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Ultrasound-guided percutaneous cryoneurolysis for treatment of acute pain: could cryoanalgesia replace continuous peripheral nerve blocks?

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Local anaesthetics, delivered percutaneously through a needle, have been used for over a century to provide perioperative anaesthesia and analgesia. However, the duration of a single-injection peripheral nerve block is usually limited to less than 24 hr, leaving untreated surgical pain that may last for weeks—or in some cases months. While prolonged analgesia may be provided using a perineural catheter and repeated/continuous administration of local anaesthetic, the duration of this modality is still usually limited to less than one week because of the risk of infection, rapid consumption of the local anaesthetic, and the burden of carrying an infusion pump and anaesthetic reservoir.[1] An analgesic modality with a prolonged duration of action could be advantageous for various surgical procedures that are associated with a typically prolonged postoperative period of pain.

Cryoneurolysis—the application of a very low temperature to a nerve that reversibly curtails signal transmission—may be one such possible long-term analgesic modality for painful surgery.[2] While cold was used to provide analgesia by the ancient Egyptians and Greeks, it was not used specifically for tissue destruction until the 19th century.[3] The first automated cryosurgical apparatus used liquid nitrogen to cool a probe—or 'cannula'—in 1961; and Lloyd and colleagues[4] first used the term 'cryoanalgesia' in 1976, noting that neuro-ablation using cold lacked the neuritis and neuralgia that commonly occurred when phenol, alcohol or surgical lesions are employed. With the advent of ultrasound-guided probe insertion,[5] cryoneurolysis was used to provide analgesia for multiple chronic pain states.[2] While cryoneurolysis has been used to treat acute pain following herniorrhaphy,[6 7] tonsillectomy[8] and thoracotomy via the surgical incision,[9] percutaneous administration theoretically increases the potential scenarios for its use to provide analgesia.[10] The use of ultrasound guidance for percutaneous perineural cannula insertion dramatically increases potential applications yet further.[11]

Recently, preliminary data were published that described the use of ultrasound-guided percutaneous cryoneurolysis to treat pain in 10 patients following total knee arthroplasty (infrapatellar branch of the saphenous nerve), rotator cuff repair (suprascapular nerve), lower limb amputation (femoral and sciatic nerves), iliac crest bone harvesting (superior cluneal and/or subcostal nerves), post-nephrostomy incisional pain (intercostal nerve) or lower extremity burns (tibial nerve).[12 13] All of these patients reported excellent post-procedure analgesia with pain scores consistently <2 on the 0–10 Numeric Rating Scale, and they required significantly less opioids for a dramatically prolonged period of time compared with historic controls. Most reported nerve block resolution 2–16 weeks following administration. There were no adverse events related to the cryoneurolysis.

These recently reported cases suggest that ultrasound-guided percutaneous cryoneurolysis may be a practical alternative analgesic modality for the treatment of various acute pain states. There now appears to be few obstacles to widespread implementation of this technique with the recent combination of: (i) United States Food and Drug Administration-approved hand-held cryoneurolysis devices,[11] (ii) the prevalence of portable ultrasound machines, (iii) public health efforts to decrease oral opioid use, and (iv) recognition that poorly controlled pain in the acute period following surgery is associated with persistent postoperative pain. However, prior to extensive application, high-quality randomized controlled trials are required to demonstrate benefits, identify and quantify risks, and optimize administration techniques and equipment.

Nonetheless, cryoneurolysis offers another potential option for acute pain medicine providers to perform peripheral nerve blocks in addition to the traditional local anaesthetic-based techniques. Because of its prolonged—and somewhat unpredictable—duration of action, cryoanalgesia will likely be most applicable to painful conditions expected to last weeks or even months. For example, many shoulder procedures result in moderate-to-severe pain lasting multiple weeks, and potent analgesia is often critical for aggressive range-of-motion exercises to avoid a frozen shoulder and optimize functional outcomes. Single-injection suprascapular nerve blocks with long-acting local anaesthetics provide high-quality analgesia following open acromioplasty and/or rotator cuff repair; however, they only add 'minimal value' because of a mean duration of action of less than 10 hr.[14] Continuous interscalene and suprascapular nerve blocks—while prolonging analgesia compared with single-injection blocks—are still usually limited to multiple days because of local anaesthetic consumption, infection risk and inadvertent catheter dislodgement.[1 15]

For the two recently reported cases of total shoulder arthroplasty treated with preoperative suprascapular nerve cryoneurolysis instead of perineural local anaesthetic infusion,[12] potent analgesia was provided for 2–4 weeks, obviating catheter care, infusion pump dependence, local anaesthetic toxicity risks and reservoir burden, as well as decreasing the risk of infection. Suprascapular cryoneurolysis inhibits only a small portion of the muscles affecting the shoulder (supraspinatus and

infraspinatus), allowing rehabilitation in the early postoperative period, while complete motor function returns by the time aggressive physical therapy begins.

In contrast, cryoneurolysis will be inappropriate when extremity muscle weakness is unacceptable, such as ablating the femoral nerve for postoperative analgesia following knee surgery, given the lack of ambulatory ability with a flaccid quadriceps muscle. However, a local anaesthetic block of the sensory-only infrapatellar nerve provides analgesic benefits following arthroscopic knee surgery limited to less than one day.[16] The pain following total knee arthroplasty often outlasts even a relatively long-duration continuous peripheral nerve block, and the recently reported three cases of ultrasound-guided infrapatellar cryoneurolysis experienced up to 4 months of cutaneous sensory deficits,[12] suggesting a prolonged period of analgesia.

Possible additional applications for treatment of acute pain extend beyond the operating room, and include rib fractures, painful burns with a long recovery period and palliative care.[13] The recently reported case in a patient with opioid-refractory pain caused by right foot burns demonstrates the utility of cryoneurolysis outside of the operating room.[13] While normally cryoneurolysis has been used to treat predominantly sensory-only nerves;[17] in this case, the most distal aspect of the posterior tibial nerve visualized by ultrasound was targeted as the majority of the pain was located in the plantar aspect of the toes and foot. This did not leave a prolonged motor block. Furthermore, mixed sensory-motor nerves have been targeted to successfully treat spasticity,[18] and two preclinical reports involving laboratory animals found no long-term changes to the structure or function of motor nerves following axonal regeneration and remyelination,[19] even after multiple treatments.[20]

Mechanism of action. Modern cryoprobes pass gas (usually carbon dioxide or nitrous oxide) at a relatively high pressure down their shaft, through a small orifice and into the closed distal tip at a much lower pressure (Fig. 1).[2] Based on the Joule–Thomson effect, a dramatic temperature decrease occurs when the gas moves from the high to low pressure state causing rapid expansion and absorption of heat. The gas is then evacuated back up through a larger-diameter tube in the middle of the shaft; importantly, this closed circuit permits no gas to remain within the body. The extreme cold that is created (approximately −70 °C) induces Wallerian degeneration—a reversible destruction of the nerve axon but retention of the endo-, peri- and epineurium. Without these structures, permanent nerve injury and neuroma formation occur; but, because the architecture is maintained during the cryo-ablative process, the nerve grows back along its normal path. The temperatures produced by the probes cannot be lower than the boiling point of the gas (nitrous oxide: −88 °C; carbon dioxide: −79 °C), which is above the level that results in irreversible degeneration (about −100 °C), providing a wide margin of safety. The ultimate result is an axonal lesion that regenerates at a rate of 1–2 mm day^{-1} without the risk of neuroma formation.[2]

Multiple factors influence the degree of freezing, induced nerve injury and duration of anaesthesia/analgesia: (i) the distance between the probe and target nerve; (ii) the cryoprobe diameter; (iii) the size of the resulting ice ball; (iv) the temperature of the immediately surrounding tissue (such as blood, which acts as a heat sink); and (v) the rate and duration of cold application. The latter two factors are highly dependent upon the gas flow rate and the number of 'freeze cycles' applied, usually with 2–3 min of freezing followed by 0.5–2 min of thawing.[2] With dramatic differences in nerve diameter and type (e.g. sensory only *vs* mixed sensory and motor), as well as a wide variation in desired analgesia intensity and duration, it is self-evident that a good deal of research is required to determine how to produce the desired results for postoperative analgesia following various surgical procedures.

Nerve localization techniques. While the present article emphasizes the exclusive use of ultrasound for nerve localization, probes that pass electric current to their tips are common, permitting an additional neurolocalization modality.[21] Computed tomographic and fluoroscopic guidance have been reported,[2] although it is doubtful these modalities will be more useful than ultrasound when providing cryoneurolysis specifically for acute pain states. Lastly, using short cryoprobes, a superficial nerve may be treated without specific localization, but rather by treating a 'line' across which the nerve is known to pass.[3 10] Relatedly, in the reported cases involving iliac crest bone harvesting, the superior cluneal nerves were targeted by applying superficial cryoneurolysis along the posterior aspect of the iliac crest.[13] Additionally, the superficial peroneal nerve was similarly treated in the patient with foot burns.[13]

Contraindications and risks. There are few relative or absolute contraindications to cryoneurolysis; these include anticoagulation, bleeding disorders, localized infection, cryoglobulinemia, cold urticarial, paroxysmal cold haemoglobinuria and Raynaud's syndrome. Risks include bleeding, bruising, and—if the ice ball involves the skin—frostbite, alopecia, depigmentation and/or hyperpigmentation. Some newer cryoprobes specifically designed to treat superficial nerves integrate a skin warmer that protects the skin and hair from the freezing temperature.[10] Damage to surrounding tissue may occur if the probe is moved prior to an adequate thaw period, as the tissues can adhere to the probe. Infection appears to be extremely rare.[2] There are no published cases of permanent nerve injury or neuroma formation,[17] although there are rare reports of transient neuritis.[22] With the initial application, there is usually mild-to-moderate pain that resolves within 30 s; and some patients have reported distress with the prolonged anaesthesia. Repeating cryoneurolysis following full axonal recovery does not result in negative sequelae, so there is no limitation of using this modality in the same anatomic location for multiple subsequent surgical procedures.[20]

With over five decades of clinical use, the published literature suggests a level of safety surpassing traditional local anaesthetic-based peripheral nerve blocks. However, it is noteworthy that two randomized controlled investigations reported a statistically significant increase in the incidence of neuropathic pain for cryo-

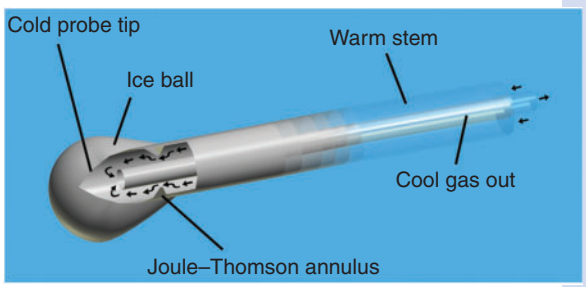

Fig 1 A modern cryoneurolysis probe ('cannula') produces extremely cold temperatures at its tip because of the Joule–Thomson effect resulting from gas flowing from a high- to low-pressure chamber [used with permission from B.M.I.].

neurolysis administered via the surgical incision in subjects at 8 weeks (resolving by 6 months),[23] 6 months and 1 yr following open thoracotomy.[24] In contrast, the majority of randomized controlled trials of cryoneurolysis via the surgical incision did not report any increased risk of persistent postoperative pain, although a few additional small studies did note a possible association that did not reach statistical significance.[9]

The reasons for these discrepancies remain unknown, and because of a myriad of confounding variables among studies (e.g. number of intercostal nerves ablated, chest drain location, number of treatment cycles, duration of treatment, cryoneurolysis temperature), no causal inferences can be made without additional data.[9] Considering the lack of reports of chronic pain following cryoneurolysis for other indications,[2] and given a small series of patients treated for post-thoracotomy neuralgias with percutaneous cryo-ablation whose pain worsened following treatment,[25] this may be an issue related exclusively to thoracotomy—possibly related to the double-crush theory because of the high incidence of surgical procedure-related nerve injury during open thoracotomy.

Many questions remain regarding ultrasound-guided percutaneous cryoneurolysis for the treatment of acute pain. For example, yet to be defined are the applicable acute pain indications,[2] the optimal cryo-ablation technique and equipment,[11] the ways to better control hypoesthesia (block) duration and an effort to determine the risk—if any—of post-procedure neuropathic pain.[9] Nevertheless, current evidence suggests that ultrasound-guided percutaneous cryoanalgesia holds enormous potential for making a dramatic leap forward in providing long-term analgesia far surpassing typical continuous peripheral nerve blocks, with minimal risk and a lower patient burden (e.g. carrying a local anaesthetic reservoir).

Authors' contributions

Participated in manuscript authorship: all authors.

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Perioperative statins surgery and postoperative pain

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In this issue of the *British Journal of Anaesthesia*, Saasouh and colleagues[1] evaluated whether statins influence postoperative pain and opioid consumption after hip surgery.[1] Using a large and long-established Cleveland Clinic database a group of patients already taking statins were matched with otherwise similar patients who were not. The authors conclude that there was no significant relationship between statin taking and postoperative pain and opioid consumption during the initial 72 h after hip surgery.

Statins are among the most widely prescribed drugs. Sixteen per cent of men and 12% of women in the UK are prescribed a statin by their primary care physician.[2] International guidelines recommend statins for high-risk patients with atherosclerotic cardiovascular disease (Table 1).[3] Lower-risk patients are also thought to benefit from the robust cholesterol reduction provided by statins.[3] A recent review evidences the efficacy of statins for both primary and secondary prevention of heart attacks and strokes.[4]

Clearly, a significant number of people presenting for surgery will be on long-term statin therapy. If we consider the mechanism of action of statins, it is important to understand how they might impact on pain.

How do statins work?

Statins reduce cholesterol synthesis and increase its clearance whilst decreasing triglycerides. They also reduce inflammatory mediators with beneficial effects on vasomotor tone, platelet function, oxidation status, coagulation and inflammation.[5] These characteristics also appear to stabilize atheromatous plaques.[5] Recently, statins have been demonstrated to induce cardiac remodelling and reduce the risk of left ventricular hypertrophy and dilation in asymptomatic high-risk patients.[6] The effects on inflammatory pathways may be particularly relevant in situations where there is tissue injury, such as occurs with surgery. To date, there has been very limited clinical study of the effects of statins on pain in the perioperative period.

Why might statins influence pain after surgery?

The anti-inflammatory effects of statins seen in preclinical studies are associated with reductions in C-Reactive Protein and pro-inflammatory cytokines. Animal neuropathy models demonstrate that statins can also reduce neuropathic pain.[7] A number of animal studies have reported analgesic effects with high-dose statins (5–300 mg kg^{-1}), although these are much larger doses than those routinely used in clinical practice (Table 1). Animal models have employed carrageenan-, formaldehyde-, acetic acid- and formalin-induced pain in both rats and mice.[8]

How statins might exert their effects on pain processing is likely to be influenced by a number of factors, including dynamic changes in somatosensory processing during the perioperative period and dose (and possibly duration) of statin treatment, all of which may alter susceptibility to pro- or anti-nociceptive effects.

Limitations of the current report

Patients in the Cleveland Clinic database were taking statins to reduce cardiovascular risk and to improve lipid profile.[1] The standard clinical doses used in these indications may be lower than those believed to support analgesia in preclinical models, and may have been suboptimal for that purpose. Total hip replacement is an uncomfortable procedure but not as painful as some other operations such as knee replacement. It is possible that statins might have been efficacious against a greater painful stimulus.