Title

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To the Editor:

Anesthesiology recently published an editorial titled "Cryoneurolysis: Interest and Caution" which addressed an accompanying study investigating the treatment of postmastectomy pain with ultrasound-guided percutaneous cryoneurolysis.[1] The editorial raised multiple important and valid limitations of the study, as well as noting that caution is warranted because "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."[2] Although we agree that an abundance of caution is indeed warranted before widespread implementation of this analgesic modality, the authors of this letter have potentially important *un*published information that will help put the cited laboratory evidence in perspective for future clinical and laboratory research.

The editorial-cited study involved the treatment of Sprague-Dawley rats with cryoneurolysis, coauthored by this letter's senior author nearly 3 decades ago (R.W.).[3] As described in the Methods, "A 3-cm incision was made… and the common sciatic nerve was exposed by blunt dissection… [and] the nerve was frozen with a cryoprobe as illustrated in Fig. 1."[3] Left unspecified in the text was that each nerve was completely exposed and elevated with forceps at least 4 mm, as can be seen in figure 1 of that article. All animals subsequently exhibited bilateral mechanical allodynia, suggesting central sensitization.[3] The investigators were intentionally inducing chronic pain to be used as an animal model for the subsequent study of various analgesics. The critical step of lifting the nerve out of the body was specified in subsequent articles describing this pain model: "…the sciatic nerve was gently freed from surrounding tissue and elevated. Elevation of the nerve involved *moderate stretching* [emphasis added]."[4,5]

What was never reported was that elevating the nerve was *required* to induce chronic pain in this animal model. In other words, neuropathic pain could not be elicited if the nerve was left *in situ* for cryoneurolysis treatment. Because the investigators were specifically describing a pain model and not studying the clinical risks of cryoneurolysis, they did not publish this information.

However, these unreported laboratory findings have significant implications when comparing percutaneous and "open" cryoneurolysis and may explain the widely varying incidence of cryoanalgesia-related postthoracotomy neuropathic pain in human-subject investigations. As noted in the editorial,[2] two randomized, sham-controlled clinical trials identified an increased incidence of neuropathic pain 3 to 6 months after open thoracotomy with cryoneurolysis applied *via* the incision.[6,7] In contrast, the majority of randomized, controlled studies failed to report a similar increase in chronic pain.[8] Notably, there were considerable differences in intraoperative cryoneurolysis technique, with some surgeons treating nerves *in situ* while others reported significant nerve manipulation that included elevation of the target nerve.[9] For example, one study with a high neuralgia incidence (20%) reported that each intercostal nerve was "*exposed* paravertebrally, *lifted* with a nerve hook, and frozen at *two close sites* [emphasis added]…," suggesting both manipulation and double-crush.[10]

Unfortunately, it is impossible to correlate technique and outcome because the majority of publications do not adequately describe the precise technique or degree of nerve manipulation. However, considering the previously unreported laboratory finding that nerve elevation was required to induce chronic pain—and treatment of the nerve *in situ* never resulted in chronic pain—it is perhaps unsurprising that the incidence of neuralgias after open surgical cryoneurolysis varies so dramatically from 0% (one series of greater than 1,500 patients)[11] to 38%.[12]

If nerve manipulation is required for the postcryoneurolysis neuropathic pain reported in patients, then ultrasound-guided percutaneous cryoneurolysis—as used in the clinical trial addressed by the editorial[1]—should carry no comparable risk. Indeed, to date, no incidence of neuropathic pain has been correlated with percutaneous administration.[13,14] However, far less data exist for percutaneous *versus* trans-incisional cryoneurolysis application. Until further studies are completed using validated neuropathic pain questionnaires, the hypothesis that percutaneous and open cryoneurolysis have different inherent risks for inducing neuropathic pain remains untested. We therefore fully agree with our colleagues who opined that great caution is warranted and that further study is required before widespread clinical adoption. It is for exactly this reason that the United States Department of Defense Congressionally Directed Medical Research Programs has funded a multicenter clinical trial (n = 216) that is intended to overcome the limitations of the recently published single-center study, including the use of a questionnaire specifically designed to identify and differentiate neuropathic pain after

surgery (NCT05444361).[15] In addition, studies directly comparing percutaneous and open cryoneurolysis in laboratory animals would provide important information regarding any differences in neuropathic injury between the two techniques.

Competing Interests

Dr. Ilfeld: The University of California at San Diego has received funding and product for research projects of this author from cryoneurolysis device manufacturers Myoscience (Fremont, California) and Epimed International (Farmers Branch, Texas); perineural catheter manufacturer Ferrosan Medical (Szczecin, Poland); infusion pump manufacturers, Infutronix (Natick, Massachusetts) and Avanos Medical (Alpharetta, Georgia); and a manufacturer of a peripheral nerve stimulation device, SPR Therapeutics (Cleveland, Ohio). This author does not perform consulting work for any private company. Dr. Wagner is an employee of TerSera Therapeutics (Deerfield, Illinois) which develops and manufactures analgesic treatments. This author has no additional conflicts of interest currently; and had no conflicts at the time of her work in the 1990s cited in this letter.

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The corresponding author of the original article referenced above has read the letter and does not have anything to add in a published reply. —Evan D. Kharasch, M.D., Ph.D., Editor-in-Chief

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