

Local Anesthetic Systemic Toxicity *Improving Patient Safety One Step at a Time*

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Archimedes would have been frustrated as a clinical scientist. Eureka moments in this business are rare: Few of us find the answer to our question when water overflows the bathtub after we gain a few extra pounds, and, contrary to Isaac Newton, we seldom discover grand theories when an apple falls on our head. By and large, progress in the clinical sciences is a slow, plodding extension of the work performed by others before us. And so it is with the outstanding work published in this issue of *Regional Anesthesia and Pain Medicine* by Australian anesthesiologist Michael Barrington and statistician Roman Kluger.¹ Based on their efforts, we now have expanded our knowledge regarding the role of ultrasound guidance in reducing the risk of local anesthetic systemic toxicity (LAST). Barrington and Kluger's laudable contribution builds upon previous work (some their own) to slowly but surely further our understanding of LAST prevention; their efforts should incrementally improve patient safety. Yet complete avoidance of LAST must await another day and further evolution of knowledge. Until then we remain at a familiar crossroads—ultrasound guidance improves selected portions of our practice but does not completely eliminate complications. Thus, one would be ill-advised to place total faith in this remarkable instrument of nerve localization at the risk of ignoring other principles of LAST prevention.²

There is every reason to expect that ultrasound guidance might reduce the incidence of LAST; it allows us to see and hopefully avoid vascular structures, to note the unexpected absence of local anesthetic spread at the moment of injection, and to confidently inject smaller volumes, which should attenuate the effects of both direct intravascular injection and delayed tissue uptake by limiting total local anesthetic dose. Confirmation of these touted benefits has been realized in a remarkably short period of time. In 2009, Abrahams and colleagues³ published a meta-analysis in which ultrasound guidance was clearly linked to a reduction of unintended vascular punctures during performance of peripheral nerve blocks. Unfortunately, it remained uncertain whether reduction in the surrogate outcome of vascular puncture correlated with likewise reduction in the true outcome of actual LAST—as might be defined by fewer episodes of subjective central nervous system excitatory changes coincident with wayward local anesthetic administration or, more significantly, by reduction in major central nervous system toxicity (seizures) and/or cardiac arrest.⁴ On the heels of this meta-analysis, 2 clinical reports that same year described conflicting results. Barrington et al,⁵ in a preliminary report from the same clinical registry used to generate their current study, found no difference in the rate of seizure (overall 95% confidence interval [CI], 0.42:1000–1.9:1000) in more than 7000 peripheral nerve blocks as a function of ultrasound guidance or peripheral nerve stimulation (PNS). In a somewhat smaller quality assurance study, Orebaugh and colleagues⁶ reported fewer seizures associated with upper-extremity blocks performed using PNS alone versus ultrasound guidance with or without adjunctive PNS ($P = 0.044$), but they found no statistical difference if all blocks were included. Subsequent case reports of LAST occurring despite the use of ultrasound continued to surface and the American Society of Regional Anesthesia and Pain Medicine's 2010 evidence-based analysis of ultrasound-guided regional anesthesia therefore concluded that the effect of ultrasound guidance on reducing LAST was essentially too close to call.⁷ Then in late 2012, 2 major studies demonstrated that ultrasound guidance might meaningfully affect the incidence of LAST. The Dartmouth Registry reported by Sites and colleagues⁸ noted only 1 LAST event in 12,668 ultrasound-guided blocks (95% CI, 0.0:1000–0.4:1000). Shortly thereafter, Orebaugh et al⁹ in a further iteration of the University of Pittsburgh's quality assurance work, reported their 6-year frequency of LAST as 6 per 5436 using landmark-PNS localization versus 0 per 9238 using ultrasound-PNS ($P = 0.006$). Slowly but surely, emerging data have proven that ultrasound guidance reduces the rate of not only unintended vascular puncture, but LAST events as well—that is, ultrasound-guidance affects the true outcome.

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The primary finding of Barrington and Kluger's current study¹ is that when compared with PNS alone, ultrasound guidance alone or combined with PNS reduced the likelihood of a LAST event by greater than 65% (odds ratio, 0.28; 95% CI, 0.12–0.65; $P = 0.003$). No matter how the investigators analyzed their data—by univariate or several multivariate models, or by propensity analysis—the results remained consistent. As the authors state, these results provide the strongest evidence to date for an affirmative effect of ultrasound on improving patient safety by reducing LAST incidence across the continuum of its severity. Several factors make this a powerful study: more than 25,000 registered peripheral nerve blocks, the long-established commitment of our Australian and New Zealand colleagues to supporting quality clinical registries, and the extremely high rate of data capture (at worst, only 7% of data were incomplete; importantly, all data related to patients with adverse events were present and confirmed by contact with the involved practitioners). Even the registry's limitations, such as the difficulty in drawing certain conclusions based on only 22 LAST episodes in more than 25,000 blocks, were addressed as best as possible by the authors' willingness to analyze their data using several statistical modalities.

The only worrisome limitation of this study is not with the registry or statistical analysis, but rather the possibility that some practitioners will naturally become overconfident in the belief that using ultrasound will absolve them from further vigilance during their use of local anesthetics. Indeed, hidden in Barrington and Kluger's study¹ are hints that overconfidence may even have affected participants in the Australian and New Zealand Registry of Regional Anaesthesia (AURORA). For instance, practitioners had a higher incidence of LAST when using (presumably safer) lidocaine, particularly in the ultrasound group, which at least raises the possibility of reduced vigilance when ultrasound guidance was used. Another observation was that 57% of the blocks performed with lidocaine contained epinephrine, but only 3% of the blocks performed with the more cardiotoxic ropivacaine contained epinephrine. This practice pattern is representative of that used in Australia and New Zealand where lidocaine but not ropivacaine is formulated with epinephrine and where it is not standard practice to freshly add epinephrine to local anesthetic as is commonly done in North America (personal e-mail communication with Michael Barrington, April 18, 2013). Despite ropivacaine's intrinsic vasoconstrictive properties, there is evidence that epinephrine reduces its peak serum concentration after thoracic paravertebral block,¹⁰ which might be expected to reduce the risk of LAST from tissue uptake. Furthermore, the American Society of Regional Anesthesia and Pain Medicine Practice Advisory on LAST recommends the use of a vascular marker such as epinephrine or fentanyl as a component of strategies designed to better detect intravascular injection of local anesthetic.² Acknowledging that there is no perfect marker of intravascular injection, it is nonetheless curious that many anesthesiologists indeed do not routinely add epinephrine to their local anesthetic injections, as documented by the AURORA, Dartmouth (61% of blocks had no additive of any kind), and University of Pittsburgh (no epinephrine used) studies. Yet there is some evidence that suggests the overall incidence of LAST has been reduced over the past 3 decades, most likely from the incorporation of multiple preventive strategies, including the early 1980s institution of the epidural test dose.¹¹ Knowing that the risk of LAST is perhaps 4- to 5-fold higher for peripheral nerve blocks as compared with epidural blocks,¹² one must at least consider the possibility that using an epinephrine marker might have even further lowered the risk of LAST reported by

Barrington et al,¹ Orebaugh et al,⁹ or Sites et al.⁸ Reassuringly, over the course of the AURORA enrollment period, the milligram-per-kilogram dose of ropivacaine actually diminished, implying that anesthesiologists gained increasing confidence in using less local anesthetic when the injection was guided by ultrasound.

Alas, unlike Archimedes or Sir Isaac, there are no eureka moments for totally preventing LAST. Despite showing progress, the AURORA study still had an overall incidence of 0.87 LAST episodes per 1000 blocks (95% CI, 0.54:1000–1.3:1000), a number reasonably similar to the previous estimate of 0.75:1000 to 2.0:1000 reported by Mulroy and Hejtmanek¹¹ and larger than the 0.25:1000 incidence of seizure reported by Auroy et al.¹² Even while acknowledging the advantage afforded by ultrasound guidance, LAST still occurred despite the use of ultrasound in 12 of 20,401 blocks (0.59:1000; 95% CI, 0.30:1000–1.03:1000). Therefore, similar to other perioperative outcomes, the AURORA study¹ reminds us that it is seldom a single intervention that improves our patients' care, but rather using the entire toolbox. The positive benefit of ultrasound guidance has now been solidified, but it does not absolve us from mindfulness of total local anesthetic dose, careful postblock monitoring, judicious use of intravascular markers, incremental aspiration and injection, and availability of checklists and lipid emulsion for when LAST occurs despite our best efforts.² Not all of these tools are fully understood, much less proven effective. Perhaps Barrington, Orebaugh, Sites, Weinberg,¹³ and others should inspire us to lay the next building block as we strive to understand, prevent, and treat this still uncomfortably common and occasionally fatal complication of regional anesthesia.

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