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GUIDELINE

Practical guide for the management of systemic toxicity caused by local anesthetics

Safety Committee of Japanese Society of Anesthesiologists[1]

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Abstract
Systemic toxicity from local anesthetics can occur in any of the wide range of situations in which these agents are used. This practical guide is created to generate a shared awareness of the prevention, diagnosis, and treatment of local anesthetic systemic toxicity among all medical professionals who perform nerve blocks. Systemic toxicity of local anesthetic is induced by an increase of its protein-unbound plasma concentration. Initial symptoms are characterized by central nervous system signs such as excitation, convulsions, followed by loss of consciousness and respiratory arrest. These symptoms are often accompanied with cardiovascular signs such as hypertension, tachycardia and premature ventricular contractions. Further increase of plasma concentration of local anesthetic induces bradycardia, conduction disturbances, circulatory collapse and asystole. The incidence of local anesthetic systemic toxicity is 1–11 cases per 10,000. Infants, patients with decreased liver function and low cardiac output are vulnerable to systemic toxicity. When performing regional anesthesia, the guideline-directed monitoring, securing a venous line, preparation of medication to treat convulsions and lipid emulsions are required. For prevention of local anesthetic systemic toxicity, small-dose, divided administration, using agents with low toxicity such as ropivacaine and levobupivacaine, performing an aspiration test are recommended. If systemic toxicity is suspected, halt administration of local anesthetic, request assistance, secure venous line, airway, administration of 100% oxygen and if necessary tracheal intubation and artificial respiration should be immediately performed. Benzodiazepines are recommended to treat convulsions. Administration of 20% lipid emulsion according to the protocol is recommended to treat severe hypotension and arrhythmia.

Keywords Local anesthetic · Systemic toxicity · Central nervous system · Cardiovascular · Lipid emulsion

Introduction

This practical guide not only addresses anesthetic management performed by members of the Japanese Society of Anesthesiologists (JSA), but can also be referenced during any procedure performed in Japan involving the use of local anesthetics when making clinical decisions to address systemic toxicity caused by these agents that could or has already occurred. However, this guide is not intended to standardize how local anesthetic systemic toxicity is managed, nor does providing medical care based on its content guarantee a positive prognosis. Therefore, this guide is not meant to controvert the validity of clinical decisions or medical actions that deviate from it, and was not formulated to inform decisions regarding legal liability.

The content of this practical guide is based on the knowledge of and treatment methods for local anesthetic systemic toxicity at the time it was created (June 2017). Because these will likely change over time, appropriate revisions should be made.

The individuals involved in creating this practical guide have no financial disclosures or conflicts of interest to declare.

Process of formulating this practical guide

The development of rapid-onset general anesthetics has led to a heightened awareness of the importance of postoperative analgesia. Furthermore, an increase in the number of patients with complicated heart diseases or

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cerebrovascular lesions, and in patients taking antiplatelet agents or anticoagulants in the perioperative period to prevent deep vein thrombosis, has created more opportunities for selecting peripheral nerve block over epidural anesthesia. Moreover, there have been many reports of surgery being performed safely in patients with severe complications using only regional anesthesia to anesthetize a specific and limited area. In ultrasound-guided nerve blocks, it is possible to visually confirm the precise anatomical relationship between the needle tip and the nerve, which has helped increase the success rate of nerve blocks and has made this method widely used not only among anesthesiologists, but particularly among orthopedic surgeons.

Reported frequencies of systemic toxicity caused by local anesthetic(s) vary widely, from approximately 1/500 to 1/10,000, due to the lack of a standard definition for local anesthetic systemic toxicity, and because incidence rates differ depending on the block technique and location. While precise figures are not available, there have been rare cases that progressed to circulatory collapse. Systemic toxicity from local anesthetics can occur in any of the wide range of situations in which these agents are used. While it has been reported that ultrasound-guided nerve block reduces the frequency of local anesthetic toxicity, the casual use of large doses of local anesthetics in nerve blocks without fully understanding the properties and toxicities of these drugs is extremely dangerous. Thus, creating a standard protocol to prevent, diagnose, and appropriately treat systemic toxicity from local anesthetics carries great significance.

To date, there have been no independent guidelines in Japan for addressing and managing systemic toxicity caused by local anesthetics. In June 2010, the European Board of Anaesthesiology and European Society of Anaesthesiology, with the support of the World Health Organization, World Federation of Societies of Anaesthesiologists, and European Patients Association, jointly proposed "The Helsinki Declaration on Patient Safety in Anaesthesiology" [1], which was signed by the Japanese Society of Anesthesiologists (JSA) in June 2015. In this document, creating protocols for anesthesia safety is listed as a principal requirement; accordingly, the JSA created this "Practical guide for the management of systemic toxicity caused by local anesthetics" as part of its guidelines project.

Overseas, the American Society of Regional Anesthesia and Pain Medicine [2] and the Association of Anaesthetists of Great Britain and Ireland [3] have formulated guidelines on dealing with local anesthetic systemic toxicity; the content of the present practical guide largely follows these overseas guidelines. The recommended treatments for local anesthetic systemic toxicity in these guidelines include lipid emulsion. While the effectiveness of this therapy is not supported by a high level of evidence [4], it is a simple method and has reportedly saved the lives of numerous patients and, therefore, merits consideration.

Purpose

This practical guide is not only intended for anesthesiologists, but was created to generate a shared awareness of the prevention, diagnosis, and treatment of local anesthetic systemic toxicity among all medical professionals who perform nerve blocks. The content of this practical guide has been scientifically scrutinized and the JSA has endorsed its content. Sharing information with JSA members and other readers will help raise the level of medical care. Accordingly, while this practical guide should be referenced to prevent, quickly diagnose, and treat local anesthetic systemic toxicity when performing regional anesthesia using local anesthetics, the decisions that need to be made in each clinical situation ultimately rest with the individual reader. The checklist included at the end of the guide is intended to help practitioners provide treatment confidently and without hesitation in dangerous situations when systemic toxicity from local anesthetic occurs. Thus, an easy-to-read, practical card that can be posted in an operating room was created.

As new information regarding the mechanisms of local anesthetic toxicity onset and/or treatment becomes available, this practical guide should be updated and revised accordingly. To improve patient safety, the information in this practical guide should be understood by all medical professionals who use local anesthetics.

Evidence level

Ideally, guidelines are based on a high level of evidence; however, the incidence of local anesthetic toxicity is exceedingly low, and randomized clinical trials involving human subjects regarding therapies for serious cases of local anesthetic toxicity have not been performed. The literature that forms the basis of this guide includes the results of animal experiments, case reports, reviews, and recommendations by specialists. Consequently, evidence or recommendation levels are not listed in the references for this practical guide.

Preventing systemic toxicity from local anesthetics

Preventing systemic toxicity from local anesthetics should be a primary concern because toxicity may lead to serious disability [5]. It is needed to consider patient background, characteristics of local anesthetics, administration routes, and purposes for preventing systemic toxicity.

Background pathology of patients who receive local anesthetics

The appearance of the effects of local anesthetics and systemic toxicity thresholds can change depending on the patient's condition. In states of acidosis, there is an increase in cationic forms of the anesthetic, which makes passage through cell membranes more difficult, thereby delaying onset of the effect. Moreover, a decreased protein binding rate means an increase in unbound fraction, which leads to a higher likelihood of systemic toxicity. Compared with older children and adults, infants have lower levels of metabolic enzyme activity in the liver. Moreover, metabolic enzyme activity can decline in the presence of liver dysfunction; therefore, increased caution is needed in such cases. In addition, when administering a large dose of an ester-type local anesthetic(s) to patients with liver dysfunction, reduced levels of plasma cholinesterase causes the blood concentration of free-base local anesthetics to rise, also requiring increased caution [6]. Patients with heart failure exhibit slower circulation, which can cause the tissue concentration of local anesthetics to rise [2].

Reducing the dose of local anesthetics

According to the United States Food and Drug Administration, limiting the dose of local anesthetics is the most highly recommended method of preventing toxicity [7]. Large doses of high-concentration local anesthetics are not recommended for use in subcutaneous infusion anesthesia, epidural, or peripheral nerve blocks. Moreover, while pharmaceutical companies provide maximum tolerated doses for local anesthetics, this can change depending on patient factors; therefore, caution should be exercised [8]. Because it can be difficult to estimate the blood concentration of local anesthetics, administration by simply referencing the maximum tolerated dose per unit of body weight is not recommended. Doses less than the maximum tolerated dose should be administered.

Small-dose, divided administration

Local anesthetics may be administered in small doses, in separate volumes of 3–5 mL, and observing the patient between doses. Rapid administration or injecting a bolus dose using intense pressure increases the risk for inadvertent injection into a vessel and may also cause nerve damage [9].

Using local anesthetics associated with less risk for causing systemic toxicity

When using local anesthetics at high doses, selecting the (*S*)-isomers ropivacaine or levobupivacaine is preferable to the racemic mixture bupivacaine because toxicity symptoms are more likely to appear with the latter [10].

Performing an aspiration test after puncture

It is preferable to perform an aspiration test from the puncture needle or catheter when administering local anesthetics to guard against intravascular administration. However, performing an aspiration test will not necessarily prevent intravascular administration. Intravascular administration of local anesthetics has been reported even when blood backflow is not observed when an aspiration test was performed upon insertion of a continuous epidural catheter [11].

Methods of detecting intravascular administration

Administering a small dose of local anesthetic as a test dose before the intended dose may help prevent inadvertent intravascular or intrathecal administration. If heart rate increases ≥ 10 beats/min, or systolic blood pressure increases ≥ 15 mmHg after administration of 10–15 μg of adrenalin (0.5 μg/kg for children) into a continuous epidural catheter, there is a high likelihood that intravenous administration has occurred [12]. However, if the patient is taking a β-blocker, is elderly, or is sedated—all of which are associated with lower heart rates—an increased heart rate may not be an ideal indicator. Administering local anesthetics with adrenaline is a useful method of preventing intravascular administration from puncture needles or catheters. However, there is no evidence demonstrating that test doses can prevent systemic toxicity.

Using ultrasound imaging to assess the location of the needle or catheter

Using ultrasound imaging to confirm the location of the puncture needle or catheter in peripheral nerve blocks is a useful method of preventing intravascular administration. However, even if ultrasound imaging is used, and even if the needle puncture is performed with the parallel approach (the needle is clearly detected when placing the ultrasound probe and needle parallel to one another), it will not necessarily prevent intravascular administration [13].

Diagnosing local anesthetic systemic toxicity

The diagnosis of local anesthetic toxicity is based on clinical features that appear after administration. Thus, careful observation and monitoring of the patient is important (Fig. 1).

Diagnosis of local anesthetic systemic toxicity

Observation and monitoring	The diagnosis of local anesthetic systemic toxicity is based on clinical symptoms that appear after administration of local anesthetics. Thus, careful observation and monitoring of patients is important.
Central nervous system symptoms	• Initial stage: symptoms of excitation accompanying blockade of cerebral cortex inhibitory symptom (tongue/lip numbness, metallic taste, talkativeness, difficult articulation, agitation, dizziness, sight and hearing impairment, unsteadiness, convulsions, etc.) • Subsequent blockade of the excitatory route causes inhibitory symptoms (delirium, loss of consciousness, respiratory arrest, etc.). • In some cases, the typical neurological symptoms do not worsen gradually; however, convulsions or cardiac arrest may occur precipitously.
Cardiovascular system symptoms	• Initial neurological symptoms may be accompanied by hypertension, tachycardia, and/or premature ventricular contractions. • This is followed by signs of inhibition, such as sinus bradycardia, conduction disturbances, circulatory collapse, and asystole. • However, in some cases, such as when a local anesthetic is injected directly into a blood vessel, circulatory collapse may occur without any neurological signs. • Characteristic electrocardiographic signs include PR lengthening and QRS widening.
Atypical symptoms	• 16% of patients present with precursor symptoms. • 41%: delayed symptoms or circulatory symptoms with no neurological symptoms. • Discovery of symptoms may be delayed with general anesthesia or deep sedation; therefore, caution is needed.
Period until onset	The period until onset varies; therefore, patients should be observed carefully as the situation requires.

Fig. 1 Diagnosis of local anesthetic systemic toxicity

Monitoring

When performing regional anesthesia, monitoring should be performed according to monitoring guidelines from the JSA. Moreover, anesthetic preparations should be made so symptoms of local anesthetic systemic toxicity can be managed adequately and treated quickly [2, 14].

1. Perform regional anesthesia under the condition that oxygen administration and airway management are promptly available. Prepare the tools needed for anesthesia and artificial ventilation, such as a bag-mask. Ensure that the tools needed for endotracheal intubation, such as a laryngoscope and endotracheal tube, are readily available for use at any time.
2. Attach an electrocardiograph monitor and pulse oximeter to the patient.
3. As a rule, measure blood pressure every 5 min.
4. Secure a venous line.
5. Prepare medication to treat convulsions (i.e., midazolam, diazepam, or barbital).
6. Ensure the facility is always stocked with lipid emulsions.
7. Know the location of the nearest facility that can perform extracorporeal circulation.
8. When local anesthetic systemic toxicity occurs, treatment will need to be initiated quickly and assistance will be required; therefore, when performing regional anesthesia, do so in an environment where multiple medical staff are present.

Signs, symptoms

Central nervous system signs and symptoms [3, 6, 9, 15] Initially, symptoms of excitation caused by blockade of the inhibitory neurons, such as tongue and lip numbness, metallic taste in the mouth, talkativeness, difficult articulation, agitation, dizziness, sight and hearing impairments, unsteadiness, and convulsions are manifested by local anesthetics. After this, blockade of the excitatory route occurs, which is accompanied by inhibitory symptoms such as delirium, loss of consciousness, and respiratory

arrest. In approximately 60% of cases, typical neurological symptoms worsen gradually; however, convulsions or cardiac arrest can occur more precipitously.

Cardiovascular signs and symptoms The initial neurological symptoms may be accompanied by hypertension, tachycardia, and premature ventricular contractions. This is followed by signs of inhibition, such as sinus bradycardia, conduction disturbances, circulatory collapse, and asystole. However, in some cases, such as direct injection of local anesthetic into a blood vessel, circulatory collapse may occur without any neurological signs. Characteristic electrocardiographic signs are PR prolongation and QRS widening.

Atypical symptoms Only 16% of patients present with precursor symptoms and, in 41%, signs and symptoms are delayed or circulatory symptoms appear without neurological symptoms [15]. Such atypical symptoms are associated with the preoperative presence of underlying diseases involving the cardiovascular or nervous systems. In addition, detection of symptoms may be delayed with general anesthesia or deep sedation; caution therefore, is needed.

Time until local anesthetic systemic toxicity appears

The time taken for systemic toxicity to appear varies [15]. Symptoms appear in one-half of cases within 50 s of administration and in three-quarters of cases within 5 min. There are immediate types caused by direct intravascular injection, and delayed types that occur after the drug migrates from tissue or active metabolites accumulate. In immediate types, onset is caused by injection into a head or neck vessel, such as the carotid or vertebral arteries. In delayed types, onset after an overdose occurs after a gradual rise in blood levels. Onset may not occur for several days after starting continuous infusion. With single administration, onset sometimes does not occur until 15 min or more after administration; therefore, when large doses are used, patients should be observed for at least 30 min.

Differential diagnosis

Table 1 summarizes the symptoms and the corresponding conditions typically observed based on the type of regional anesthesia performed, the amount of drug solution, and other factors.

Treating local anesthetic systemic toxicity

Facilities that use local anesthetics should maintain a stock of 20% lipid emulsion in their pharmacies [2, 3]. Departments that use local anesthetics frequently (surgery, obstetrics) should maintain a stock of lipid emulsion (stored at room temperature) that can be used immediately (Fig. 2).

A. If local anesthetic toxicity is suspected, perform the following:
   1 Halt administration of the local anesthetic.
   2 Request assistance.
   3 Attach blood pressure monitor, electrocardiograph, pulse oximeter.
   4 Secure venous line.
   5 Secure an airway and administer 100% oxygen; if necessary perform tracheal intubation and initiate artificial respiration.
   6 Treat convulsions (benzodiazepines are recommended; propofol cannot be used in patients with unstable blood pressure, heartbeat).
   7 Collect blood to measure blood concentration of local anesthetics (if time and resources permit).

B. If severe hypotension or arrhythmia occurs:
   1 Administer 20% lipid emulsion according to the method described below.
   2 Initiate resuscitation according to standard procedures.
   3 Prepare for extracorporeal circulation.

Table 1 Summary of typical reactions and symptoms associated with systemic toxicity from local anesthetics

Reaction	Symptom/condition
Reactions to vasoconstrictors	Tachycardia, hypertension, headache, uneasiness
Vagal reflex	Sudden bradycardia, hypotension, pallor, fainting
Allergy	Anaphylaxis (hypotension, bronchospasm, edema)
High-level spinal anesthesia, high epidural anesthesia	Gradual appearance of bradycardia, hypotension, respiratory arrest
Complications	Asthma, stroke, myocardial infarction, etc.
Use of sedatives	Talkativeness, difficult articulation due to benzodiazepine-linked disinhibition, drowsiness, loss of consciousness, respiratory arrest due to overdose

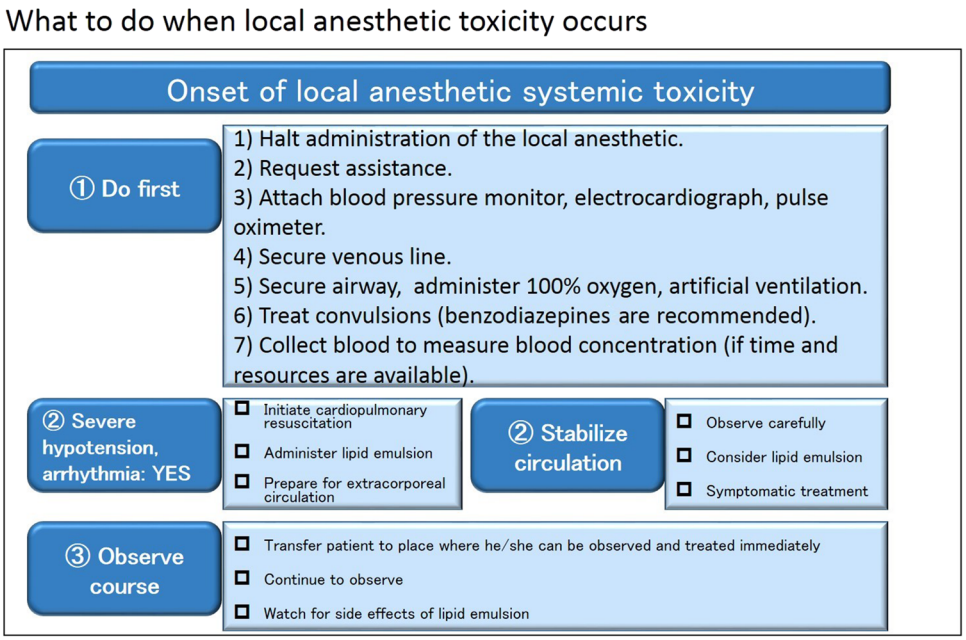

Fig. 2 What to do when local anesthetic toxicity occurs

If severe hypotension or arrhythmia are not observed, provide symptomatic treatment while continuing to consider administering lipid emulsion based on careful observation of the patient [3]. In either case, transfer the patient to a place where he/she can be treated immediately, and continue observation.

C. Outline of lipid emulsion administration method (70 kg patient) (Fig. 3)

1 Administer 1.5 mL/kg (100 mL) over approximately 1 min. Then, initiate continuous administration at 0.25 mL/kg/min (17 mL/min approximately 1000 mL/h).
2 If circulation has not improved after 5 min, administer 1.5 mL/kg (100 mL) while doubling the continuous administration dose to 0.5 mL/kg/min (2000 mL/h). After an additional 5 min, administer 1.5 mL/kg (100 mL) (bolus administration is limited to 3 attempts).

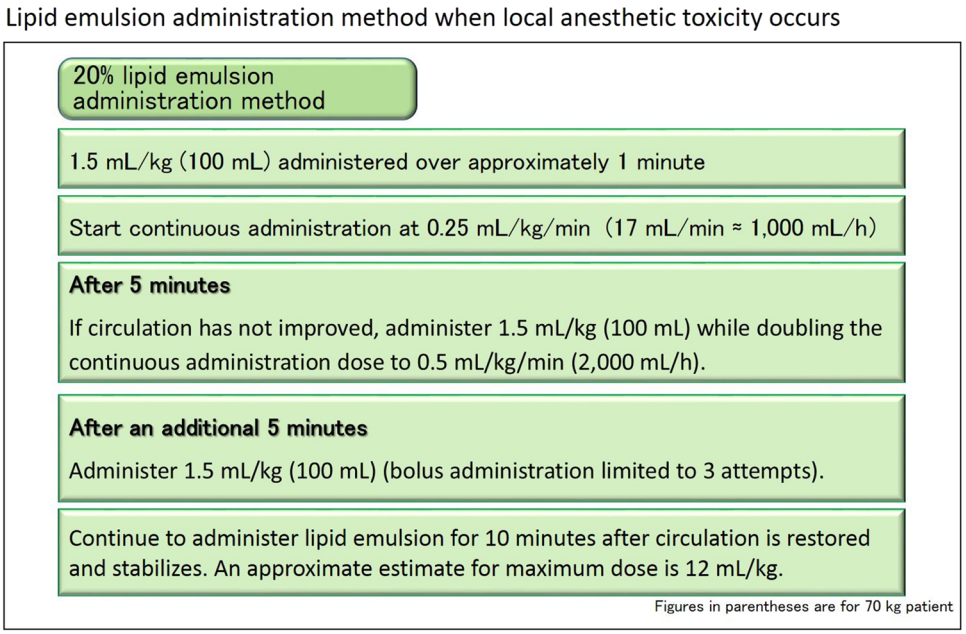

Fig. 3 Lipid emulsion administration method when local anesthetic toxicity occurs

3 Continue to administer lipid emulsion for 10 min after circulation is restored and stabilizes.
4 Studies have reported a resuscitation effect at a total dose of ≤ 10 mL/kg [16]; therefore, 12 mL/kg can be used as an approximate estimate for the maximum dose [3].

D. Areas of caution

1. Do not use lidocaine to treat tachycardia or arrhythmia.
2. To treat convulsions, benzodiazepines, thiopental, or propofol can be used; however, all should be administered at low doses [3]. Although propofol contains lipid emulsion as a solvent, it should not be used as a substitute for lipid emulsion because it acts as a direct cardiac suppressant and its lipid concentration is as low as 10% [2, 3, 6].
3. The adrenaline dose should be based on resuscitation guidelines such as those of the American Heart Association. The American Society of Regional Anesthesia and Pain Medicine standard of < 1 μg/kg does not need to be strictly adhered to [2].
4. Note that resuscitation from local anesthetic systemic toxicity can sometimes take a long time.
5. Lipid emulsion has been reported to be effective at similar doses per unit of body weight for both children and adults [16].
6. After starting lipid emulsion administration, the blood concentration of local anesthetics may rise temporarily compared with before administration [17].
7. Calculations based on animal experiments suggest that the fatal dose of lipid emulsion in humans is 67 mL/kg [18].

E. Side effects of lipid emulsion

In most cases when lipid emulsion is used to treat local anesthetic toxicity, the therapy is effective and free from side effects if the dose is under the maximum described above [16]. There have recently been reports describing side effects of lipid emulsion [19]; however, most of these occurred after therapy for toxicity caused by drugs other than local anesthetics. Of 10 patients who were treated with lipid emulsion for local anesthetic systemic toxicity in a previous study, none exhibited side effects. However, of 30 patients who were treated for toxicity due to other drugs, there was 1 case each of hyperamylasemia (dose: 1000 mL), hyperlipidemia (1000 mL) and bronchospasm (4.5 mL/kg) [20]. The reason for this is believed to be because while blood concentration rises relatively quickly from rapid local absorption when local anesthetics are used, such as for nerve blocks, most of the other toxic drugs were taken orally; consequently, absorption occurred in the gastrointestinal tract and persisted over a long period of time. Thus, these patients often required large doses of lipid emulsion given over long periods.

Regarding serious side effects, severe bradycardia and cardiac arrest have been reported soon after lipid emulsion administration for toxicity caused by high-dose circulatory agonists [21]; however, it is unclear whether the cause in these cases was lipid emulsion. Furthermore, pulmonary impairment (100 mL) [22] and pancreatitis (10.5 mL/kg) [23] have been reported in young patients when lipid emulsion was used to treat drug toxicity not caused by local anesthetics. In the former case, adrenaline administered during resuscitation may have had an effect. Hemofiltration has been attempted after lipid emulsion administration; however, filter clogging has been reported [24]. After administering lipid emulsion, respiratory status and chest radiographs should be given close attention, and tests for lipase and amylase should be performed.

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Compliance with ethical standards

Conflict of interest All authors have no conflict of interest.

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