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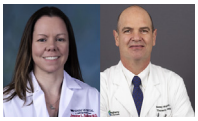
The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.



REPLY FROM AUTHORS: THE POWER OF RANDOMIZATION

Reply to the Editor:

Liposomal bupivacaine was developed to improve analgesia by providing longer analgesic action than the relatively short-acting bupivacaine with epinephrine. Liposomal bupivacaine performed relatively well in retrospective studies, but the results of randomized studies were less conclusive. In cardiothoracic surgery, 2 randomized studies failed to show the benefit of liposomal bupivacaine for postoperative pain control.[1,2]

In the current issue of *JTCVS Open*, Arnold and Antonoff[3] make comments regarding one of those trials.[2] The authors bring a few good points that merit consideration. Our randomized study was a "pure" study attempting to isolate the benefits of liposomal bupivacaine. As such, it made sense not to use Enhanced Recovery After Thoracic Surgery (ERATS) and to carefully exclude patients at high risk for requiring greater doses of narcotics (chronic users of narcotics, those with fibromyalgia, etc). The study by Martin and colleagues[4] cited by the authors as proof that ERATS is beneficial not only is retrospective but used spinal morphine in all anatomic lung resections. The spinal injection of morphine explains the differences in morphine equivalent dosage (MED) use and clouds comparisons with our study. We are believers in ERATS, and since our manuscript, we have adopted several ERATS steps. However, we recognize that randomized trials have not evaluated the role of ERATS in minimally invasive lung surgery. ERATS and liposomal bupivacaine make sense, but do they work? Clark and colleagues[5] used ERATS and compared prospectively collected data on consecutive patients undergoing minimally invasive thoracic surgery. The control group used intercostal nerve block with bupivacaine and epinephrine, and the study group used liposomal bupivacaine. In the study of Clark and colleagues,[5] the control group (bupivacaine with epinephrine) used 8 times the MED used in our study, and the study group (liposomal bupivacaine) used 4 times the MED used in our study despite ERATS. It is easy to see that the role of ERATS after minimally invasive lung surgery still requires careful studies.

Arnold and Antonoff[3] also point out that our volume and perhaps the dose of liposomal bupivacaine used for each nerve block was low. We designed the study to attempt to give an equivalent dose of bupivacaine to both groups. Our control arm had 5 mg of bupivacaine, whereas the liposomal bupivacaine group had 8.6 mg of bupivacaine per intercostal space (266 mg diluted in 30 mL). This is an important point. Ilfeld and colleagues[6] point out that many studies provided patients with a greater dose of bupivacaine in the liposomal form compared with patients in the nonencapsulated form, perhaps proving that more bupivacaine is better for pain but not necessarily that liposomal bupivacaine is superior to nonencapsulated bupivacaine.

Our finding that liposomal bupivacaine is not superior to nonencapsulated bupivacaine is not unique. Recently, 2 manuscripts published in *Anesthesiology*, one a review[6] and the other a meta-analysis,[7] call into question whether liposomal bupivacaine in equivalent dosage is better than nonencapsulated bupivacaine for nerve block. In an astounding turn of events, the maker of liposomal bupivacaine sued the American Society of Anesthesiology for libel.[8]

In the history of medicine, there are many examples of procedures or drugs that make sense but do not work. A painful recent example is high-dose chemotherapy and bone marrow transplant for patients with metastatic breast cancer. Although it makes sense that high-dose chemotherapy and autologous bone marrow transplantation would work, randomized studies did not show improvement in survival.[9] This is the power of randomization, ie, the ability to take out of the equation impressions, "in my experience," anecdotal evidence, and of course investigator bias and produce high-level scientific evidence. If Arnold and Antonoff truly believe that ERATS and increased injection volume/dose will make a significant difference in the use of liposomal bupivacaine, the field is ripe for another careful randomized study that may or may not confirm our findings. Until that time, the best-available evidence is not in favor of the use of liposomal bupivacaine in minimally invasive thoracic surgery.

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