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Cryoanalgesia: A Review

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Abstract: ***Chronic pain is a significant global health problem. Conventional treatment strategies often prove insufficient or inadequate and associated with undesirable side effects. Interventional pain management techniques, including neuromodulation, are becoming increasingly popular as alternative therapeutic options. Cryoneurolysis, employing extreme cold to modulate pain pathways, is proving effective and enjoying a resurgence in chronic pain management. (1)***

Keywords: chronic pain; neuromodulation; peripheral nerve stimulation; ; pain management; interventional pain therapy

1. Introduction

Chronic pain is a global health problem affecting millions and posing a significant burden on healthcare systems. According to the International Association for the Study of Pain (IASP), chronic pain is defined as pain that persists or recurs for more than three months, associated with psychosocial, functional, and economic challenges. Despite pharmacological interventions, physical therapy, and psychological support, many patients continue to endure intractable pain. often experiencing the side effects of long-term medication use. Interventional pain therapies and neuromodulation techniques, target specific pathways within the nervous system to attenuate nociceptive signal transmission.

Clinical interest in cryoneurolysis has snowballed because of its efficacy in managing refractory pain conditions mediated by sensory and mixed nerves, its favorable safety profile, especially against high-dose analgesics and reversibility. Recent advances in image guidance (e.g., ultrasound, fluoroscopy, and computed tomography) have vastly improved the accuracy of nerve localization and enhanced procedural success along with a low incidence of complications.

Historical Aspects

The use of cold temperatures to alleviate pain dates back to ancient times. Cryoneurolysis first appeared in 460 BC when ancient Egyptians and Greeks, used ice and snow to treat wounds. Hippocrates described pain relief from injuries by the topical application of snow. In 1845-51 British physician James Arnott (1797-1883) described the use of iced salt solutions to freeze advanced cancers in accessible sites, producing reduction in tumor size and amelioration of pain. Emperor Napolean's surgeon Dominique Jean, Baron Larrey (1766-1842) observed that soldiers with frozen limbs experienced little pain and bleeding during amputation and advocated the controlled use of ice as a natural anaesthetic and limit surgical shock. Around this time, topical anesthesia was also discovered as diethylether and ethyl chloride spray for drainage of abscesses. In 1961 Dr Irving S Cooper (1922-1985) an American neurosurgeon, used liquid nitrogen to treat Parkinsonism and destroy brain tumours. In 1981, Dr John Lloyd and his coworkers treated 85 cases of facial pain using cryogenic nerve blocks and reported a 11-day median duration of pain relief and significant pain relief for up to 224 days in some cases. (2,3)

In 1965, Selig Percy Amoils (1933-1994) introduced a cryoprobe based on the principle of high-pressure gas expansion through a small orifice. (4) Incisional approach gave way to percutaneous techniques that was integrated with imaging technologies enabling its foray into acute and chronic pain management. (Fig 1)

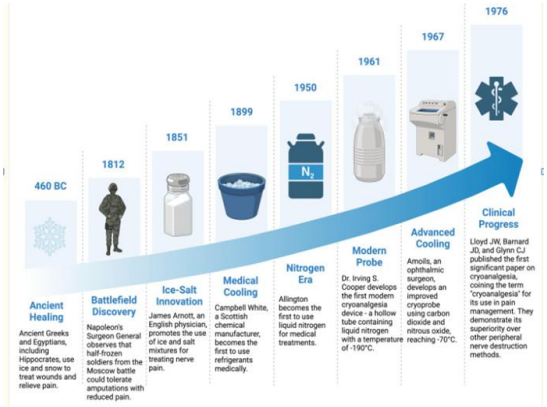

Figure 1: Evolution of cryotherapy

Neuronal Anatomy

Nerves consist of individual axons bundled together. The endoneurium, a layer of connective tissue, envelops each axon. These axons are organized into fascicles, with each fascicle encased by the perineurium, another connective tissue layer. Multiple fascicles are further enclosed by the epineurium, which serves as the outermost protective layer of the nerve. In myelinated nerves, the axons are sheathed in a myelin sheath formed by Schwann cells, providing insulation and facilitating nerve signal transmission.

Pathophysiology of Cryoneurolysis

Intense cold triggers Wallerian degeneration and disruption of afferent and efferent signal transmission along axons. As the nerve's endoneurium, perineurium, and epineurium remain intact, the axon regenerates along the exoskeleton at an approximate rate of 1 to 2 mm/day. As the axon reconnects with the sensory receptor, conduction is restored and axonal regrowth into the perineurium restores sensation. Hence, cryoneurolytic procedures may have to be repeated after an interval, without any adverse effects.

The extent of tissue freezing and its effect on a nerve depends on the proximity of the probe to the nerve, the size of the cryoprobe, the cryoprobe temperature, rate and duration of and the temperature of the surrounding tissues influenced by local heat sinks, such as cerebral spinal fluid and blood flow.

The various effects of low temperatures on nerves are as follows:

1) **Reversible effects**
   - Neuropraxia (1st degree): This is an interruption of conduction with a short recovery time observed at +10 to -20 °C.
   - Axonotmesis (2nd degree): This is a loss of axon continuity with noticeable Wallerian degeneration. There is preservation of endo-, peri-, and epineurium; this is observed at -20 to -100 °C.
2) **Irreversible effects**
   - Neurotmesis (3rd/4th degree): There is some loss of continuity of epineurium and perineurium, with or without disruption of the endoneurium at -140 °C and colder.
   - Transection (5th degree): There is a gross loss of continuity; this is not observed in cryoanalgesia.
   - Cryoprobe temperatures below −140°C lead to irreversible tissue damage. Sequestered protein release can trigger an autoimmune response and result in a prolonged therapeutic effect. (4,5,6)

The Cryoablation Technique

Cryoprobes in sizes 1.4 to 2 mm with integrated nerve stimulators set for sensory (100 Hz) or motor (2 Hz) responses, and introducer sheaths for skin protection are commercially available. The cryprobe consists of 3 parts, a cryogen source, a cryo-destructive section, and an insulated handle. These probes use nitrous oxide, carbon dioxide, or argon gas to achieve core temperatures. from -20°C to -80°C. The bayonet-shaped cryoprobe is a metallic tube with a central internal channel and the cooling agent circulates through it. Nitrogen devices employ a simple rigid cryoprobe without internal channels; thermal contact with the cooling agent creates a gas pressure drop and adiabatic cooling. (7)

Cryoprobes come with various needle tips, generating ice balls of varying dimensions on targeted superficial peripheral nerves. Available probes range in size from 1.4 to 2 millimeters, with integrated nerve stimulators for precise nerve localization and thermistors to monitor probe tip temperature. The nerve stimulator allows selecting between sensory (100 Hz) or motor (2 Hz) responses. Using an introducer is recommended as it isolates electrical current to the probe tip, shielding the skin from the ice ball when treating superficial structures, and facilitates local anesthetic infiltration. Typically, a large gauge intravenous catheter is the introducer, characterized by a sharp tip that easily penetrates tissues. The stylet can be removed for straightforward probe insertion. For the 2.0 mm probe, a 12-gauge catheter is used, while the 1.4 mm probe pairs with a 14- or 16-gauge catheter. These portable devices come with a compact charging dock, enabling widespread use in both hospital and outpatient clinical environments. The confluence of accessible ultrasound devices, the increasing expertise of anesthesia providers in ultrasound imaging, and the availability of handheld cryoanalgesia devices have transformed cryoanalgesia into a pragmatic intervention for acute and chronic pain management.

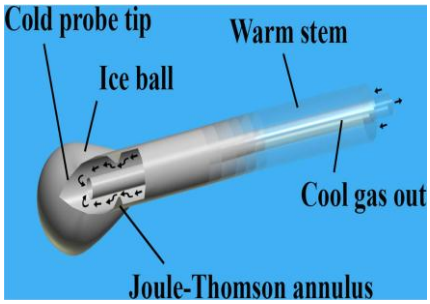

Figure 2: Details of the cryoprobe

Preparation and patient positioning depend largely on the target location and the implicated nerve. Access to all necessary personnel and equipment should be verified. Room temperature gas should be purged from the system. Sedation is seldom necessary, and deep sedation should be avoided to facilitate patient localization of stimuli. Appropriate informed consent should be obtained. The patient should be positioned comfortably. A pre-procedural pause and time-out are then performed, identifying the correct patient, side, site, and allergies. An aseptic technique should be observed.

Diagnostic nerve stimulation or a diagnostic block with local anesthetic is performed to confirm the correct placement of the probe. The targeted nerve should reliably respond at 0.5 volts or less, followed by maximum stimulation to rule out the presence of nearby nerves. The probe is then activated, typically using 2- or 3-minute freeze cycles interspersed with half-minute defrosting periods between applications, to allow the tissues to warm up to above 0 °C before initiating the subsequent freeze cycle. Following the final freeze cycle, meticulous care is taken to ensure proper thawing for two minutes before removing the cryoprobe to prevent tissue damage when detaching it from adhered frozen tissue. During the sheath's withdrawal, a small volume of local anesthetic can infiltrate the tissues. CO_2 is vented through the inner cannula, with no gas released into the patient's body. If cryoanalgesia is conducted bilaterally, the left side is done first followed by the right side. Nerve stimulation response and ultrasound procedural images must be monitored continuously when freezing near sensory and motor nerves. (8)

Argon-based machines are capable of inducing temperatures as low as −100°C and producing a relatively large ice ball through the rapid expansion of gas, at the tip of the probe. (9)

Cold slurry injections composed of normal saline with 15% glycerol -9º C has also been used for cryoneurolysis as it affects myelinated fibers and spares unmyelinated C fibers, eliminating mechanical pain sensitivity while preserving thermal pain sensitivity. These injections can be repeated as their effect wears out. (10)

Acute Pain Management

Cryoneurolysis in peripheral nerve blocks for acute pain is gaining popularity. Intercostal nerve ablation during thoracotomy mastectomy, knee osteoarthritis, total knee arthroplasty, shoulder rotator cuff repair, postherpetic neuralgia, thoracoabdominal aneurysm repair, trauma, allodynia, neuralgias, childbirth are its varied applications. Vagal blockade (Vbloc) cryoablation for patients with BMI of 35 to 45 kg/m^2 targeting the anterior and posterior vagal trunks near the esophagogastric junction during standard laparoscopic surgery is a game-changing procedure. A rechargeable neuroregulator placed subcutaneously on the thoracic wall ensures decreased appetite and/or weight loss. (11, 12, 13)

Chronic Pain Management

The multifaceted nature of cryoanalgesia in managing chronic pain across multiple conditions is well established. Cryoneurolysis of peripheral nerve blocks is effective in managing various chronic pain conditions. Obturator neurolysis provides long-lasting adductor spasticity and alleviates phantom limb pain in amputees, occipital nerve neuralgia, chronic peripheral neuropathy pain, temporomandibular joint, nerve entrapment, post herpetic neuralgia, orofacial pain and lumbar facet joint syndrome. (14,15,16 17,18,19,21,22,23,24,25)

Oncological Pain Management

Cryoneurolysis is effective for neuropathic pain like plexopathies, radiculopathies, and peripheral neuropathies stemming from tumor compression or invasion. Ablating affected nerves for patients unsuited for surgical resection results in substantial relief from nerve-related pain and reduces reliance on systemic opioids. The application of cryoneurolysis in oncologic pain management are diverse, allowing for tailored approaches based on patient needs and clinical contexts. Percutaneous cryoneurolysis is a minimally invasive modality that enables direct access to nerves impacted by tumors, such as in cases of bone metastasis affecting the pelvis or vertebrae. This approach effectively targets neuropathic and somatic pain components without necessitating extensive surgical intervention. Ultrasound-guided cryoneurolysis further refines precision, allowing for the specific targeting of nerves in anatomically complex regions. This technique is advantageous for managing post-surgical pain requiring meticulous nerve localization. (26)

For palliative care in advanced stages, repeated cryoneurolysis can be applied periodically to sustain pain control in chronic pain syndromes associated with recurrent or progressive disease. This approach is particularly beneficial for reducing or avoiding opioid dependency in patients with pain from metastatic disease affecting spinal or peripheral nerves. In scenarios where visualization is limited, landmark-based cryoneurolysis provides a reliable technique for managing nerve-related pain in hard-to-reach areas, such as the spine or deep pelvic structures, addressing complex metastatic pain that may not respond adequately to conventional treatments. (27)

Efficacy and Safety Profile

Cryoneurolysis has a safe profile and reduces opioid consumption. The standardized mean difference (SMD) at each follow-up point indicates a more significant reduction in pain, improved functional abilities and motor function. Risks during cryo-analgesia can be eliminated by proper pre and post-procedure care and regular follow-up. Complications are minor and in the range of 0.9 to 1.78%, similar to those of other needle-based percutaneous procedures, including bleeding and bruising. All of these resolve within one month. There is no evidence of neuroma formation or permanent nerve injury with this modality. Clinicians should educate patients about expected numbness, potential discomfort, and realistic outcomes of the procedure. Informed consent remains essential. While there is no evidence of neuroma formation or permanent nerve injury

Specific procedure-related risks include permanent nerve injury, injury to the surrounding tissue, and discoloration of the skin if the cannula is retracted before resolving the ice ball and is allowed to contact other areas near the target site.1.2% patients can develop severe dysesthesia in the treatment area, which interfered with their sleep cycle and adversely affecting their quality of life.

Cryoneurolysis is inadvisable in Raynaud syndrome, cryoglobulinemia, cold urticaria, bleeding disorders and myopathies. intercostal cryoanalgesia for thoracotomy has been linked to moderate to severe neuralgia, making it a relative contraindication. (28)

Assessment

After 1-month, Patients' Global Impression of Change and the Brief Pain Inventory (interference subscale) is employed to assess the improvement or otherwise in either group after the initial post-treatment week. (29)

2. Conclusions

Cryoanalgesia presents a non-opioid alternative, minimizing infection risk and avoiding complications seen in other pain management techniques. With its safety margin and efficacy, cryoanalgesia is a promising option in the current opioid epidemic, offering improved pain management in perioperative and office-based settings. Cryoanalgesia holds promise, but its use requires careful consideration of contraindications and potential risks to ensure patient safety and realistic expectations.

Cryoanalgesia demands a collaborative and multidisciplinary approach involving physicians, advanced practitioners, nurses, pharmacists, and other healthcare professionals, each contributing unique skills and roles to enhance patient-centered care. Physicians and advanced practitioners are responsible for meticulous patient assessment, selection, and procedural expertise.

Cryoneurolysis has improved patient outcomes and contributed to more efficient healthcare delivery.

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