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Original Research Article

Observational Study Of Lidocaine Induced Systemic Toxicity When Used By Various Methods Of Administration

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Abstract:

Background: Systemic local anesthetic toxicity is rare but can be fatal because of relative resistance of local anesthetic–induced cardiac arrest to standard resuscitative measures.
Aim: To observe Lidocaine induced systemic toxicity when it is used by its various methods of administration and review treatment and management strategies available for lidocaine toxicity.
Method: Prospective , observational study conducted on 120 patients, between the age group of 20-60 years (of either sex) of ASA grade 1-2, undergoing surgical procedures in which lidocaine (0.25-4%) was administered by different modes at various associated hospitals of GMC Srinagar.
Results: In the present study, out of 120 patients, 7 patients developed systemic symptoms following lidocaine administration by different routes. Patients were categorised into three groups- epidural group, brachial plexus blockade group and local infiltration group (40 patients in each group). 4 patients developed symptoms following epidural administration and 3 patients following brachial plexus blockade and none with local infiltration. Systemic manifestations were more when lidocaine was used for epidural anesthesia followed by brachial plexus blockade and least with local infiltration. **Conclusion:** We concluded that the dose and route of administration of lidocaine are statistically significant factors in considering systemic manifestation. The treatment of systemic toxicity is primarily supportive with oxygenation, fluid administration and administration of benzodiazepines.CNS toxicity is either self limiting or quite amenable to treatment with benzodiazepines. Cardiac toxicity may require resuscitation with fluids but the prognosis after return to spontaneous circulation is often very good.

Keywords: Systemic Toxicity, lidocaine, Epidural, Brachial Plexus, Local Infiltration.

INTRODUCTION:

Local anesthetic systemic toxicity (LAST) is a life-threatening adverse event associated with the increasingly prevalent utilization of local anesthetic (LA) techniques throughout various health care settings, with an incidence currently estimated to be 0.03%, or 0.27 episodes per 1,000 peripheral nerve blocks. The evolution of LA techniques, such as the emergence of high-volume fascial plane approaches,[1,2] the growing relevance of continuous catheter techniques,[3] employing multiple

LA techniques in the same patient,[4] and the use of tumescent anesthesia [5] all contribute to the ongoing risks of LAST. The underlying pathophysiology of LAST and its treatment have been the subject of significant investigation in recent years, and our understanding of these has evolved substantially.

Lidocaine is a local anesthetic drug that produces transient loss of sensory, motor, and autonomic function when the drug is injected or applied in proximity to neural tissue. It is the most common local anesthetic and is used in almost all medical specialties. [6,7] It also is commonly used as an anti arrhythmic agent to depress ventricular arrhythmias. Infusions of lidocaine (and procaine) have been used to supplement general anesthetic techniques, as they are capable of reducing the minimum alveolar concentration of volatile anesthetics by up to 40% as well as providing pain relief in the peri-operative phase. It is in the class of the local amide anesthetics, which, compared to the ester-type local anesthetics, is usually well tolerated with only rare occasions of allergic reactions. Amide local anesthetics are metabolized (N-dealkylation and hydroxylation) by microsomal P-450 enzymes in the liver.

Applied either by injection, inhalation, or as a topical agent to provide anesthesia, lidocaine has a good safety margin before reaching toxic blood levels. Since it can be applied in various forms to the same patients, however, care must be taken to keep track of the total dose given to minimize its systemic toxicity. In addition, clinicians should take into account the dose of any other local anesthetics that may have been administered to the same patient, as toxic doses appear to be additive. Lidocaine toxicity not only is determined by the total dose (usually 4.5 mg/kg) but also by the rate of absorption, which is dependent on the blood flow of that tissue. To reduce blood flow to the injection site and therefore the rate of absorption, vasoconstrictors such as epinephrine 1:200000 are frequently used and may increase the toxic dose to 7 mg/kg.[8,9]

METHODS:

The study protocol was approved by the Medical Ethics Committee of the GMC Srinagar. After obtaining written informed consent, Prospective , observational study conducted on 120 patients, between the age group of 20-60 years (of either sex) of ASA grade 1-2, undergoing surgical procedures in which lidocaine (0.25-4%) was administered by different modes at various associated hospitals of GMC Srinagar. Patients with a contraindication for epidural anesthesia, and patients with a history of allergy, sensitivity, or any other reaction to an amide-type local anesthetic, were excluded from the study. Also excluded were patients with a history of, or abnormal laboratory findings indicative of, renal or hepatic disease and patients with diseases that could interfere with postoperative pain experience or render clinical assessments difficult or unreliable, such as significant respiratory or neurologic disease or a psychiatric history. Further exclusion criteria included significant alcohol, drug, or medication abuse and participation in a clinical trial of a nonregistered drug within the 3-month period before admission to the study. Finally, pregnant women and women not practicing adequate contraception were also excluded.

Routine physical examinations were performed 2 or 3 days before inclusion in the study. Laboratory screenings (hematology and clinical chemistry) were performed 2 or 3 days before inclusion in the study.

Patients were randomly assigned to one of three groups (40 patients in each group), (Group A) lidocaine (0.25-4%) through epidural route, (Group B) Brachial Plexus Block (0.25-4%) and Group C Local Infiltration (0.25-4%). These dosing rates were anticipated to produce effective analgesia in all groups.

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Anesthetic Procedures

In the operating room, monitoring equipment was attached and intravenous cannulae for fluid and drug administration. A preload of a minimum of 500 ml crystalloids was administered before the start of the epidural puncture.

Balanced electrolyte solutions were also administered during surgery and postoperatively, as necessary. With the patient in either the sitting or the lateral decubitus position, 16- to 18-gauge epidural needle was inserted *via* the L2–L3 or the L3–L4 interspace with use of the paramedian approach. After identification of the epidural space with use of the loss-of-resistance- to-saline technique, and provided that neither cerebrospinal fluid nor blood was obtained during careful aspiration, an epidural catheter was introduced and advanced 5 cm cephalad. Subsequently, a test dose of 3 ml lidocaine, 10 mg/ml, was injected, and, 5 min later, in the absence of signs of an intravascular or subarachnoid injection.

The axillary block was performed under ultrasound guidance. The ultrasound transducer was placed in a vertical orientation at the level of the anterior axillary fold. The axillary artery was identified and placed in the center of the image. Minor adjustment of scanning planes facilitated the identification of the median, ulnar, and radial nerve complexes surrounding the axillary artery. The musculocutaneous nerve was then identified in a connective tissue plane between the biceps and the coracobrachialis muscles. The identity of each nerve was confirmed by tracing the nerve from the axilla to a fixed reference point and then back to the axilla. The ulnar nerve was traced to and from the medial epicondyle. The median nerve was traced to and from the antecubital fossa, where it lies medial to the brachial artery. The radial nerve may be seen to emerge in a fascial plane within the triceps muscle at the midhumeral level and may be traced back to the axilla. The musculocutaneous nerve can be identified in a fascial plane between biceps and coracobrachialis muscles and traced backwards to the axilla.

A 50-mm 24-gauge insulated blunt regional anesthesia needle was introduced percutaneously at the center of the transducer, directly parallel to the scanning beam. A needleout- of-plane approach was used, and the needle was advanced to positions adjacent to the median, ulnar, and radial nerves in this order. The study volume of 2% Lidocane was injected adjacent to each nerve. The injectate was administered slowly in 0.5-ml aliquots, and evidence of inadvertent intraneural injection was sought. After blockade of the ulnar, median, and radial nerves, the block needle was withdrawn to the subcutaneous tissues and redirected toward the musculocutaneous nerve by using a needle-in-plane approach. The study volume of 2% Lidocane was injected adjacent to the musculocutaneous nerve in 0.5-ml aliquots ensuring perineural local anesthetic placement. A single skin puncture was used for the entire block procedure. No subcutaneous local anesthetic infiltration was used before block needle insertion.

Local infiltration with lidocaine was performed to ensure that all layers of the surgical incision are infiltrated under direct visualization in a controlled and meticulous manner. This was done with a 22-gauge, 1.5-inch needle. The needle was inserted approximately 0.5 to 1 cm into the tissue plane (e.g., peritoneal, musculofascial, or subdermal planes), and local anesthetic solution was injected while slowly withdrawing the needle, which should reduce the risk of intravascular injection.

Conflict of interest: Nil

Funding: Nil

RESULTS:

In our study, profile of 120 patients was studied. Patients were categorised into three groups- epidural group, brachial plexus blockade group and local infiltration group (40 patients in each group). 7 patients developed systemic symptoms following lidocaine administration by different routes. 4 patients developed symptoms following epidural administration and 3 patients following

brachial plexus blockade and none with local infiltration. Patients were comparable with regard to demographic profile The statistical analysis between three groups was not significant with regard to age, sex, height, weight and ASA class of distribution (p= 0.50) (Table 1).

Table.1: Demographic profile of the study population:-

Variables	Group A N=40	Group B N=40	Group C N=C	P Value	Remarks
Age (Years)	42.6±14.58	43.76±15.08	42.98±14.10	0.50	NS
Gender M/F	28/22	31/19	29/11	0.65	NS
Height	160.3±6.49	163.2±6.07	162.4±5.44	0.20	NS
Weight	61.50±8.89	62.67±10.74	60.56±9.78	0.82	NS
ASA I/II	31/9	27/13	30/10	0.86	NS

NS-not significant

The mean values of pre- operative changes in heart rate, MAP and SPO_2 at different time intervals among the three groups were statistically not significant with a p value of >0.05 (Table 2).

Table -2:- Pre Operative Vitals

Vitals	Groups	Mean±SD	P-value	Remarks
HR (bpm)	A	74.30±3.541	0.145	NS
	B	76.40±4.122		
	C	75.38±3.876		
MAP (mmHg)	A	95.56±6.07	0.07	NS
	B	94.87±5.65		
	C	75.98±6.34		
SPO_2	A	98.15±0.745	0.711	NS
	B	99.05±0.826		
	C	98.99±0.311		

NS-not significant

The mean values of intraoperative heart rate at different intervals among the three study groups were statistically not significant with a P value of > 0.05 except at 5 to 10 minutes and was managed accordingly (Table 3).

Table.3: Intra-operative vitals (HR) among the study population:-

Time	Groups	Mean±SD	P Value	Remarks
0 min	A	77.05±4.08	0.458	NS
	B	76.25±3.90		
	C	74.30±3.54		
5 min	A	92.45±5.89	<0.05	S
	B	86.56±5.65		
	C	76.34±4.98		
10 min	A	102.51±7.56	<0.05	S
	B	92.76±6.24		
	C	88.87±7.45		
15 min	A	89.71±5.56	0.465	NS
	B	79.44±4.68		
	C	77.65±6.41		
20 min	A	79.65±5.22	0.241	NS
	B	76.93±4.98		
	C	77.43±5.22		
25 min	A	75.05±3.15	0.469	NS
	B	76.70±3.10		
	C	75.56±3.89		
30 min	A	74.56±2.99	0.543	NS
	B	73.68±3.01		
	C	72.78±2.89		

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The mean values of intra operative changes in mean arterial pressure at 0min, 5min, 10min, 15 min,15min,20min, 25min, and 30 min among three groups were statistically significant values at five to ten minutes with a p value of <0.05. After that there was no statically difference among the study population with a p vale of > 0.05 (Fig 1).

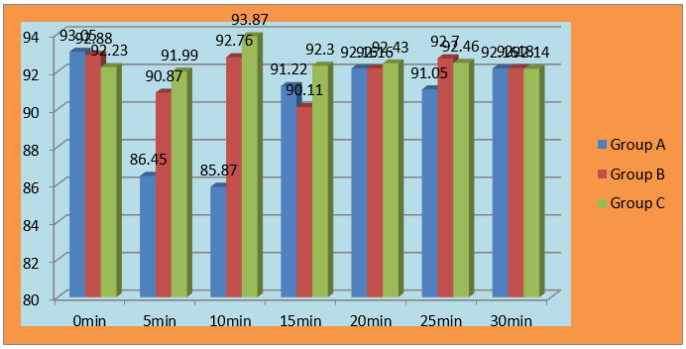

Fig.1:

The mean values of intra-operative oxygen saturation at different intervals among three groups were statistically not significant with a p value of > 0.05 (Fig 2).

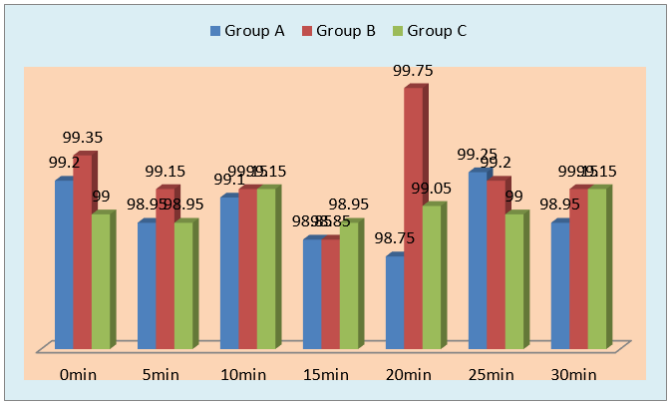

Fig. 2:

Four patients developed symptoms following epidural administration and 3 patients following brachial plexus blockade and none with local infiltration. Systemic manifestations were more when lidocaine was used for epidural anesthesia followed by brachial plexus blockade and least with local infiltration (Fig 3).

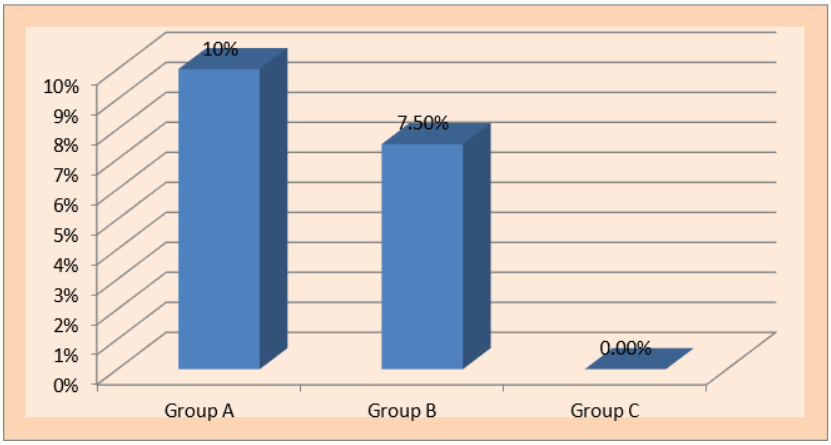

Fig.3:

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DISCUSSION:

Lidocaine toxicity to muscles and peripheral or neuraxial nerves can occur locally at the site of injection. Transient neurologic symptoms (TNS) after high concentration lidocaine spinal anesthetics have been described multiple times and have led to either reducing the concentration of the dose or switching to a different agent.

In addition to direct nerve toxicity, systemic toxicity affecting the brain and/or cardiac muscle can lead to sudden and dramatic changes in the patient's vital signs. Finally, there are the side effects of a relative overdose at the site of injection, which can be quite dramatic.

Toxicity to local nerves and muscles is thought to be a consequence of the prolonged application of high drug concentrations or the effect of preservatives in the local anesthetic solution or both.[10,11] Systemic local anesthetic toxicity is due to high systemic plasma levels of lidocaine due to the absorption of large doses of lidocaine, which depends mostly on the blood flow at the site of injection: tracheal > intercostal > caudal > paracervical > epidural > brachial plexus > subcutaneous. Also, blind injection of large volumes into a large muscular area, such as for lumbar plexus block or sciatic nerve blocks, can lead to systemic lidocaine toxicity. Spinal anesthetics are very low in total volume and do not cause systemic lidocaine toxicity. Inadvertent intra-arterial injections may cause local anesthetic toxicity in the tissue beds supplied by that artery even in doses below the systemic toxic concentration. This complication is seen primarily with injections into the neck, causing central nervous system (CNS) symptoms often during the injection or shortly thereafter without progressing to cardiac toxicity.

All sexes are affected equally by lidocaine toxicity. Patients who are likely to be more susceptible to local anesthetic toxicity are patients at the extremes of age and women who are pregnant. Rates of severe systemic toxicity (seizures with or without cardiac arrest) occur on the order of 1:10,000 for epidurals and up to 1:2000 for peripheral nerve blocks, depending on the type of block.

In our study, 120 patients, between the age group of 20-60 years (of either sex) of ASA grade 1-2, undergoing surgical procedures in which lidocaine (0.25-4%) was administered by different modes at various associated hospitals of GMC Srinagar.

In the present study, out of 120 patients, 7 patients developed systemic symptoms following lidocaine administration by different routes. Patients were categorised into three groups- epidural group, brachial plexus blockade group and local infiltration group (40 patients in each group).4 patients developed symptoms following epidural administration and 3 patients following brachial plexus blockade and none with local infiltration. Systemic manifestations were more when lidocaine was used for epidural anesthesia followed by brachial plexus blockade and least with local infiltration.

Prevention should be the priority for reducing the frequency and severity of LAST. [12] No single intervention eliminates the risk, and therefore, prevention is a multi factorial process.

Ultrasound has been shown to reduce the risk of LAST by60%–65% as compared to peripheral nervous stimulation alone. [13, 14,15] There are several explanations for this risk reduction. Increased accuracy of delivery permits reduction in volume and, therefore, dose of LA; the incidence of vascular puncture may be reduced; and visual cues signaling in travascular injection allow termination of injection before a significant dose is delivered. However, LAST events continue to occur despite the use of ultrasound, [13] and ultrasound guidance does not impact the risk of LAST resulting from systemic absorption of LA.

Restricting the drug dosage may contribute to LAST risk reduction. It is advisable to perform fractionated injection of LA in aliquots of 5 mL, pausing for 30–45 seconds between injections,

[16] with gentle aspiration before injection. This latter measure is still useful despite a false-negative rate of around2%. [12] Markers such as epinephrine may also mitigate the risk of intravascular injection, where addition of 15 μgmL–1 will increase the heart rate by ≥10 beats per minute or systolic blood pressure by ≥15 mmHg. Practical interventions such as clear labeling of LA-containing syringes and meticulous handling of these syringes may be of benefit. The transition from Luer connectors to new ISO 80369 standard small-bore connecters might also reduce the risk of wrong route injection. [17,18]
All patients receiving injections of LA in doses sufficient to cause LAST should have oxygen, standard monitoring, and intravenous access applied. Monitoring should continue for at least 30 minutes after completion of injection, as delayed presentations are increasingly occurring. [19,20] Immediate access to a LAST Management Checklist is advisable, and all medications and resuscitation equipment required should be immediately available, preferably in the form of a "LAST Rescue Kit". Despite data suggesting inconsistent adherence to standardized protocols, the value of these guidelines cannot be understated.

Immediate management involves the general safety and resuscitation measures that are essential in any emergency. First, stop LA injection and call for help. The immediate priority is to manage the airway, breathing, and circulation.

Prompt and effective airway management is crucial to prevent hypoxia, hypercapnia, and acidosis (metabolic or respiratory), which are known to potentiate LAST. The airway should be secured and 100% oxygen administered, bearing in mind that hyperventilation and respiratory alkalosis have also been demonstrated to be injurious. [21]

Recent advances in understanding of the mechanisms of action of lipid emulsion underscore the importance of this therapeutic modality in the management of LAST. Data suggest that lipid emulsion may shuttle any LA agent from high blood flow organs – such as the heart or brain – to storage or detoxification organs such as muscles or the liver. [22] Lipid emulsion therapy may also improve the cardiac output and blood pressure (hence further facilitating the shuttling effect),while post conditioning myocardial protection may also occur.[23-26] There is a paucity of large-scale, high-quality data demonstrating the clinical efficacy of lipid emulsion therapy, primarily due to the difficulties in valid data collection and the limited feasibility of prospective studies. [27,28] However, animal studies demonstrate strong support for the use of lipid emulsion therapy in reducing mortality when applied in conjunction with resuscitative interventions. [29]Early administration of 20% intravenous lipid emulsion therapy should, therefore, be an immediate priority after airway management in any LAST event that is judged to be potentially serious.

Seizure activity may exacerbate metabolic acidosis, and prompt prevention and termination is crucial. Due to their cardio stable profile, benzodiazepines are the first-line therapy. Propofol should be avoided where there are signs of cardiovascular compromise, in view of the effect of large doses on depressing cardiac function, but small doses may be used. If seizures persist despite all efforts, low-dose neuromuscular blockade can be considered to reduce metabolic acidosis and hypoxia from ongoing muscular contraction.

Advanced Cardiac Life Support algorithms for cardio pulmonary resuscitation must be followed should cardiac arrest occur. Chest compressions should be initiated immediately and continued until return of spontaneous circulation. If epinephrine is used, small initial doses of ≤1 μgkg–1 are preferred to avoid impaired pulmonary gas exchange and increased after load. [30] Vasopressin is not recommended foruse as it has been associated with adverse outcomes in animal models. In the

absence of rapid recovery following advanced life support measures and intravenous lipid emulsion therapy, early consideration should be given to cardio pulmonary bypass for circulatory support.

CONCLUSION:

We concluded that the dose and route of administration of lidocaine are statistically significant factors in considering systemic manifestation. The treatment of systemic toxicity is primarily supportive with oxygenation, fluid administration and administration of benzodiazepines.CNS toxicity is either self limiting or quite amenable to treatment with benzodiazepines. Cardiac toxicity may require resuscitation with fluids but the prognosis after return to spontaneous circulation is often very good.

REFERENCES:

1. El-Boghdadly K, Pawa A. The erector spinae plane block: plane and simple. Anaesthesia. 2017;72(4):434–438.

2. Forero M, Adhikary SD, Lopez H, Tsui C, Chin KJ. The Erector Spinae Plane Block. Reg Anesth Pain Med. 2016;41(5):621–627.

3. Il feld BM. Continuous peripheral nerve blocks: a review of the published evidence. Anesth Analg. 2011;113(4):904–925.

4. Pawa A, Wight J, Onwochei DN, et al. Combined thoracic paravertebral and pectoral nerve blocks for breast surgery under sedation: a prospective observational case series. Anaesthesia. 2018;73(4): 438–443.

5. Conroy PH, O'Rourke J. Tumescent anaesthesia. Surgeon. 2013;11(4): 210–221.

6. Wright TF, Brunetti GF, Kennedy P. Lidocaine safety after saphenous vein tumescent anesthesia. Phlebology. 2019 Dec;34(10):683-689.

7. Lemming K, Fang G, Buck ML. Safety and Tolerability of Lidocaine Infusions as a Component of Multimodal Postoperative Analgesia in Children. J Pediatr Pharmacol Ther. 2019 Jan-Feb;24(1):34-38.

8. Lee JT, Sanderson CR, Xuan W, Agar M. Lidocaine for Cancer Pain in Adults: A Systematic Review and Meta-Analysis. J Palliat Med. 2019 Mar;22(3):326-334.

9. Dokken K, Fairley P. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Jul 18, 2022. Sodium Channel Blocker Toxicity.

10. Bailey M, Corcoran T, Schug S, Toner A. Perioperative lidocaine infusions for the prevention of chronic postsurgical pain: a systematic review and meta-analysis of efficacy and safety. Pain. 2018 Sep;159(9):1696-1704.

11. Sekimoto K, Tobe M, Saito S. Local anesthetic toxicity: acute and chronic management. Acute Med Surg. 2017 Apr;4(2):152-160.

12. Neal JM, Barrington MJ, Fettiplace MR, et al. The Third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity: Executive Summary 2017. Reg Anesth Pain Med. 2018;43(2):113–123.

13. Barrington MJ, Kluger R. Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. Reg Anesth Pain Med. 2013;38(4):289–297. Affas F. Local infiltration analgesia in knee and hip arthroplasty efficacy and safety. Scand J Pain. 2016;13:59–66.

14. Orebaugh SL, Kentor ML, Williams BA. Adverse outcomes associated with nerve stimulator-guided and ultrasound-guided peripheral nerve blocks by supervised trainees: update of a single-site database. Reg Anesth Pain Med. 2012;37(6):577–582.

15. El-Boghdadly K, Chin KJ. Local anesthetic systemic toxicity: Continuing Professional Development. Can J Anaesth. 2016;63(3):330–349.

16. Litman RS, Smith VI, Mainland P. New solutions to reduce wrong route medication errors. Paediatr Anaesth. 2018;28(1):8–12.

17. Risk Management Analysis Committee of the French Society for Anesthesia and Critical Care (SFAR), French Society for Clinical Pharmacy (SFPC), Piriou V, Theissen A, Arzalier-Daret S. Preventing medication errors in anesthesia and critical care (abbreviated version). Anaesth Crit Care Pain Med. 2017;36(4):253–258.

18. Gitman M, Barrington MJ. Local Anesthetic Systemic Toxicity: A Review of Recent Case Reports and Registries. Reg Anesth Pain Med. 2018;43(2):124–130.

19. Vasques F, Behr AU, Weinberg G, Ori C, di Gregorio G. A Review of Local Anesthetic Systemic Toxicity Cases Since Publication of the American Society of Regional Anesthesia Recommendations: To Whom It May Concern. Reg Anesth Pain Med. 2015;40(6):698–705.

20. Mochizuki T, Sato S. Hypocapnia prolongs bradycardia induced by bupivacaine or levobupivacaine in isolated rat hearts. Can J Anaesth. 2008;55(12):836–846.

21. Fettiplace MR, Lis K, Ripper R, et al. Multi-modal contributions to detoxification of acute pharmacotoxicity by a triglyceride microemulsion. J Control Release. 2015;198:62–70.

22. Rahman S, Li J, Bopassa JC, et al. Phosphorylation of GSK-3β mediates intralipid-induced cardioprotection against ischemia/reperfusion injury. Anesthesiology. 2011;115(2):242–253.

23. Lou P-H, Lucchinetti E, Zhang L, et al. The Mechanism of Intralipid-Mediated Cardioprotection Complex IV Inhibition by the Active Metabolite, Palmitoylcarnitine, Generates Reactive Oxygen Species and Activates Reperfusion Injury Salvage Kinases. PLoS One. 2014;9(1):e87205.

24. Stehr SN, Ziegeler JC, Pexa A, et al. The effects of lipid infusion on myocardial function and bioenergetics in l-bupivacaine toxicity in the isolated rat heart. Anesth Analg. 2007;104(1):186–192.

25. Fettiplace MR, Ripper R, Lis K, et al. Rapid cardiotonic effects of lipid emulsion infusion. Crit Care Med. 2013;41(8):e156–e162.

26. Weinberg G. Current evidence supports use of lipid rescue therapy in local anaesthetic systemic toxicity. Acta Anaesthesiol Scand. 2017;61(4):365–368.

27. Harvey M, Cave G. Lipid emulsion in local anesthetic toxicity. Curr Opin Anaesthesiol. 2017;30(5):632–638.
28. Fettiplace MR, Mccabe DJ. Lipid emulsion improves survival in animal models of local anesthetic toxicity: a meta-analysis. Clin Toxicol. 2017; 55(7):617–623.

29. Association of Anaesthetists of Great Britain and Ireland. AAGBI Safety Guideline: Management of Severe Local Anaesthetic Toxicity. https:// www.aagbi.org/sites/default/files/la_toxicity_2010_0.pdf. Accessed July 08, 2018.

30. Wang QG, Wu C, Xia Y, et al. Epinephrine deteriorates pulmonary gas exchange in a rat model of bupivacaine-induced cardiotoxicity: a threshold dose of epinephrine. Reg Anesth Pain Med. 2017;42(3):342–350.