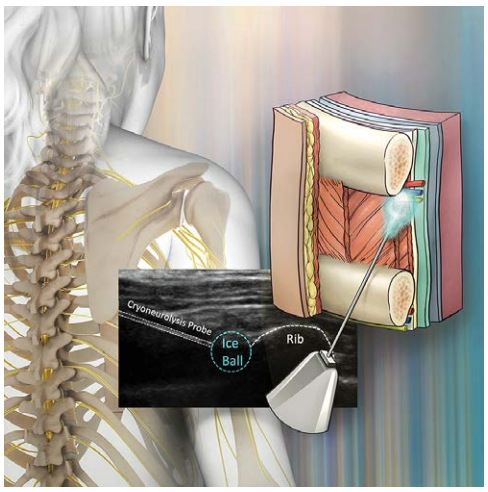
Cryoneurolysis: Interest and Caution

James P. Rathmell, M.D., Joseph D. Forrester, M.D., M.Sc., Kristin Schreiber, M.D., Ph.D.

The ability of cold temperature to render regions of our bodies insensate is second nature. Cryoanalgesia, or the use of cold temperatures to treat pain, as in icing after a sports injury, causes neuropraxia, or slowing of peripheral nociceptive transmission. Such neuropraxia is *different* from the application of focal extreme cold to nerve branches, where nerve injury including Wallerian degeneration is induced (cryoneurolysis). Cryoneurolysis has been studied in humans and other animals with mixed results, depending on the time frame studied, and symptoms assessed. In this issue of Anesthesiology, Ilfeld *et al.*[1] present a small, carefully conducted randomized controlled trial of percutaneous, ultrasound-guided preoperative intercostal nerve cryoneurolysis and its impact on pain outcomes to 1 yr.



"Cryoneurolysis [achieved] astounding results […however] potential for postinjury chronic neuropathic pain remains the loudest note of caution when considering widespread application of cryoneurolysis."

Modern cryoneurolysis began in the 1970s to 1980s, with thoracotomy patients reporting lower pain scores and opioid consumption in the early postoperative time period.[2] Concerns over the development of longer-term neuropathic pain initially limited widespread adoption. In the past decade, however, cryoneurolysis has experienced a resurgence. A more recent series of studies in pectus excavatum patients again demonstrated lower pain scores, opioid use, and hospitalization among patients receiving cryoneurolysis, but once again long-term outcomes were not assessed. With improved cryoneurolysis probes and ultrasound guidance, the use of cryoneurolysis by nonsurgeons has become more common. Skin-graft patients receiving ultrasound-guided cryoneurolysis of the lateral femoral cutaneous nerve reported lower pain scores and opioid consumption and less sleep disturbance during early recovery (3 weeks).[3]

Onto this background of predominantly small observational studies and clinical trials with limited long-term follow-up comes Ilfeld and colleagues' new rigorously conducted trial of preoperative intercostal cryoneurolysis, appearing in this issue of the Journal.[1] In this new study, 60 patients undergoing elective mastectomy were randomly assigned to active or sham percutaneous, preoperative, ultrasound-guided intercostal neurolysis after receiving paravertebral blocks with local anesthetic. The primary outcome was average pain over the preceding 24 h reported on postoperative day 2, and showed cryoneurolysis patients (n = 31) had a median [interquartile range] pain score of 0 [0 to 1.4] *versus* 3.0 [2.0 to 5.0] in sham patients (n = 29), with an average difference of –2.5 (97.5% CI, –3.5 to –1.5), which is both statistically significant ($P < 0.001$) and clinically meaningful. Lower postoperative opioid consumption and pain severity scores at several time points out to 12 months were observed. Phantom breast pain was present in 10 to 19% of control patients at various time points out to 12 months, but in none of the cryoneurolysis patients. Chronic pain at 1 yr was reported in five (17%) patients receiving sham treatment and one (3%) patient receiving cryoneurolysis. At face value, these are astounding results. So, should they trigger widespread adoption of this treatment?

As the first well-controlled, longitudinal trial of preoperative cryoneurolysis, this study has limitations. Despite

Image: A. Johnson, Vivo Visuals Studio.

This editorial accompanies the article on p. 529. This article has a related Infographic on p. A19. This article has an audio podcast.

Accepted for publication August 19, 2022.

James P. Rathmell, M.D.: Department of Anesthesiology, Perioperative, and Pain Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Joseph D. Forrester, M.D., M.Sc.: Department of Surgery, Stanford University, Palo Alto, California.

Kristin Schreiber, M.D., Ph.D.: Department of Anesthesiology, Perioperative, and Pain Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, Massachusetts.

 Anesthesiology 2022; 137:521–3. DOI: 10.1097/ALN.0000000000004365

<zdoi;. DOI: 10.1097/ALN.0000000000004365>

promising outcomes, the study size was modest (just 60 patients) and was insufficiently powered to assess for differences in the development of persistent postsurgical pain. Cryoneurolysis is still technically difficult and time consuming, requiring 40 to 50 min—double that for bilateral mastectomies—even when performed by this expert group. One patient receiving active cryoneurolysis withdrew on day 7. In a study with such small numbers, the impact of one patient who might have developed chronic pain would double the incidence and change the statistical testing of that outcome. Although the Brief Pain Inventory, a simple, well-validated tool with subscales for assessing both pain severity and functional interference, was used, only the proportion of patients reporting pain severity greater than 3 was reported as higher in the control group, and no difference in the pain interference was observed between groups in the long term, raising a question of clinical significance. The Brief Pain Inventory has no questions aimed at identifying neuropathic symptoms. The authors did report a question about phantom breast sensations, but it is unclear what significance the answer to this single question has. Some aspects of neuropathy (numbness) may not be associated with pain, and careful questioning regarding different symptoms, and detailed sensory testing, are needed to assess for neuropathic pain.[4] Without the use of a validated neuropathic pain questionnaire, we are left wondering if this study was conducted in a way that may have led to under- or overreporting of various aspects of neuropathic symptoms in either group. Studies longitudinally tracking different types of neuropathic symptoms in large samples of postmastectomy patients have allowed development of a validated neuropathic pain scale for postsurgical patients.[5] These studies suggest that numbness diverges from other, positive/painful neuropathic symptoms (burning, shooting, among others), underscoring careful longitudinal assessment of individual symptoms.[6]

Potential for such postinjury chronic neuropathic pain remains the loudest note of caution when considering widespread application of cryoneurolysis. Neuropathic pain is produced so reliably after cryoneurolysis that it has been used as a model of chronic pain development in rodents since the 1990s.[7] After sciatic cryoneurolysis, behaviors directed at the nerve-injured limb first peak at 14 days, and subsequent increased bilateral mechanical sensitivity persists even after anatomical resolution of injury, as long as 10 weeks, suggesting the presence of central sensitization. Timing of assessment is crucial. Future studies would do well to carefully assess for neuropathic symptoms other than numbness at later stages. Careful handling of interindividual variability is also crucial, because the range of damage and physiologic changes induced by cryoneurolysis is wide, even in highly controlled animal studies. Although classical Wallerian degeneration was common, a more significant anatomical disruption occurred in a subsample. Variability in the degree of regrowth and reestablishment of a normally functioning system was also observed, even given the same initial injury. It is concerning that two randomized controlled trials in thoracotomy patients do report a greater frequency of neuropathic pain symptoms 3 to 6 months after surgically applied cryoneurolysis.[2]

Untangling surgical and cryoneurolysis-induced injury will be difficult. How will cryoneurolysis-induced neuropathic pain be distinguished from persistent postsurgical pain? Although our patients might easily live with some persistent numbness, it is more to ask of them to live with persistent allodynia. Given extensive preclinical literature and some hints from the clinical literature that neuropathic pain may occur after cryoneurolysis, is it reasonable to ask patients to take this potential risk, even if such nerve injury–induced hyperalgesia and allodynia are rare? Despite these words of caution, Ilfeld *et al.* should be applauded for their pioneering, carefully conducted trial. Ilfeld's new study and commercial promotion of this technology will inevitably lead to more widespread adoption and future studies of cryoneurolysis. We remain cautiously optimistic that future studies will employ detailed, longitudinal, and well-validated measures of both pain and neuropathy. We are keenly interested in the replication of these promising findings in larger cohorts of patients, to truly assure that this nerve injury–based treatment does not introduce a new source of neuropathic pain in a subgroup of vulnerable patients.

Competing Interests

Dr. Forrester has received funding from Varian (Palo Alto, California) for an investigator-initiated trial (https://clinicaltrials.gov/ct2/show/NCT04482582). The other authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Rathmell: jrathmell@bwh.harvard.edu

Supplemental Digital Content

Authors' note: An alphabetical listing of all primary references used to assemble this editorial can be found in Appendix: Additional References (http://links.lww.com/ALN/C915).

References

1. Ilfeld BM, Finneran JJ IV, Swisher MW, Said ET, Gabriel RA, Sztain JF, Khatibi B, Armani A, Trescot A, Donohue MC, Schaar A, Wallace AM: Preoperative ultrasound-guided percutaneous cryoneurolysis for the treatment of pain after mastectomy: A randomized, participant- and observer-masked, sham-controlled study. Anesthesiology 2022; 137:529–42

2. Cha PI, Min JG, Patil A, Choi J, Kothary NN, Forrester JD: Efficacy of intercostal cryoneurolysis as an analgesic adjunct for chest wall pain after surgery or trauma: systematic review. Trauma Surg Acute Care Open 2021; 6:e000690
3. Finneran JJ IV, Schaar AN, Swisher MW, Godat LN, Lee JG, Higginson SM, Ilfeld BM: Percutaneous cryoneurolysis of the lateral femoral cutaneous nerve for analgesia following skin grafting: a randomized, controlled pilot study. Reg Anesth Pain Med 2022; 47:60–1
4. Sloan G, Selvarajah D, Tesfaye S: Pathogenesis, diagnosis and clinical management of diabetic sensorimotor peripheral neuropathy. Nat Rev Endocrinol 2021; 17:400–20
5. Mejdahl MK, Christoffersens KB, Andersen KG: Development and validation of a screening tool for surgery-specific neuropathic pain: Neuropathic pain scale for postsurgical patients. Pain Physician 2019; 22:E81–90
6. Flowers KM, Beck M, Colebaugh C, Haroutounian S, Edwards RR, Schreiber KL: Pain, numbness, or both? Distinguishing the longitudinal course and predictors of positive, painful neuropathic features vs numbness after breast cancer surgery. Pain Rep 2021; 6:e976
7. DeLeo JA, Coombs DW, Willenbring S, Colburn RW, Fromm C, Wagner R, Twitchcll BB: Characterization of a neuropathic pain model: sciatic cryoneurolysis in the rat. Pain 1994; 56:9–16