprobe, the rate at which the tissue thaws, and the size of the lesion attained by the cryoprobe. Thus, cryoneurolysis is best utilized in conditions in which the nerve is small and well localized.

The cryoprobe is composed of an outer tube and a smaller inner tube that terminates in a terminal common chamber (Figure 1) [14]. High-pressure gas

![Figure 1. Schematic illustration of the structure of the probe. The probe contains an insulated electrode for nerve stimulation and localization, an insulated thermocouple for monitoring of tissue temperature, and a common chamber for gas expansion to reduce the temperature of the probe.](Image)

(650-800 lb/in²) is passed between the two tubes and is released via a small orifice into a terminal common chamber within the tip of the probe. Gas expands with a marked pressure drop (80 to 100
Cryoneurolysis and root postherpetic of ilioinguinal abdominal (intercostal nerves) 

Various studies have shown that this procedure, although successful in the immediate postoperative period, seems to increase the incidence of long-term pain after thoracotomy.[21-25]. Cryoneurolysis for acute post-herniorrhaphy pain involves intra-operative freezing of the ilioinguinal nerve, which is easily identified during dissection of the herniorrhaphy. Additionally, cryoanalgesia has been utilized as a treatment for hip adductor spasticity and obturator neuralgia.[26]. Furthermore, cryoanalgesia has been shown to be a useful adjunct to the management of intractable pain in the temporo-mandibular joint (TMJ) and paroxysmal trigeminal neuralgia.[27-28]. Short-term pain relief can be achieved, and long-term relief is possible in some, deferring more complex and costly treatments. Moreover, cryoanalgesia has been shown to provide long term pain relief in selected patients with phantom limb pain and neuroma.[29-30].

Intercostal nerve injury has been suggested to be a major factor contributing to the etiology of post-thoracotomy persistent pain. Motor evoked potentials were stimulated and recorded from 13 patients undergoing thoracotomy to determine the effects of rib retractor.[31]. Measurements were taken before and after entering the pleural space, after removal of the rib retractor and after intercostal space closure. There were no changes in the normal functioning of the intercostal nerves before and after exposing the pleural space. After the rib retractor was removed, there was a total conduction block in the nerve immediately above the incision in every patient and in the intercostal nerve two ribs above the incision in a large majority of the patients. Similarly, there was total or partial block in most patients immediately below the incision or two ribs below the incision. Intercostal space closure did not affect the neurophysiologic assessments. There was no neurophysiologic impairments detected in the intercostal nerves throughout the operation in a patient where rib retraction was not employed. Thus, rib retraction is a key culprit producing intercostal nerve injury.

Indications

Various conditions with persistent, intractable pain can be managed with cryoneurolysis, as long as a diagnostic nerve block with local anesthetic has been successful.[15]. Common targets of cryoneurolysis include the intercostal nerves (intercostal neuralgia, postthoracotomy pain, postmastectomy pain, rib fractures, costochondritis, abdominal wall pain due to nerve entrapment or neuroma), the intercostal nerves and the ilioinguinal nerves (postherniorrhaphy pain, nerve entrapment in laparotomy scar), the genitofemoral nerves (pain in scrotum and inner thigh), the lateral femoral cutaneous nerves (meralgia paresthetica), the pudendal nerves (intractable perianal, vaginal, perineal pain), and sacral nerve roots (S1 and S5) (perineal pain and coccydynia). The use of cryoneurolysis should not be performed in situations where a diagnostic nerve block has failed.

Persistent thoracic pain resulting from postherpetic neuralgia, a thoracotomy scar, nerve root pain from compression fracture of the vertebra, and cancer may amenable to cryoneurolysis. Cryoneurolysis has also been tested in postoperative pain management, such as thoracotomy and herniorrhaphy, as well as chronic pain syndromes.[20]. However, as a method to treat acute post-thoracotomy, intercostal cryoanalgesia has largely abandoned as studies have shown that this procedure, although successful in the immediate postoperative period, seems to increase the incidence of long-term pain after thoracotomy.[21-25]. Cryoneurolysis for acute post-herniorrhaphy pain involves intra-operative freezing of the ilioinguinal nerve, which is easily identified during dissection of the herniorrhaphy. Additionally, cryoanalgesia has been utilized as a treatment for hip adductor spasticity and obturator neuralgia.[26]. Furthermore, cryoanalgesia has been shown to be a useful adjunct to the management of intractable pain in the temporo-mandibular joint (TMJ) and paroxysmal trigeminal neuralgia.[27-28]. Short-term pain relief can be achieved, and long-term relief is possible in some, deferring more complex and costly treatments. Moreover, cryoanalgesia has been shown to provide long term pain relief in selected patients with phantom limb pain and neuroma.[29-30].

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should produce at least 50% pain reduction. Equivocal results should be challenged with a repeat block. The purpose of the diagnostic block is to exclude other causes or alternative nerves to be causatively linked to the chronic pain syndrome.

The cryosystem consists of a cryoprobe (as described above), a cryoneurolysis machine with an in-built stimulator, and gas cylinders. Liquid nitrogen is most commonly used to cool the probe to -70°C. The cryoneurolysis machines has indicators for freeze and defrost, a flowmeter to monitor and control high-pressure gas flow, and a pressure gauge to monitor cylinder content.

Patients are positioned to facilitate localization of the target nerve. Minimal or no sedation is recommended so that the patient is able to respond to nerve stimulation and provide reliable feedback. Ultrasound guidance (or fluoroscopy guidance where applicable) is often useful to accurately identify the nerve and placing the probe. The operating site is prepared with sterile technique. A local anesthetic is used to numb the skin overlying the target nerve. A small incision (~5mm) is made to facilitate insertion of the probe, then a 10 gauge, 3 inch angiocatheter (3.4 × 76 mm) (which fits with both sizes of the cryoprobe) is inserted and directed at the target nerve. The styllet is removed and replaced by a cryoprobe, which is further advanced slowly and carefully with intermittent test stimulation. Electrical stimulation at low intensities (0.1-0.4V) helps to confirm precise placement of the probe in proximity to the target nerve. Two freeze-thaw cycles are usually carried out to increase the destructive effects[32]. Each cycle is timed for 2 minutes from the establishment of a steady low temperature of about -70°C. After each freeze the temperature returns to above 0°C before refreezing or withdrawal of the probe[14]. Two lesions are usually made. The probe can only be removed after the ice ball at the tip of the probe has thawed (a process that usually takes 2 minutes).

It is critically important to understand the anatomy of the target nerve and its surrounding structures, in order to correctly place the probe and avoid complications. Here we use intercostal nerve as an example to illustrate this point. The intercostal nerves originate from the anterior rami of thoracic nerve roots 1-12. The roots exit through the intervertebral foramina into the paravertebral space which is bounded by the pleura anteriorly, the vertebral body medially, and the transverse spinous processes and musculature posteriorly. After the nerve enters the paravertebral space, it divides into the anterior and posterior branches with intercostal nerves forming from the anterior branch. Along the inferior margin of each rib is a groove that houses the intercostal nerve, artery, and vein, with the nerve being most inferior. As the nerve runs laterally around the thorax, the lateral branch of the intercostal nerve, which provides sensation to the lateral chest wall, arises close to the posterior axillary line. Any blocks performed anterior to this line will not achieve complete intercostal nerve anesthesia due to this lateral branch originating close to the posterior axillary line. Intercostal nerve neurolysis can technically be performed anywhere along the entire length of the nerve but is limited by the overlying scapula posteriorly. Efforts to achieve complete anesthesia of the anterior and lateral nerves should be performed at the posterior axillary line. The simplest approach is the posterior intercostal block. This is performed with the patient prone and the arms hanging at their sides in order to get the scapulae to move laterally. The rib is easily palpable in the prone position, the intercostal groove is broadest and deepest, and therefore the nerve and vessels are not as closely adjacent to one another. The ribs can then be palpated several centimeters from midline with the inferior margins marked. The site of entry for neurolysis can thus be determined.

Intercostal nerve cryolysis can be achieved with closed or open approaches[14]. In the closed approach, the skin is anesthetized with local anesthetic and an introducer is used to create a track through the tissues, through which the probe in inserted. The probe is advanced with great caution to avoid pneumothorax[33]. Using the stimulator, maximum response with minimum current indicates that the tip is lying adjacent to the target tissue. A cryolesion is then produced. In the open approach, the nerve is exposed surgically under local or general anesthesia and the cryoprobe is applied under direct vision.

**Outcomes of cryoanalgesia**

After the first successful clinical application of cryoanalgesia by Lloyd et al[14], Katz et al. further compared intercostal block by a freezing technique with blockade by local anesthetics or no blockade as a method of treating acute post-thoracotomy pain[16]. They reported significantly less postoperative pain in patients who received cryotherapy than those in the control groups and concluded that cryoanalgesia has definite advantage.
over other forms of therapy for post-thoracotomy pain. They suggested the interruption of nerve function produced by cryotherapy was temporary and there were no adverse sequela. Post-thoracotomy pain control is important in maintaining pulmonary toilet and avoiding atelectasis or pneumonia. It has been shown to have improved forced vital capacity and forced expiratory volume in one second compared to an opiate only group[25,34]. In a doubled-blind randomized study, Pastor et al. observed superior postsurgical pain control with intercostal cryoanalgesia, compared with pharmacological analgesia ad libitum in patients undergoing posterolateral thoracotomy[35].

In a recently comparative study of the effects of cryoanalgesia, 50 patients undergoing thoracotomy were randomized to two groups, cryoanalgesia combined with intravenous patient-controlled analgesia (IVPCA) (n = 25), or IVPCA alone (n=25) during the four days following surgery[36]. Subjective pain intensity was assessed on a verbal analogue scale at rest and during coughing. The intensity and the incidence of post-thoracotomy pain, numbness, epigastric distension and/or back pain, the analgesic requirements, as well as the blood gas values and respiratory function tests were evaluated up to the second postoperative (postop) month. Hemodynamic data and episodes of nausea and/or vomiting were recorded over the four postop days. It was found that in the cryoanalgesia group there was a statistically significant improvement in postop pain scores, reduction in consumption of morphine and other analgesics, optimization (less acidosis) of the pH values of blood gases (over 72 hours postop and on the first and second postop months), increase in systolic blood pressure (over 96 hours postop), reduction in heart rate (over 96 hours postop), increase in values of FEV1 and FVC at the first and second postop months, reduction in the incidence of nausea (over 18 hours postop), numbness, epigastric distension and back pain (at days 5, 6, 7, 14, 30 and 60 following surgery). It was concluded that cryoanalgesia is a simple, safe, inexpensive, long-term form of post-thoracotomy pain relief. Cryoanalgesia effectively restores FEV1 values at the second postop month.

However, controversies exit on intraoperative use of cryoanalgesia for acute and long-term pain control after thoracotomy. Mustola et al (2011) evaluated effects of thoracic epidural analgesia combined with intercostal nerve cryoanalgesia or epidural analgesia alone on acute and long-term pain after posterolateral thoracotomy in a double blind, randomized study of 42 patients[21]. They found that the cryoanalgesia group had statistically more neuropathic-type pain compared with the epidural-alone group 8 weeks after operation. The cryoanalgesia group had also more pain on normal daily activities 8 weeks after the operation. After 6 months, there were no statistically significant differences between groups. They concluded that intercostal cryoanalgesia seems to increase the incidence of long-term pain after thoracotomy. A recent review of 12 articles concluded that the evidence does not support the use of cryoanalgesia alone as an effective method for relieving post-thoracotomy pain[37]. An early review also concluded that cryoanalgesia, which is successful in the immediate postoperative period, has been abandoned for its brief duration and increased incidence of chronic pain[22].

Green et al. observed the long-term efficacy of cryoanalgesia for the management of chronic thoracic pain due to intercostal neuralgia[38]. They retrospectively reviewed the medical records of patients who underwent percutaneous cryoanalgesia following successful intercostal nerve blockade for chronic chest pain (presumed to be predominantly due to intercostal neuralgia). Sixty percent of the patients (N=43) reported significant pain relief immediately following their cryoanalgesia procedure. Three months follow-up of patients receiving cryoneurolysis for control of chronic thoracic pain revealed that 50% of patients reported continued significant pain relief with no reports of neuritis or neuroma formation. In another retrospective study, the effect of cryoablation of the intercostal nerves on pain levels in patients with histories of post-thoracotomy pain syndrome was reported[39]. The average preprocedural pain score in eighteen patients was 7.5 +/- 2.0, which decreased to 1.2 +/− 1.9 immediately after the procedure. After a mean follow-up period of 51 days, the average pain score was 4.1 +/- 1.7. The difference between preprocedural and postprocedural pain scores was statistically and clinically significant. It was concluded that cryoneurolysis of the intercostal nerves statistically significantly decreased pain scores in patients with post-thoracotomy pain syndrome. More recently, we performed a retrospective study of 51 patients with chronic neuropathic pain and found an average pain reduction of 62% at 1 to 3 month follow-up visit after neurolysis[40].
With the advent of minimally invasive surgery, video-assisted thoracic surgery (VATS) has emerged for diagnostic and therapeutic procedures in thoracic surgery. With concomitant use of cryoneurolysis with VATS, it has been shown to decrease length of stay, decrease narcotic requirements, morbidity, and cost[41]. Zhao et al. performed a prospective randomized trial of cryoanalgesia in 200 patients who underwent thoracotomy with 100 patients in the cryoanalgesia group and 100 patients in the control group[42]. Cryoanalgesia was performed at four levels of intercostal nerves above and below the incision for 90 seconds. Pain intensity, opioid requirements, and pulmonary function were recorded on post-operative days 3, 7, 15, 20, and 90. The pain score (numerical rating scale) was 2 for the cryotherapy group and 7 for the control group. It was concluded that cryoanalgesia of intercostal nerves during thoracotomy provides effective post-operative analgesia. Hypoesthesia/dysesthesia, which has been one of the concerns that some clinicians have with the use of cryoanalgesia during thoracotomy, was not observed.

Cryoanalgesia has been shown to spare the patient late neurological sequelae other than a sense of hypoesthesia or occasionally dysesthesia in the scar[43]. In a prospective randomized study, even with prolonged application times up to 120 seconds, no permanent nerve damage was noticed histologically at 6 months follow-up. And with exposure to even shorter application times of 30 to 60 seconds, recovery of the nerve occurred by one month[44]. Somatosensory evoked potential (SEP) and sensory conduction velocity (SCV) were measured in rabbit sciatic nerves following graded cold lesioning[45]. The SEP latency was prolonged after creating lesions a -100 to -180°C, compared with both the sham operated and the -20°C groups. It was suggested that the cryolesion produced at temperatures between -60 and -100°C is most suitable for altering the electrophysiological conduction of the nerve.

Cryoneurolysis was tested to treat phantom limb pain (PLP) in the small group of patients[29]. The nerve stump specific to the location of PLP was identified by stimulation and diagnostic nerve block using a local anesthetic. Cryoneurolysis was then performed and the patients were followed for 2.5 years. Three out of 5 patients had excellent results (>90% pain reduction) and other two patient had noticeable and clinically significant pain relief (20-40% pain reduction). It was suggested that although both central and peripheral components are likely involved in PLP, identification and treatment of a peripheral pain etiology with cryoanalgesia can result in long-term pain relief and should be considered.

The long-term effects of cryoneurolysis have recently been reported in a retrospective study to treat lumbar facet joint syndrome, which accounts for 15-54% of the patients with low-back pain[46]. In a 4-year period, 117 cryoneurolyses were performed in 91 patients under CT guidance. The mean pain score (VAS) reduced from 7.70 before treatment to 3.72 post treatment. The scores maintained low, 4.22 at 3 months follow-up, and 4.99 at later follow-ups (mean 1.7 years, range 6-52 months). The pain reduction was accompanied with significant improvements in the pain disability index, as well as hospital anxiety and depression scale (HADS) scores. It was concluded that cryoneurolysis for LFJS can lead to favorable results with sustained pain relief, amelioration of pain-related disability and reduction of depression scores.

Interestingly, long term benefits was reported to use cryoaiblation of branches of the trigeminal nerve to treat paroxysmal trigeminal neuralgia in 145 patients[28]. The follow up duration ranged from 1 month up to 6 years. The mean nerve relief pain period was 13 months for the long buccal, 17 months for the mental and 20 months for the infra-orbital nerves. It was observed that the patients regained normal sensation long before the return of pain.

Cryoanalgesia was investigated to treat TMJ pain[27]. In a five-year retrospective study, 17 patients with severe pain that had failed to respond to all forms of conventional conservative treatment were treated with cryoanalgesia. After successful diagnostic injections of bupivacaine to the TMJ to relieve the pain, the cryoprobe was applied in the region of the auriculotemporal nerve and TMJ capsule. There was a significant improvement in VAS pain scores from 6.8 (range 4-10) to 2.0 (range 0-7). The mean number of pain-free months after treatment was 7. It was concluded that cryoanalgesia is a useful adjunct to the management of intractable pain in the TMJ. Short-term pain relief can be achieved, and long-term relief is also possible in selected patients.

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Side Effects and Complications
As with all invasive procedures, side effects and complications such as post-procedural pain, bleeding, infection, and damage to adjacent structures can occur. Pneumothorax or hemothorax is of particular concern with procedures around the pleural space. Careful attention and evaluation for pneumothorax is indicated, especially when targeting multiple levels per procedure. Treatment should be initially conservative with 100% oxygen to de-nitrogenate the pneumothorax to aid in reabsorption. A chest tube may be needed for severe cases.

Other complications include frostbite or skin lesion due to the probe being too close to the skin surface, nerve damage by introducer cannula or by removing the probe before the ice ball thaws, neuritis or persistent dysesthesia, and undesirable numbness in the scalp (occipital nerve), nipples (3rd and 4th intercostal nerve), and clitoris ( pudendal nerve). Other complication may include moderate to severe neuralgia after cyroanalgesia in the late postoperative period of thoracotomy[47].

Conclusions
Cryoanalgesia is an effective technique that can be considered in various intractable pain conditions, especially with nerves which are relatively small and superficial. Cryoanalgesia appears to be a relatively inexpensive technique to provide intermediate-term pain relief without long-term histological nerve damage. Solid anatomy knowledge and adequate training of procedural skills are required to safely and effectively perform the procedure.

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