

undergo standardization and only some machines undergo the laborious acoustic parameter assessment in the laboratory. This is mainly for cost and time savings, but the difference is likely to be small. But practicing vigilance may help to detect the unknown or an extremely rare event.

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Safety of Ultrasound-guided Regional Anesthesia

To the Editor:

Four years ago, *ANESTHESIOLOGY* published a clinical concepts and commentary article that reviewed the use of ultrasound guidance for regional anesthesia.¹ This article described the underlying principles and available literature of this nascent field. General efficacy and safety of these approaches have been borne out in a large number of subsequent clinical trials.² However, a recent letter to the editor has raised the theoretical concern that bioeffects may be harmful to patients undergoing regional anesthesia procedures guided by ultrasound.³

Although it is clear that there are thermal and mechanical bioeffects of ultrasound, there are no confirmed adverse bioeffects when diagnostic levels of ultrasound are used.* Most bioeffects simply dissipate during the duty cycle of pulse sequence ultrasound and are significantly attenuated by the perfusion of living tissue.⁴ Moreover, when using a handheld probe for imaging during peripheral nerve block, it would be very unlikely for a transducer to be maintained in a fixed position for an extended period. Interestingly, some of the postulated bioeffects of high-intensity ultrasound actually include the promotion of nerve regeneration and conduction block,^{5,6} two effects potentially beneficial to those patients undergoing regional anesthesia procedures. Nonetheless, prudent use of ultrasound means using the lowest levels of exposure to achieve the desired goals (as low as reasonably achievable principle).

When studied *in vitro*, the threshold for ultrasound producing reduction in peripheral nerve compound action potentials was approximately 100–200 W/cm² (continuous wave, 30-s burst, reported intensity as the spatial peak temporal average).⁷ This reduction correlated with nerve temperature elevation from ultrasound exposure and was more pronounced at low frequencies. Irreversible effects only occurred at more than 400 W/cm², well above the current Food and Drug Administration imposed limit of 720 mW/cm² (intensity as the spatial peak temporal average) for diagnostic imaging.⁸ Admittedly, the interaction between local anesthetic toxicity and ultrasound has not been experimentally studied by such models, and the concerns that have been raised will hopefully encourage such investigations.

* Statement on mammalian *in vivo* ultrasonic biological effects. Available at: <http://www.aium.org/publications/statements.aspx>. Accessed December 6, 2009.

The low incidence of significant adverse neurologic outcomes prevents definitive conclusions regarding these complications after regional anesthesia. The difficulties involved in investigating these low frequency, zero tolerance, events can be appreciated by the fact that the relative safety of using nerve stimulation *versus* a paresthetic technique has never been adequately resolved, despite decades of debate. Although the relatively high incidence of transient postoperative neurologic symptoms after regional block can be used to assess the relative risk,⁹ the validity of these symptoms as a surrogate marker of significant injury is speculative. Although substantive data concerning significant injury are lacking, a large retrospective study recently reported five seizures and three nerve injuries in 3,290 patients undergoing peripheral nerve blocks guided by nerve stimulation, but no such events in 2,146 patients undergoing similar blocks guided by both nerve stimulation and ultrasound.¹⁰ There are obviously substantial limitations to such retrospective reviews. Nonetheless, these data, and the published and unpublished experience with ultrasound in this setting, fail to raise alarm and instead imply greater safety by the addition of ultrasound imaging. Whether this is indeed true is obviously of great interest.

Dr. Cory's letter raises important questions regarding the potential impact of beam intensity on neurologic outcomes after regional anesthesia. Beam intensity is only one of the numerous differences between ultrasound guidance and other approaches to regional blockade that could impact safety, all of which mandate rigorous investigation.

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In Reply:

I would like to thank Dr. Shankar for his response regarding my concerns about ultrasound-guided regional anesthesia and for clarifying some of the ultrasound parameters. However, my main reason for writing was that we do not understand the interaction of ultrasound and local anesthetics. No literature exists, that I could locate, addressing the combination effects that have the potential to be significant. The literature also does not support a reduced nerve injury rate when ultrasound guidance is used. In the cases of nerve injury unrelated to positioning, especially pan-plexopathies, when the needle tip was visualized away from the nerve during injection, something other than direct trauma must be playing a role, and assumptions that direct trauma, nerve ischemia, or injection trauma were primarily responsible may be too simplistic.

As I pointed out in my original letter, ultrasound is demonstratively cytotoxic *in vitro* at intensities used for regional anesthesia, and comparison dosimetry with ionizing radiation has been performed.^{1,2} Also, local anesthetics have long been known to be neurotoxic above critical concentrations. Furthermore, the mechanisms of toxicity are different for the two agents. Although both ultrasound and ionizing radiation work primarily by free radical formation, activation of the mitogen-induced protein kinase system is likely responsible for local anesthetic neurotoxicity.³ The mechanism for an ultrasound-related nerve injury may be the formation of hydrogen peroxide from hydroxyl ion and subsequent membrane lipid peroxidation.⁴ This may be offset by the observation that local anesthetics have been shown capable of free radical scavenging, especially hydroxyl ions.⁵ The observations suggest that the combination may actually protect from any ultrasound-related toxicity. If another ultrasound neurotoxic effect is at play, the combination of the two agents may have additive or even synergistic effects. We simply do not know. When a chemotherapeutic agent, that is, cisplatin or methotrexate, is added to the mix, the effects on neurotoxicity may be dramatic.^{6,7}

Regarding the references given by Dr. Shankar and myself to other neurologic effects in animals and humans, I do not read the literature as showing decades of animal research demonstrating clear safety. Rather, there seems to be a fair amount of noise in the literature with some compelling data showing adverse effects on fetal neuronal migration, opening of the blood brain barrier, and adult locomotor abnormalities in mice exposed *in utero* to diagnostic ultrasound levels.⁸⁻¹⁰ The study he quotes in