Clinical Presentation of Local Anesthetic Systemic Toxicity

A Review of Published Cases, 1979 to 2009

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Abstract: The classic description of local anesthetic systemic toxicity (LAST) generally described in textbooks includes a series of progressively worsening neurologic symptoms and signs occurring shortly after the injection of local anesthetic and paralleling progressive increases in blood local anesthetic concentration, culminating in seizures and coma. In extreme cases, signs of hemodynamic instability follow and can lead to cardiovascular collapse. To characterize the clinical spectrum of LAST and compare it to the classic picture described above, we reviewed published reports of LAST during a 30-year period from 1979 to 2009. Ninety-three cases were identified and analyzed with respect to onset of toxicity and the spectrum of signs and symptoms. Sixty percent of cases followed the classic pattern of presentation. However, in the remainder of cases, symptoms were substantially delayed after the injection of local anesthetic, or involved only signs of cardiovascular compromise, with no evidence of central nervous system toxicity. Although information gained from retrospective case review cannot establish incidence, outcomes, or comparative efficacies of treatment, it can improve awareness of the clinical spectrum of LAST and, theoretically, the diagnosis and treatment of affected patients. The analytic limitations of our method make a strong case for developing a prospective, global registry of LAST as a robust alternative for educating practitioners and optimizing management of LAST.

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The seminal editorial by Albright[1] in 1979 served to raise general awareness among the anesthesiology community about the dangers of local anesthetic systemic toxicity (LAST). He reported cases of severe cardiac toxicity associated with use of the long-acting local anesthetics (LA) bupivacaine and etidocaine and made the prescient observation that the potential for causing cardiac toxicity was related to the drug's lipophilicity. Optimal treatment of LAST requires early detection and intervention, and although the phenomenon has been extensively studied in the laboratory, its actual clinical spectrum has not been rigorously evaluated. Signs of LAST are highly species and model–dependent, and the findings of laboratory studies can only be extrapolated to the clinical setting with caution. The classic symptom complex for LA overdose presented in textbooks includes a progression from prodromal symptoms, for example, tinnitus or agitation, immediately after an intravascular injection or systemic uptake of LA, to seizures then, if sufficiently high blood concentration is achieved, ventricular arrhythmias and cardiac arrest. However, it is clear from the medical literature that not all cases of LAST fit so neatly into this paradigm. The very low incidence of LAST hampers its study by prospective human trials and randomization is neither scientifically appropriate nor ethical. Therefore, we performed an extensive review of reported cases of LAST to test the hypothesis that many cases do not adhere to the classic or "textbook description" of LAST.

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METHODS

Reports of LAST published during the 30-year period October 1979 to October 2009 were reviewed with a focus on clinical presentation. Mechanisms of toxicity, drug comparison, LA doses, and treatment are beyond the scope of this article. Cases were identified by a search of medical literature search engines, including MEDLINE–PubMed (US National Library of Medicine and National Institutes of Health), Biological Abstracts, Web of Science, and Bandolier. Key words and search terms included the following: local anesthetic, toxicity, cardiac, bupivacaine, levobupivacaine, ropivacaine, lidocaine, cardiac arrest, seizure, resuscitation, detection, and diagnosis. We reviewed only articles in English, French, and German because these provided more thorough and accessible descriptions than reports in other languages that were either difficult for us to translate or provided less clinical detail. We only included reports related to regional anesthesia published in the form of case reports, letters to the editor, and reviews. Reports were excluded from the review if they provided incomplete descriptions of the patient, LA used, nerve block performed, timing, or nature of the clinical presentation. When presenting our results, we have elected not to individually cite the scores of reports that contributed to the calculation of global data points, such as the breakdown of LAST by sex or the number of reports wherein central nervous systemic toxicity was present. We do cite those specific references that report more unusual presentations, such as markedly delayed onset of LAST.

RESULTS

Setting of LAST

We identified 93 separate LAST events occurring during regional anesthesia, reported in 74 different articles[1–74] since 1979. Sixty-five percent of these articles were published within the last 10 years (Fig. 1). The most common anesthetic techniques associated with LAST were epidural block (33%), followed by axillary (17%) and interscalene (13%) blocks.

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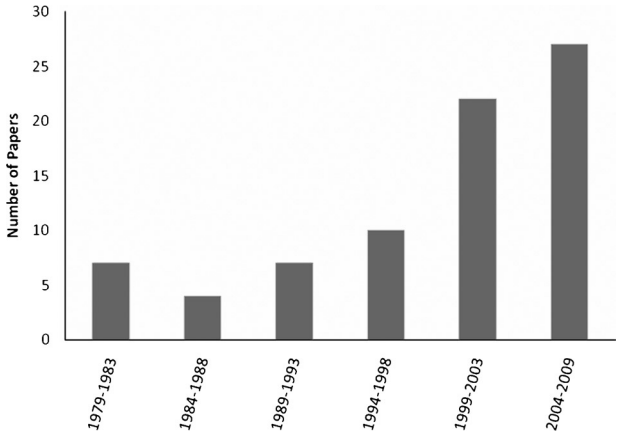

FIGURE 1. The distribution of published case reports of LAST shown in 5-year intervals during the past 30 years.

Seventy-seven cases occurred after a single injection of LA, 14 were related to continuous infusion of LA,[3,5–7,17,24,32,48,72] and 2 involved continuous infusion with symptoms occurring after a supplementary single injection.[67] Fifty-two events (55%) were related to bupivacaine, 28 (30%) to ropivacaine, 4 (4%) to levobupivacaine, and 9 (11%) to other LA.

Patient Characteristics

Approximately 63% of the patients were female. Sixteen percent were younger than 16 years and 29% were older than 60 years. We identified 5 reports of severe LAST in newborns receiving epidural analgesia.[12,48,49,63] Thirty-seven percent of events involved patients with a history of cardiac, pulmonary, neurologic, and/or metabolic disease, for example, diabetes mellitus, renal failure, or isovaleric acidemia.

Timing of LAST

The 77 cases of toxicity after a single injection of LA included a wide range of times to the onset of signs of toxicity. A non-numeric description was often given for the shortest times, for example, "immediate" or "rapid" onset. In these instances, a value of 30 secs was imputed for the purpose of analyzing the timing of symptoms. This value was a compromise between 0, which carries statistical and arithmetic problems, and 60 secs, a typical circulation time. We considered the imputation a statistically conservative method for calculation of descriptive statistics. The data did not fit a normal distribution. The median time after single injection was 52.5 secs (25%–75%, 30–180 secs), and the geometric mean for the interval was 88.6 secs (95% confidence interval, 66.5–120 secs). The distribution of time intervals is shown in Figure 2. Notably, in 19 (25%) of 77 cases, the symptoms occurred at 5 mins or more after the injection. The greatest time interval between a single LA injection and the onset of signs of systemic toxicity was 60 mins.[10] Sixteen reports of LA toxicity were identified during continuous infusion of LAs, about half occurring in pediatric patients. The onset of symptoms related to toxicity in this setting was generally delayed, occurring hours or days after the starting the infusion.

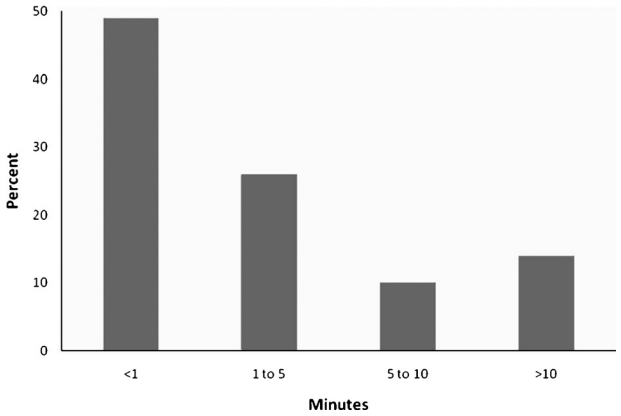

FIGURE 2. The timing for onset of signs of LAST after a single injection of LA (from a total of 77 incidents).

Clinical Spectrum of LAST

Neurologic Signs of Toxicity

Symptoms of central nervous system (CNS) toxicity occurred in 83 (89%) of 93 cases and were isolated, that is, occurring with no cardiovascular (CV) symptoms in 42 of these cases (45% of all reports; Fig. 3). The most common CNS sign of toxicity was seizure, which occurred in 63 (68%) of 93 cases. Using the total number of reported CNS symptoms as denominator (in place of total number of cases) gives an idea of the range and proportion of specific symptoms in a given category (Fig. 4). Because most patients experienced multiple signs or symptoms of toxicity, the denominators exceed the number of patients (100 reported CNS symptoms; 83 CV symptoms). By this method, seizure, agitation, and loss of consciousness were the most frequent signs of CNS toxicity (together, 82%) and the remaining prodromal signs, for example, dysarthria, perioral numbness, confusion, obtundation, and dizziness, were individually uncommon and, in the aggregate, accounted for 18% of reported symptoms and occurred in 15 (16%) of the 93 patients.

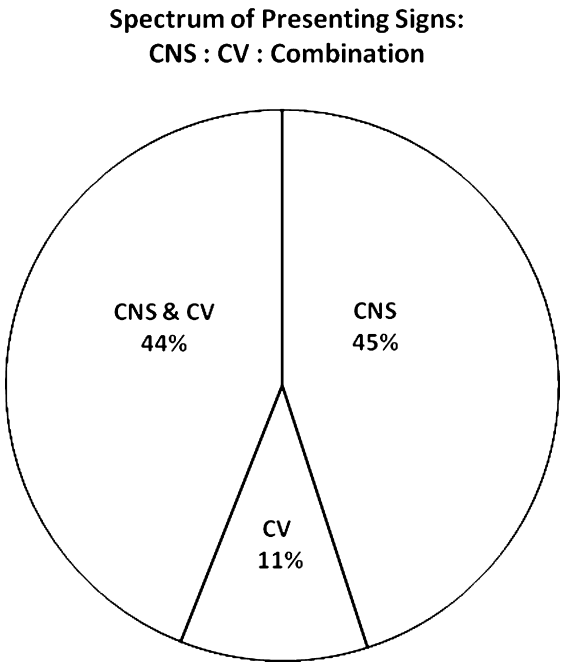

FIGURE 3. The frequency of symptoms and signs referable to CV, CNS, or both is given for the 93 cases in this review.

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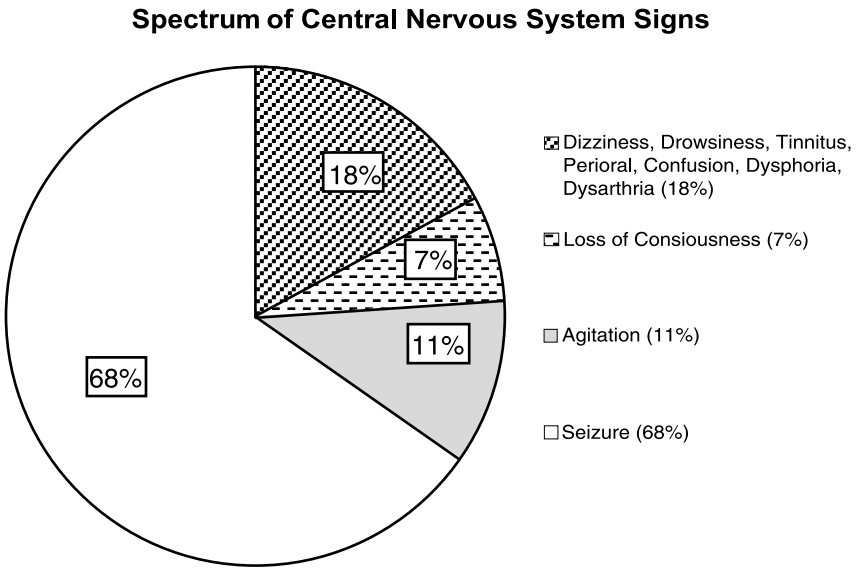

FIGURE 4. The distribution frequencies of all reported signs of CNS toxicity among published cases of LAST.

Cardiovascular Signs of Toxicity

Symptoms of CV toxicity were reported in 51 (55%) of 93 patients (Fig. 3). These occurred in concert with CNS signs in 41 patients (44%) and alone (without evidence of CNS toxicity) in only 10 patients (11% of all reports).[12,13,24,34,38,48,55,63,70,72] Bradycardia or hypotension was often described as the first change in vital signs that eventually progressed to more dramatic signs including asystole or malignant ventricular arrhythmias. Asystole occurred in 11 (12%) of 93 patients. The overall spectrum of reported signs of CV toxicity is shown in Figure 5. Arrhythmias as a whole account for most reported signs of CV toxicity; bradyarrhythmias were the most common, and together with tachycardia and pulseless ventricular arrhythmias, account for roughly half of all the reported signs of CV toxicity.

Atypical Presentations of Toxicity

We chose to classify 2 clinical presentations as atypical, that is, differing from the classic description of LAST: (1) a time to onset of symptoms of 5 mins or more after initiation of regional anesthesia, including both single injection and continuous infusion of LA; and (2) occurrence of isolated CV signs with no evidence of CNS toxicity. Of the 93 patients, 35 (38%) reported delayed symptoms (19 occurring after a single injection and 16 during continuous infusion) and 10 (11%) had no apparent CNS signs of toxicity. Overlap (redundancy) between these groups and the potential for double counting of individual reports precludes adding these numbers to determine an overall rate of atypical presentation. However, by scoring each of the 93 patients, 38 (41%) were found to meet 1 or both criteria.

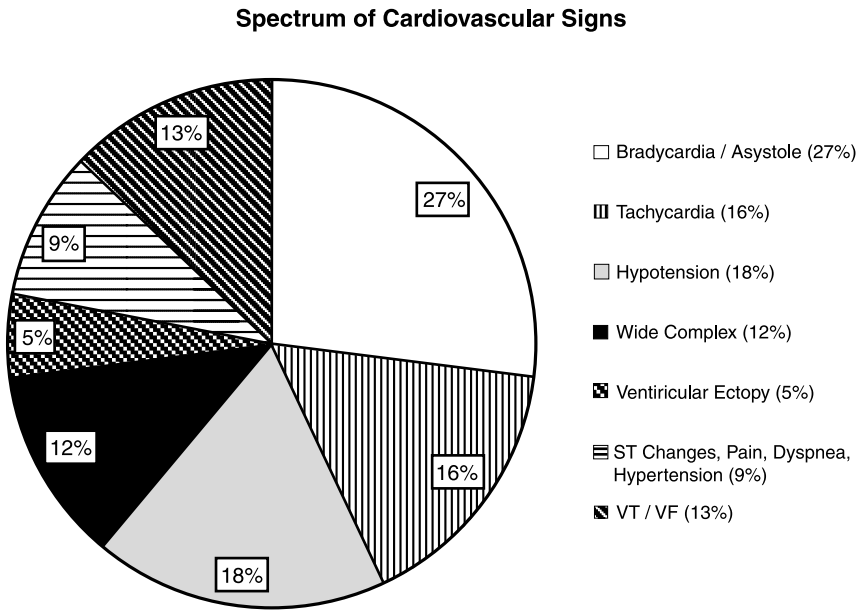

FIGURE 5. The distribution frequencies of all reported signs of CV toxicity during LAST.

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DISCUSSION

We found that the clinical presentation of LAST reported in the peer-reviewed literature is generally very similar to the classic description found in anesthesiology textbooks. Nonetheless, more than 40% of the published case reports had clinical presentations that we consider atypical. The clinical spectrum of LAST encompasses a wide range of symptoms and signs as well as extreme variation in their timing that confirm our hypothesis that many cases do not adhere to the classic description. The documented clinical variability of LAST demands that practitioners be aware of its myriad clinical permutations to improve the detection and treatment of this potentially fatal complication of regional anesthesia.

Timing

We found that the onset of LAST is usually very rapid, following a single LA injection by 50 secs or less in half of cases, and occuring before 5 mins in three-quarters of the cases. LAST can result from intravascular injection, absorption from a tissue depot, accumulation of active metabolites, or a combination of these processes. The predominance of toxic events occurring within the span of a few circulation times after a single injection suggests that most LAST results from intravascular injection. However, virtually all instances of LAST during continuous infusion were substantially delayed, often occurring days after initiation of the infusion. This variation presumably represents differences in infusion rates, interpatient sensitivity to LAST, LA pharmacokinetics, and the quality of clinical monitoring among the various settings.

Signs and symptoms of acute LA toxicity are prone to recur or persist. For instance, seizures have recurred minutes to hours after their initial resolution[3,48] including an instance of recurrent seizure activity 40 mins after successful treatment with lipid emulsion.[46] Symptoms such as bradycardia and hypotension can persist for several hours after injection of even small amounts of LA, for example, bupivacaine 1 mg/kg.[24,34] These observations are highly relevant to the clinical management of LAST in both its detection and treatment.

Signs and Symptoms

Central nervous system symptoms are the most common clinical presentation of LAST and usually precede evidence of CV toxicity, which rarely occurs in isolation. Seizure was the most commonly reported sign of LAST, occurring in two-thirds of cases. Prodromal symptoms are generally viewed as typical of LAST but were observed in less than a fifth of patients, with each symptom reported only a few times, suggesting that no one prodromal was a reliable predictor of impending LAST. This observation could challenge the notion of a "classic prodrome" that includes auditory changes, circumoral numbness, metallic taste, and other symptoms that progress to more dramatic forms of CNS excitation. However, it is also likely that cases involving transient and minor CNS toxicity are never reported. Evidence of CV toxicity occurred in roughly half of the patients, and frequently presented with any of a broad spectrum of reported electrocardiographic abnormalities: tachyarrhythmia, bradyarrhythmia, conduction defects, or wide complex QRS interval.

Atypical Clinical Presentation

Our chief goal was to determine the frequency with which LAST presents atypically. Because prodromal symptoms were reported in only 16% of patients, we did not view their absence as constituting sufficient stringency to warrant their inclusion in our definition of atypical presentation. To establish robust criteria for atypical presentation, we instead chose the complement, or absence of those features most closely associated with LAST, namely rapid onset and predominance of CNS symptoms. Therefore, we defined an atypical presentation as having an onset that is delayed 5 mins or more and/or occurring with isolated CV symptoms. We found that 41% of the 93 cases met one or more of these criteria. Most of these (35/93 or 38% of all cases) were due to delayed onset of symptoms.

Two factors seemed to influence the occurrence of CV toxicity without signs of CNS toxicity. Four of the 10 events occurred during general anesthesia and 1 during propofol infusion, together accounting for 50% of cases of isolated CV toxicity. By comparison, only 2 of 83 instances of neurologic toxicity (with or without CV toxicity) occurred during general anesthesia. This suggests that general anesthesia or heavy sedation can influence the clinical pattern of LAST, favoring an atypical presentation. Furthermore, among the 10 patients with CV-only symptoms, 3 occurred before 5 mins, comprising only 5% of the cohort with early-onset of symptoms. By comparison, 7 CV-only events occurred among the 35 patients showing delayed toxicity, or 20% of this group. This suggests that the likelihood of having signs of toxicity limited to the CV system is greater in the group with delayed toxicity. We speculate that this could result from a higher percent of these patients being beyond the close scrutiny typically provided to patients in the period immediately after injection of LA. As a result, CNS symptoms may have been missed before recognition of more serious cardiac events.

Our retrospective analysis suggests a heretofore unrecognized, or at least infrequently discussed, observation. It seems that preexisting cardiac or neurologic disease might lower the threshold for symptomatic LA overdose. Although our study was not designed to test this hypothesis, it is interesting that among the first 7 case reports of lipid-based resuscitation for cardiac toxicity, 6 had ischemic heart disease—alone,[64] or associated with conduction defects,[59] arrhythmias,[19] valvular disease,[36] cardiac risk factors,[70] or a combination.[35] Another patient resuscitated with lipid emulsion had carnitine deficiency,[72] a metabolic derangement that could theoretically potentiate bupivacaine-induced cardiac toxicity. Thus, preoperative cardiac conduction deficits, evidence of coronary artery disease, cardiomyopathy, arrhythmias, valvular abnormalities, and carnitine deficiency could potentially predispose patients to the development of cardiac toxicity at conventional doses of LA. Similarly, in 4 reports of LA-induced neurologic toxicity, the patients were found to have preexisting neurologic disease, particularly cerebral palsy.[3,43,56,72] Extremes of age might be considered another risk factor in lowering the threshold for LAST. Infants (<4 months old) have been shown to have low α_1-acid glycoprotein plasma concentrations and a lower intrinsic clearance of bupivacaine. As a result, the risk of systemic LA toxicity may be increased.[75,76]

Limitations

This study is hindered by the many limitations expected of a retrospective literature review. Case reports from diverse clinical settings and many different authors during the course of 3 decades comprise an extremely heterogeneous cohort of patients, events, and their analyses. None of the key elements required in a well-designed clinical trial can be obtained in a study of such an agglomeration. Specific inclusion and exclusion criteria and statistical assumptions are unknown; reliability and validity of clinical definitions and key metrics is suspect. Further, the absence of baseline and control data, and the heterogeneity of data capture, analysis, and reporting all hamper the confident extrapolation of our conclusions to clinical practice.

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TABLE 1. Recommendations for Diagnosing LAST

- Classic descriptions of LAST depict a progression of subjective symptoms of CNS excitement (agitation, auditory changes, metallic taste, or abrupt onset of psychiatric symptoms) followed by seizures or CNS depression (drowsiness, coma, or respiratory arrest). Near the end of this continuum, initial signs of cardiac toxicity (hypertension, tachycardia, or ventricular arrhythmias) are supplanted by cardiac depression (bradycardia, conduction block, asystole, decreased contractility). However, there is substantial variation in this classic description, including the following:
  - Simultaneous presentation of CNS and cardiac toxicity
  - Cardiac toxicity without prodromal signs and symptoms of CNS toxicity

  Thus, the practitioner must be vigilant for atypical or unexpected presentation of LAST. **(I, B)**
- The timing of LAST presentation is variable. Immediate (<60 secs) presentation suggests intravascular injection of LA with direct access to the brain, while presentation that is delayed 1–5 mins suggests intermittent or partial intravascular injection, delayed circulation time, or delayed tissue absorption. Because LAST can present >15 mins after injection, patients who receive potentially toxic doses of LA should be closely monitored for at least 30 mins after injection. **(I, B)**
- Case reports associate LAST with underlying cardiac, neurologic, pulmonary, renal, hepatic, or metabolic disease. Heightened vigilance is warranted in these patients, particularly if they are at the extremes of age. **(IIa, B)**
- The overall variability of LAST signs and symptoms, timing of onset, and association with various disease states suggests that practitioners should maintain a low threshold for considering the diagnosis of LAST in patients with atypical or unexpected presentation of CNS or cardiac signs and symptoms after receiving more than a minimal dose of LA. **(IIa, B)**

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

An apparent sex effect may reflect a higher percentage of women having regional anesthesia than men.

Ascertainment bias operates at multiple levels and we have no knowledge of what causes some events to be reported, or accepted for publication, whereas others are not. As mentioned previously, the true occurrence of minor CNS symptoms and transient CV effects are likely to be underrepresented by published case reports. It is disappointing that these data do not provide useful information about outcomes associated with LAST. We found only 1 report of death secondary to LA toxicity. Yet, it is clear from closed claims data and communication with colleagues that many more instances of fatal LA overdose have occurred during the 1979 to 2009 interval. Lee et al[77] examined the American Society of Anesthesiologists Closed Claims Database analyzing the patterns of injuries associated with eye blocks and peripheral nerve blocks from 1980 to 2000. They found that "LA toxicity is a major cause of death or brain damage in these claims" and that LA toxicity was associated with 7 of the 19 claims with death or brain damage. The reporting of only a single fatal case in the past 30 years is consonant with a strong positive bias in the clinical literature—bad outcomes are rarely published.

Furthermore, it is likely that reported cases may be published specifically because they are in some way "remarkable" or "distinguishable" from the usual and therefore not representative of the most common clinical course of LAST. These data do not provide accurate denominators to allow us to calculate the frequency or incidence of LAST—a number critical to future improvements in quality of practice. Rigorous comparisons of different groups with respect to treatments and their comparative efficacy are similarly not possible and statistical evaluation of specific interventions or patient characteristics cannot be performed. Nevertheless, we did find general patterns of clinical characteristics in these published case reports and acquired some initial insights into the spectrum of clinical presentation and the types of comorbidities that might contribute to toxicity.

These results provide, in the aggregate, pilot data that clinicians can use to establish future guidelines for detection of LAST and on which potential future studies can be based. The main goal of this review was to determine whether the literature supports the accuracy of standard textbook descriptions of LA toxicity. We found that 40% of the published cases had clinical features that fell outside the standard description of LAST. An important byproduct of the study was the confirmation that we lack a precise and accurate portrayal of the clinical spectrum of LAST and its optimal treatment. This deficiency begs the development of a prospective data collection tool in the form of a robust, comprehensive registry of LAST events designed to avoid the many shortcomings of a retrospective literature review noted previously.

RECOMMENDATIONS

The timing of onset, severity of initial manifestations, progression to CV compromise, and duration and recurrence of toxicity reflect the interaction of a large number of independent variables including the choice of LA, anesthetic dose, injection rate, site of administration, patient comorbidities, and individual patient sensitivity to LA. Because of recent advances in the treatment of LAST, perhaps the most important first step in improving patient outcome is to have a low threshold for considering the diagnosis. Systemic LA toxicity should be considered in any patient having received a LA injection and experiencing CNS and/or CV instability or symptoms. The threshold for entertaining this diagnosis should be lowered and toxicity should be considered a higher probability when the patient is in a group considered to be at higher risk for LA toxicity, for example, preexisting cardiac, pulmonary, metabolic, or neurologic disease, or at the extremes of age. Signs and symptoms of LAST may present after a longer-than-expected interval from LA dosing and, particularly during deep sedation or when significantly delayed, can occur without signs of neurologic toxicity. These recommendations can be considered as corresponding to a Level of Evidence C (Table 1).

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