# Treatment of Local Anesthetic Systemic Toxicity (LAST)

Guy L. Weinberg, MD

Abstract: Severe, systemic local anesthetic toxicity is arguably the most feared complication of regional anesthesia. A combination of old and new therapies is recommended to reduce the morbidity and mortality of symptomatic local anesthetic overdose. Prevention remains the criterion standard for improving patient safety during regional anesthesia. However, when local anesthetic toxicity occurs, considering the diagnosis is the doctor's first step to successful treatment. Preparing a plan of action ahead of time and having the necessary tools readily at hand will likewise contribute to saving the patient's life. Airway management, oxygenation, ventilation, and good basic life support are the sine qua non of successful resuscitation. Seizure suppression is key, and we recommend communicating with a perfusion team for possible cardiopulmonary bypass. Lipid infusion should be considered early, and the treating physician should be familiar with the method. We also recommend avoiding vasopressin and using epinephrine only in small doses. Vigilance, preparedness, and quick action will improve outcomes of this dreaded complication.

(Reg Anesth Pain Med 2010;35: 188-193)

A dverse outcomes from severe (central nervous system [CNS] and cardiac) local anesthetic systemic toxicity (LAST) have been recognized for well over a century.<sup>1</sup> In 2001, the American Society of Regional Anesthesia and Pain Medicine convened a Symposium on Local Anesthetic Toxicity in Miami and later published a series of related articles that included a review of resuscitation strategies for local anesthetic cardiac toxicity.<sup>2</sup> A number of novel, potential treatments were presented, including intravenous lipid emulsion infusion, which reversed toxicity in rodent and canine models of bupivacaine overdose. Subsequently, several case reports have appeared to validate the efficacy of this technique in rescuing patients with severe cardiovascular compromise in the setting of regional anesthesia.<sup>3–10</sup> Editorials<sup>11–14</sup> have advocated lipid for treating severe LAST and the method is gaining acceptance in the anesthesiology community.<sup>15</sup>

This article is a logical continuation of the efforts leading to the 2008 ASRA Practice Advisory on Neurological Complications of Regional Anesthesia and Pain Medicine—the focus is similarly on advancing patient safety during regional anesthesia. It frames recent advances within a historical and clinical context and emphasizes fundamental components of resuscitation as applied specifically to LAST. Areas of controversy are addressed, areas of ignorance are acknowledged, and specific guidelines for treatment are proposed. Although

Accepted for publication November 25, 2009.

Address correspondence to: Guy L. Weinberg, MD, Department of

Preliminary versions of this article were presented at the 33rd Annual Regional Anesthesia Meeting and Workshops, May 1–4, 2008, Playa del Carmen, Cancun, Mexico.

ISSN: 1098-7339

DOI: 10.1097/AAP.0b013e3181d246c3

the advent of lipid therapy is arguably the most significant recent change in treating LAST, it is important we not overlook other key elements of treatment and other possible modes of therapy. Cyclodextrins, for instance, could theoretically be developed to scavenge and inactivate specific local anesthetics. Although no work along these lines is currently published, its utility as a potential future antidote to drug overdose should not be ignored.

## **METHODS**

The medical literature was surveyed for articles pertaining to treatment of severe, systemic local anesthetic toxicity. Specifically, the PubMed database was interrogated using combinations of the following search terms: *local anesthetic, regional anesthesia, nerve block, toxicity, cardiac arrest, resuscitation, myocardial depression, epinephrine, vasopressin, vasopressor, cardiopulmonary bypass, lipid, lipid rescue, emulsion, bupivacaine, levobupivacaine, mepivacaine, lidocaine, ropivacaine,* and *etidocaine.* Searches were then run with selected limits including human and animal studies, case reports, and English and French language. Notably, the cited references date from 1960 to 2009, covering nearly half a century of research on the topic. Earlier works are cited in the chapter on history of local anesthetic toxicity.

# Primacy of Airway Management

Moore and Bridenbaugh<sup>16</sup> emphasized the importance of airway management and the prevention of acidosis and hypoxia in treating LAST. They reported no instances of irreversible cardiac collapse among 112 cases of severe toxicity managed with mask ventilation and oxygenation. Interestingly, although their data were collected from 1948 to 1955, in a "prebupivacaine" era, it indicated an incidence of severe toxicity (respiratory arrest, grand mal seizures, or cardiovascular collapse) after peripheral nerve blocks that is in agreement with recent estimates (excluding spinals and epidurals, 16/12,229; 0.6%).<sup>17</sup> Moore et al<sup>18</sup> continued to strongly advocate for treatment focused on reversing hypoxia and acidosis and later reported their experience with 28 patients who had seizures among 20,748 bupivacaine-based regional (intercostal and epidural) anesthetics over 12 years (toxicity prevalence, 0.13%).<sup>19</sup> No patient progressed to cardiovascular collapse, prompting the comment, "Our experience is that immediate treatment of convulsions within 15 to 30 secs of their onset especially correcting hypoxia and acidosis is not associated with cardiac catastrophe." However, this apparent lack of local anestheticinduced cardiac arrest among a small cohort of patients with CNS toxicity obviously does not indicate that such events will never occur. Indeed, in cases of lipophilic local anesthetic overdose (eg, bupivacaine), cardiac arrest can occur simultaneously with convulsions even in the absence of hypoxemia. Nevertheless, laboratory investigations confirm that acidosis and hypoxemia exacerbate local anesthetic toxicity<sup>20,21</sup> and presumably hinder resuscitation.

# Seizure Suppression

A corollary to the importance of maintaining metabolic homeostasis is the need to suppress seizures to prevent or reduce

From the University of Illinois College of Medicine, Jesse Brown VA Medical Center, Chicago, IL.

Anesthesiology, M/C 515, University of Illinois Hospital, 1740 Taylor St, Chicago, IL 60612 (e-mail: guyw@uic.edu).

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the severity of resulting metabolic acidosis. Benzodiazepines have been shown experimentally to prevent local anestheticinduced seizures in a variety of animal models<sup>22-24</sup> and are the preferred treatment for this purpose. Propofol, however, can produce cardiovascular depression, an effect that could be detrimental in the setting of preexisting or evolving cardiovascular compromise. Because a proportion of patients exhibiting early signs of local anesthetic toxicity will progress to cardiac arrest, the concern is that adding propofol could potentially exacerbate or accelerate this problem. This caveat should be weighed against laboratory evidence reported by Ohmura et al<sup>25</sup> that propofol can attenuate bupivacaine-induced arrhythmias and depression of mean arterial blood pressure during continuous infusion of bupivacaine in rats. On balance, it seems reasonable to administer small doses of propofol for seizure suppression when a benzodiazepine is not immediately available, given that the patient shows no evidence of cardiac compromise. However, benzodiazepines should be considered the agents of choice for local anesthetic-induced seizures. One other agent to consider for intractable seizure activity is succinvlcholine. Although this approach will provide no benefit for the abnormal CNS electrical activity, rapidly stopping the tonic-clonic muscular activity, as when it is used in electroshock therapy, should attenuate the metabolic acidosis of generalized seizures.

# **Circulatory Support**

Sustaining coronary perfusion is key to treating cardiac arrest. This obvious statement derives from the less-than-obvious fact that local anesthetic itself does not irreversibly damage cardiac myocytes. In theory, therefore, prompt and appropriate therapy should reverse cardiac effects of local anesthetics. There is experimental evidence that, with adequate coronary perfusion, bupivacaine rapidly leaves cardiac tissue with a parallel return of normal cardiac function.<sup>26,27</sup> The lack of a permanent cardiac injury after local anesthetic toxicity in the absence of tissue hypoxia is confirmed by reports of resuscitation from severe bupivacaine-induced toxicity with the use of cardiopulmonary bypass.<sup>28</sup> Cases of successful lipid reversal of toxicity with normal hemodynamic function after prolonged cardiac arrest provide similar support for notion that drug-induced cardiac arrest does not itself lead to irreversible myocardial damage.<sup>7</sup>

The interdependent effects of tissue acidosis, decreased myocardial contractility, and reduced coronary perfusion can generate a self-perpetuating cycle of tissue intoxication that is most directly reversed by reestablishing coronary artery perfusion, which in turn both allows egress of bupivacaine from cardiac tissue and ameliorates tissue hypoxia. The most effective means of doing this would be a treatment, such as lipid infusion, that draws down myocardial content of the offending toxin, thereby allowing improved contractility and perfusion, which in turn further enhances recovery.<sup>27</sup> This is consistent with the observation in experiments using an open-chest canine model of overwhelming bupivacaine toxicity that myocardial tone and contractility return when the surface of the heart turns white from the lipid bolus washing through the coronary circulation. An important clinical corollary to the reversibility of local anesthetic toxicity is that resuscitation can be successful even after prolonged intervals of cardiac arrest. Therefore, it is reasonable to continue prolonged resuscitation in the absence of compelling evidence that it is unlikely to work (eg, prolonged asphyxia).

Cardiopulmonary bypass has saved patients with otherwise fatal LAST. A particularly dramatic example involved a patient in ventricular fibrillation after a popliteal block with bupivacaine.<sup>29</sup> Fortunately, the patient was in a room located just a few feet from the cardiac suite where a bypass machine was available and primed. The patient had an emergency sternotomy, and the aorta and right atrium were rapidly cannulated: she was on bypass within 30 mins of the arrest and subsequently had full cardiac and neurologic recovery. This case points out the need to think early in the resuscitation sequence about the possibility of establishing cardiopulmonary bypass should other measures fail to reestablish independent circulation. If the case is in a center where cardiac surgery is performed routinely, the perfusion team should be notified early. If the arrest occurs in an outpatient facility, calls should be made to arrange for possible transfer to a cardiac center while advanced cardiac life support is continued and protocols for such transfer should be in effect. Other, less extreme resuscitative measures might succeed, but if not, cardiopulmonary bypass could be the patient's last hope.

# Lipid Infusion

Lipid emulsion therapy was mentioned as one of several novel therapies in the 2001 symposium, and since then, it has been the only such treatment that has been used with apparent success in a clinical setting. Propofol, insulin/potassium/glucose, and nanoparticles had previously all been shown to attenuate laboratory models of bupivacaine toxicity; however, none of these has been used in the successful treatment of clinical local anesthetic toxicity in a patient. Cyclodextrins specifically designed to capture local anesthetics have also been suggested as a possible antidote to local anesthetic overdose, but no data supporting this method have been published to date. Therefore, although future studies might point to new therapeutic options, none of the alternative, novel modes of treatment can be recommended at this point.

Evidence for a beneficial effect of lipid infusion in LAST was first published more than a decade ago in a rat model of bupivacaine-induced asystole.<sup>30</sup> Subsequent studies in dogs<sup>31</sup> confirmed the efficacy of lipid in reversing severe bupivacaine cardiac toxicity. Experiments in rat isolated heart suggested that underlying mechanisms involve both partitioning (lipid sink)<sup>27</sup> and metabolic effects<sup>32</sup>; other possible mechanisms have not been excluded. Rosenblatt et al<sup>7</sup> published in 2006 the first clinical report of lipid emulsion used to reverse cardiac arrest in the setting of local anesthetic toxicity—a translational milestone that bridged laboratory experience to the clinic. Since then, there have been multiple reports of the successful use of lipid in treating local anesthetic–induced cardiovascular collapse.

The patient reported by Rosenblatt et al<sup>7</sup> had a history of coronary artery disease and had failed more than 20 mins of standard life support therapy including ventilation with oxygen, chest compressions, vasopressors, and multiple countershocks. A lipid infusion rapidly restored normal hemodynamic parameters. The patient recovered completely with no evidence of myocardial damage. The similarity of several subsequent reports suggests that underlying ischemic heart disease or cardiac conduction defects may predispose to local anesthetic cardiac toxicity. One might infer that lipid infusion is superior to standard resuscitation medications for this problem because many reported patients have responded to lipid after having failed to respond to standard therapy including high-dose pressors (see Vasopressor Therapy).

# **Generalization of Lipid Therapy**

A case of successful resuscitation using lipid for a combined bupropion and lamotrigine overdose was reported by Sirianni et al.<sup>33</sup> The patient was a 17-year-old who attempted suicide and had a witnessed arrest in the intensive care unit. After failing more than 70 mins of resuscitation with multiple countershocks, maximal adrenergic therapy, sodium bicarbonate, and amiodarone, normal vital signs were reestablished at less than 1 min after a bolus of lipid emulsion. Another case involved reversal of haloperidol-induced torsades. The patient failed 15 mins of conventional resuscitation and regained circulation and consciousness shortly after receiving an intravenous lipid bolus. A puppy with an overdose of moxidectin that resulted in coma and ventilator dependence<sup>34</sup> woke up shortly after infusion of lipid emulsion. Other anecdotes of reversal of drug overdoses can be found at www.lipidrescue.org (under the section Post Your Cases). Haloperidol (Haldol), bupropion, moxidectin, and bupivacaine have nearly identical octanol-water partition coefficients. In the aggregate, these cases provide support for use of lipid for treating toxicity due to lipophilic drug overdose.

# Vasopressor Therapy

Positive effects of vasopressors in animal models of cardiac arrest have not translated into a clear advantage for their use in the clinical setting.<sup>35</sup> Epinephrine has been associated with suboptimal outcomes in models of various shock states<sup>36</sup> and strong clinical evidence of efficacy in enhancing long-term survival after cardiac arrest is lacking.<sup>37</sup> Furthermore, recent studies suggest that adding vasopressin provides no advantage over epinephrine alone in treating out-of-hospital cardiac arrest.<sup>38,39</sup> Notably, with the exception of patients responding to initial cardioversion, survival rates after resuscitation from cardiac arrest to hospital discharge are appallingly low (~2%). However, cardiac arrest per se is etiologically heterogeneous, and treatment strategies should ideally address the underlying cause for each event and should differentiate between ischemia and toxin-induced arrest. The enticing possibility of an antidote to toxin-induced cardiac arrest suggests the possibility of better outcomes for this subgroup, particularly when applied to the witnessed in-house arrest where rapid intervention prevents severe asphyxia. If lipid infusion is a specific treatment of local anesthetic overdose, where does that leave vasopressor/ vasoconstrictor therapy?

Given the importance of restoring coronary circulation, the positive inotropic and vasopressor effects of epinephrine provide a strong rationale for its use in local anesthetic toxicity, which may be characterized by contractile depression, arrhythmias, and hypotension. Epinephrine should also counter bupivacaineinduced inhibition of cyclic 3',5'-adenosine monophosphate production, a possible contributor to its cardiodepressant effects.<sup>40</sup> Although epinephrine is generally effective in restoring circulation in animal models of toxicity, it is also highly arrhythmogenic. Recent studies comparing resuscitation with lipid versus epinephrine in a rodent model of bupivacaine-induced asystole showed better outcomes with lipid.41 Epinephrine provoked severe arrhythmias and was associated with poor recovery of hemodynamic and metabolic parameters. Notably, systolic pressures were elevated for the first few minutes after treatment with epinephrine then declined progressively over 10 mins to values that were no different from the saline controls. Thus, early elevation of systolic pressure did not predict good recovery, suggesting that systolic hypertension was not indicative of improved coronary perfusion. Vasopressin has been suggested as an alternative means of improving coronary perfusion without the attendant arrhythmias caused by epinephrine. However, in a similar rodent model, Di Gregorio et al<sup>42</sup> showed that vasopressin was associated with very poor hemodynamic and metabolic profiles and resulted in pulmonary hemorrhage in virtually all animals. Lipid infusion, by contrast, allowed for hemodynamic recovery of all study animals and resulted in a far better metabolic profile (pH, central venous oxygen tension [CcvpO<sub>2</sub>], lactate) than observed with any of the vasopressor regimens (epinephrine and vasopressin, alone or the combination). Laboratory investigation is needed to determine whether use of vasopressors with lipids provides any advantage over lipid alone. Interestingly, Mayr et al43 showed in a pig model of bupivacaine overdose that recovery was much better among subjects receiving epinephrine plus vasopressin than for pigs receiving lipid. It is possible that differences in the model and experimental end points account for this apparent contradiction with results from the Weinberg laboratory.<sup>44</sup> The bupivacaine challenge (5 mg/kg) in the study by Mayr et al43 was smaller than that used in the rat studies (20 mg/kg) and was supplemented with a period of prolonged apnea up to and beyond the point of asystole. Hence, treatments were given in a setting of hypoxia, a condition for which lipid therapy has never been proposed. Further, Mayr et al<sup>43</sup> scored recovery by systolic pressure, an end point that Di Gregorio et al<sup>42</sup> showed does not correlate with metabolic or circulatory recovery in the rat model of bupivacaine overdose. Clearly, the selection of experimental design, metrics, and end points can influence the outcome and even invert the conclusions drawn from otherwise apparently similar studies.

# Unanswered Questions Regarding Lipid Therapy

# **Timing and Safety**

Lipid infusion was originally recommended as a therapy of last resort for use only after standard resuscitative efforts had failed. However, frequent reports of successful resuscitation with lipid infusion have led clinicians to use it progressively earlier in the toxic syndrome, and positive reports from such cases suggest that early infusion of lipid might avoid progression of toxicity to cardiac arrest. Early use is reasonable if one assumes that lipid infusion carries a minimal risk. While there are no published reports of adverse outcomes related to acute lipid infusion for resuscitation, the safety of acute, high-volume lipid emulsion infusion is not precisely known. Therefore, the logic behind early use cannot be extrapolated to pretreatment, that is, before evidence of systemic toxicity, because the relative risks of lipid infusion versus LAST are unknown. On balance, signs of rapid progression of the toxidrome, or detection of cardiac compromise in terms of either an electrocardiographic abnormality or depressed cardiac output, would constitute reasons for early treatment with lipid.

## **Treatment Regimen**

The clinical recommendation that the initial lipid bolus should be followed with a continuous infusion was based on laboratory observations in rats and dogs that the return of normal circulation after lipid bolus was often followed by a decline in blood pressure that would respond to a subsequent lipid infusion. This approach is consonant with the clinical observation that hemodynamic compromise due to LAST can persist or recur after initial treatments (for examples, see Levsky and Miller<sup>45</sup>). This phenomenon seems to argue against a simple binding model for lipid's beneficial effect. It seems prudent to monitor a patient for at least 12 hrs after a toxic event that included evidence of significant cardiovascular compromise (eg, ventricular arrhythmias or hypotension requiring intervention).

## Use in Children

Evidence for the efficacy of lipid emulsion in children is limited. There is 1 published report of successful lipid resuscitation of a 13-year-old girl with electrocardiographic changes

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after a brachial plexus block. Lipid emulsion has been successful in a neonate<sup>46</sup> with severe cardiac compromise after caudal analgesia with bupivacaine. Establishing safe dosing limits for lipid will be important in neonates and children because complications from lipid overload have been reported in neonates receiving intravenous nutritional support.<sup>47</sup>

#### **Alternative Formulations**

Laboratory and clinical experiences with lipid-based resuscitation, to date, have primarily used Intralipid (Fresenius Kabi, AG, Bad Homburg, Germany), a soy-based lipid emulsion containing predominantly long-chain fatty acids). However, there is no evidence that this preparation is uniquely effective as an antidote, and other similar formulations have recently been reported to be effective in resuscitating patients with LAST. These include Liposyn (also soy-based; Hospira, Lake Forest, Ill) and Medialipid (B. Braun, Melsungen, Germany; this preparation contains a mixture of long- and medium-chain tri-glycerides). Van de Velde et al<sup>48</sup> found that acute administration of Medialipid in chronically instrumented dogs resulted in increased systemic vascular resistance and reduced ventricular contractility-effects that could be potentially detrimental in local anesthetic overdose. An important caveat regarding another lipid-containing formulation is that propofol cannot be used as a source of lipid to treat anesthetic toxicity. Although low-dose propofol might be useful for treating convulsions, the volume of standard formulation (1% propofol in 10% lipid emulsion) needed to deliver enough lipid for treating LAST would carry a massive, potentially lethal, dose of propofol.

## Treatment of CNS Symptoms of Toxicity

Neurological symptoms typically occur early in the toxic syndrome of local anesthetic overdose. Recent case reports sug-

gest that treatment with lipid emulsion infusion can ameliorate altered mental status, obtundation, agitation, or seizures.<sup>3,5,49</sup> In these cases, lipid was infused with the intent of preventing progression to cardiac compromise, and authors noted resolution of CNS symptoms. This has both clinical and scientific significance. Improvement in neurologic signs with lipid infusion speaks against a metabolic mechanism for its antidotal effects because the brain does not use lipid as an energy source. Hence, antagonism of bupivacaine's inhibitory metabolic effect could not be a mechanism for reversal of neurologic symptoms, and the clinical reversal of neurologic symptoms by lipid infusion thereby provides indirect support for a more generic effect in reversing toxicity (eg, the lipid sink).

#### Dosing

It is critical to emphasize the importance of prevention-a far better method of managing local anesthetic toxicity than any known treatment. Nevertheless, systemic toxicity will continue to occur even in the context of good clinical practice. Continued mindfulness of the possibility of local anesthetic toxicity during and after regional anesthesia will also improve patient safety by increasing the likelihood of timely intervention. Current recommendations for lipid dosing (eg, Association of Anaesthetists of Great Britain and Ireland Guidelines for the Management of Severe Local Anaesthetic Toxicity; http://www.aagbi.org/ publications/guidelines/docs/latoxicity07.pdf) are of necessity guided by laboratory studies and anecdotal clinical reports rather than rigorous clinical studies of efficacy and toxicity. This is not a condition for which there will be evidence-based treatments identified in randomized clinical trials. Fortunately, the typical doses reported for resuscitation are far lower than the maximal rates recommended by the Association of Anaesthetists of Great Britain and Ireland and, earlier, by Weinberg.<sup>50</sup> Among

TABLE 1. Recommendations for Treatment of Local Anesthetic Systemic Toxicity (LAST)

- If signs and symptoms of LAST occur, prompt and effective airway management is crucial to preventing hypoxia and acidosis, which are
  known to potentiate LAST (I; B).
- If seizures occur, they should be rapidly halted with benzodiazepines. If benzodiazepines are not readily available, small doses of propofol or thiopental are acceptable. Future data may support the early use of lipid emulsion for treating seizures (I; B).
- Although propofol can stop seizures, large doses further depress cardiac function; propofol should be avoided when there are signs of cardiovascular compromise (III; B). If seizures persist despite benzodiazepines, small doses of succinylcholine or similar neuromuscular blocker should be considered to minimize acidosis and hypoxemia (I; C).
- If cardiac arrest occurs, we recommend standard advanced cardiac life support with the following modifications:
  - $\circ$  If epinephrine is used, small initial doses (10- to 100-µg boluses in adults) are preferred (IIa; C).
  - Vasopressin is not recommended (IIB; B).
  - Avoid calcium channel blockers and beta-adrenergic receptor blockers (III; C).
- If ventricular arrhythmias develop, amiodarone is preferred (IIa; B); treatment with local anesthetics (lidocaine or procainamide) is not recommended (III; C).
- Lipid emulsion therapy (IIa; B):
  - o Consider administering at the first signs of LAST, after airway management.
  - Dosing
    - 1.5 mL/kg 20% lipid emulsion bolus
    - Infusion of 0.25 mL/kg per minute, continued for at least 10 mins after circulatory stability is attained
    - If circulatory stability is not attained, consider giving another bolus and increasing infusion to 0.5 mL/kg per minute
    - Approximately 10 mL/kg lipid emulsion over 30 mins is recommended as the upper limit for initial dosing.
- Propofol is not a substitute for lipid emulsion (III; C).
- Failure to respond to lipid emulsion and vasopressor therapy should prompt institution of cardiopulmonary bypass (IIa; C). Because there
  can be considerable lag in beginning cardiopulmonary bypass, it is reasonable to notify the closest facility capable of providing it when
  cardiovascular compromise is first identified during an episode of LAST.

The class of recommendation and level of evidence for each intervention are given in parenthesis.

the 12 published cases where lipid was successfully used for resuscitation, the mean total (bolus plus infusion) lipid dose over the first 30 mins was 3.8 mL/kg (range, 1.2-6.0 mL/kg). Most important, no overt complications related to use of lipid emulsion for resuscitation have been reported to date.

Based on the available information, we recommend an initial bolus of 20% lipid emulsion using 1.5 mL/kg (of lean body mass) followed by an infusion at 0.25 mL/kg per minute until circulatory stability is achieved. The bolus could be repeated for failure to restore circulation, and the infusion could be increased to 0.5 mL/kg per minute for recurring hypotension after initial recovery. However, volume overload is certainly a risk, and lipid overdose might also carry as yet unknown risks. Defining the maximal safe dose for acutely administered 20% lipid emulsion for this novel use is important and will require appropriate (large) animal studies and possibly experiments with volunteers receiving subtoxic doses of bupivacaine. We currently recommend an upper limit of approximately 10 mL/kg over the first 30 mins. This would allow for 2 boluses plus a continued infusion at 0.25 mL/kg per minute, more than twice the average published dose shown above. The overall approach can be synthesized into a sequence summarized in Table 1.

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