# Perioperative Lidocaine Infusion: Does the Risk Outweigh the Benefit?

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**GLOSSARY**

**LAST** = local anesthetic systemic toxicity; **MH** = malignant hyperthermia; **PCB** = paracervical block

## A PREDICTABLE PROBLEM RECURS

Local anesthetic systemic toxicity (LAST) is a rare but potentially life-threatening iatrogenic event. Recent practice advances have made regional anesthesia safer, and some thought leaders have even considered whether LAST might no longer be something to fear.[1] Unfortunately, it continues to occur.[2] Comorbidities that sensitize patients to LAST, physician error, system deficiencies, and chance events prevent us from completely eradicating the problem. The risk of LAST is context-sensitive and, by some measures in specific situations, the incidence has not declined over the past decade.[3] Moreover, the recent adoption of perioperative lidocaine infusion at some institutions as a component of Enhanced Recovery After Surgery could increase the risk for LAST.[4] Intentionally infusing lidocaine over an extended time frame means that clinically significant, even fatal events can happen. We must now determine whether the benefits of this practice outweigh such risk.

## HISTORICAL PERSPECTIVE

New methods of using local anesthetics can be accompanied by associated risks that are often at first underappreciated by practitioners. The modern era of awareness for LAST began with Dr Albright's[5] 1979 editorial in which he described 7 cases of cardiovascular collapse including a fatal event involving a parturient. However, the specter of LAST originated much earlier. The first reports of severe local anesthetic–associated toxicity occurred very shortly after Carl Koller introduced clinical use of cocaine as local anesthetic in 1884. Some physicians at the time viewed cocaine as entirely safe, but this opinion lost support as others drew attention to cases of fatal toxicity, both reported and unreported. Sufficient concern developed over the next 40 years that the American Medical Association commissioned a "General Committee for the Study of the Toxic Effects of Local Anesthetics" headed by Mayer[6] to study the problem. They disseminated a questionnaire to practitioners and reported, in their 1924 paper, 29 fatalities related to use of cocaine, procaine, or the combination occurring between 1918 and 1923. Four years later, Dr Mayer[6] described another 13 such cases that came to his attention between 1925 and 1927. None of these 42 cases was previously reported in the literature.

Paracervical block (PCB) was first described for labor analgesia by Gellert in 1926[7] and, by 1967, was considered worldwide as the most popular method for providing labor analgesia for Stage I.[8] Associated fetal bradycardia was well recognized but long thought to be sporadic and clinically unimportant. Nevertheless, published case reports of fetal death after PCB and studies linking it to reduced fetal pH[9] and worsening Apgar scores[10] eventually led to the conclusion that PCB was causally related to fetal distress. This evolution in thought led to change in practice, and PCB is no longer routinely used for labor analgesia.

At roughly the same time, highly potent lipid soluble local anesthetics were introduced to clinical practice primarily for the benefit of their prolonged duration of action. Some experts at the time considered bupivacaine devoid of specific cardiac toxicity and ascribed the cardiovascular instability related to use of these drugs to concurrent hypoxia resulting from associated seizures or apnea.[11] Their recommended treatment for cardiac toxicity based on this belief therefore focused on airway management,

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Accepted for publication November 5, 2020.

Funding: None.

Conflicts of Interest: See Disclosures at the end of the article.

Reprints will not be available from the author.

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DOI: 10.1213/ANE.0000000000005322

especially giving oxygen. At the time of its publication, Albright's[5] editorial was considered radical and must be viewed in this context. He proposed that the cardiovascular instability associated with bupivacaine and etidocaine was specifically due to direct cardiotoxicity and could not be reversed simply by establishing normoxia. In all the cases he described, cardiovascular collapse occurred very quickly after injection and without apparent hypoxemia. The parturient did have seizures, but she rapidly deteriorated and died despite resuscitative efforts. Several of the others recovered only after prolonged resuscitation. Albright[5] made the case that something was distinct and essentially different about these more lipophilic local anesthetics in terms of their disproportionate cardiotoxicity—a point no one would argue today. This opinion became even more relevant at the time given contemporaneous reports of severe LAST events related to obstetric epidural analgesia using 0.75% bupivacaine[12] or those occurring during intravenous regional anesthesia with bupivacaine.[13] Our aggregate clinical experience of these rare but highly adverse events led both to specific changes in practice and a search to understand better the mechanisms of local anesthetic—induced cardiac toxicity. Similar shifts in our practice and attention are needed now.

## ALARMS AND QUESTIONS

The advent of infusing lidocaine for analgesia follows on the earlier use of lidocaine for its anti-inflammatory effects in patients having abdominal surgery.[4] The pressure to minimize opiate use has led some to consider increased reliance on intravenous lidocaine as an alternative for pain relief,[14] in a variety of settings and indications.[15–17] More recently, it has also been proposed as a means of modifying the risk of cancer recurrence.[18] Unfortunately, regardless of the proposed indication, increased use of intravenous lidocaine infusion increases the likelihood that associated LAST events will occur, arguably to the point of virtual certainty. For healthy patients, but especially among those with predisposing comorbidities, infusing local anesthetic intravenously makes occurrences of severe LAST inevitable. A bad outcome may be more likely when the event occurs (a) long after therapy is started so the temporal relation to cause is not obvious and/or (b) away from the operating room where caregivers might be less familiar with the risk and its treatment. Both temporal and physical dislocation from the operating room are common in postoperative lidocaine infusion. While LAST can occur anytime local anesthetics are injected, it can be viewed as an essentially stochastic event in the setting of peripheral nerve block. However, when we begin infusing a local anesthetic directly into the patient's vein, the occurrence of LAST at some point becomes inescapable. It is time to address this problem, and I will begin by asking 3 questions.

Should we study these events? LAST is probably under-reported in general and specifics of fatal events are especially unlikely to be published. I argue that it is necessary we learn the actual scope of the problem, identify the responsible factors, and find ways to prevent or reduce patient harm related to intravenous lidocaine infusion. The American Medical Association did exactly this 1 century ago and made recommendations that arguably saved lives by informing practitioners of the risk of LAST. Similarly, a working group established a decade ago by the American Society of Regional Anesthesia and Pain Medicine partly as a response to Albright's[5] editorial, published advisories that address LAST generally but focused primarily on the setting of nerve block.[19] One argument against a similar undertaking for lidocaine intravenous infusion is that severe toxicity associated with this practice is very rare. But I have doubts that our current system is sufficiently sensitive to detect a danger signal. Without a rigorous examination, we cannot really be sure at what rate such events occur. Hence, I propose forming a group similar to that organized by Dr Mayer[6] to study the problem. Much of the data necessary for determining incidence might already be available in large, administrative databases. Experts could also focus on identifying the cause(s) of such events and potential methods of risk reduction. Subsequently, standardized guidelines could be established for safely administering lidocaine and capturing LAST events when, or preferably before, they occur.

Can we mitigate the risk? Answering this question clearly relies on identifying the root cause(s) of each event. We can then determine the relative contributions of both known and unrecognized problems and analyze them with an eye to correcting them and ultimately to preventing such occurrences. I expect the range of underlying issues would involve simple and complex failures—both obvious and obscure—including, among other possibilities, errors or faults in: physician and staff education, systems design, equipment, drug preparation, operator performance (eg, programing a pump), patient susceptibility and selection, drug–drug interactions, and patient monitoring and surveillance. It is possible there are methods to reduce risk we have not yet adopted such as required learning among relevant staff, or point of care serial lidocaine blood concentration determinations on all patients. Overall, this approach could help judge whether the problem is entirely tractable—a topic that plays directly to my third question.

Is the risk justifiable? Very bad outcomes related to an entirely elective approach to medical care call into question the applicable risk–benefit relationship. Intravenous lidocaine infusion was clearly adopted

as a solution to several problems, not least being the need for an alternative to opiates for pain relief. Do the perceived benefits really outweigh the risk of selecting intravenous lidocaine infusion over other options for perioperative analgesia? I am not certain they do. A systematic review by Weibel et al[20] in the Cochrane database analyzed 68 trials including 4525 randomized participants and concluded they were "…uncertain whether IV lidocaine improves postoperative pain compared to placebo or no treatment at early timepoints (1 to 4 hours)….after surgery" and "….ruled out a clinically relevant reduction in pain with lidocaine at intermediate (24 hours) and at late time points (48 hours)." This result calls into question the rationale for using intravenous lidocaine to achieve perioperative analgesia. In a single institution study, De Oliveira and Eipe[21] reported on 394 patients and found that 56% of them experienced a "clinically important difference" in pain after receiving perioperative lidocaine infusion, typically ~1 mg/kg/h. However, 37 of these patients experienced symptoms consistent with local anesthetic toxicity including one patient having cardiac arrest who recovered after receiving 2 minutes of cardiopulmonary resuscitation and intravenous lipid emulsion. If nearly 10% of patients develop symptoms of LAST in order to provide roughly half of them with some analgesic benefit, are we simply inviting one type of clinical (and professional) catastrophe to avoid another set of potential risks? Answering this question will require input from experts in pain medicine and medical ethics, a range of other clinicians and possibly informed lay persons as well.

## CONCLUSIONS AND RECOMMENDATIONS

I am not certain that even 1 fatality related to lidocaine infusion for analgesia is acceptable. The benefits of this approach might very well outweigh the risks, but we must know this with certainty before more widely adopting the practice. Are we justified in addressing concerns about opiate use by subjecting patients to a different and yet incompletely understood risk? Is it reasonable to substitute one risk for another without having carefully studied the problems created by our newly-preferred method? Our practice should be evidence-based and rational. Albright's[5] prescient thesis was novel for the era and altered our view of local anesthetic toxicity. Severe LAST events before and after his editorial have repeatedly informed and revised anesthesia practice leading, for instance, to the cessation of PCB and 0.75% epidural bupivacaine for labor analgesia as well as the abandonment of bupivacaine for Bier blocks. Another change might be needed now.

LAST is considered a "rare event," yet it occurs at a rate several orders of magnitude greater than malignant hyperthermia (MH), another life-threatening complication of anesthesia (~1:1000 nerve blocks versus 1:30,000–100,000, https://www.mhaus.org/faqs/what-is-the-incidence-of-mh/). Moreover, the anesthesiologist is arguably more responsible (or perhaps more liable) for LAST compared to MH where an event is more sporadic than iatrogenic especially given the contribution of the patient's genetic makeup. Infusing lidocaine is completely elective; therefore, the safety standard for continuing this practice should be very high. This begs a debate that I recommend we as a specialty should entertain. It is perhaps novel to propose empanelling a formal group to study the risk of LAST in lidocaine infusion, but this was done a century ago when issues with LAST were first recognized and again a decade ago to establish a rational approach to its management. Since political and public health issues play into pressure for reducing opiate use, I suggest that epidemiologists and medical ethicists take part in the discussion. This will help address the balance of risk versus benefit. In any case, the solution must be data driven, and I urge the community to begin addressing it now. In the meantime, perhaps we should altogether rethink the practice of perioperative lidocaine infusion.

## DISCLOSURES

**Name:** Guy L. Weinberg, MD.
**Contribution:** This author conceived and wrote the article.
**Conflicts of Interest:** G. L. Weinberg is an officer and shareholder of ResQ Pharma, Inc.
**This manuscript was handled by:** Ken B. Johnson, MD.

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