

Use of lipid emulsion therapy in local anesthetic overdose

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ABSTRACT

اكتسب استخدام مستحلب الدهون في الوريد (ILE) للعلاج نطاق واسع كأدوية السمية الجهازية. هناك بيانات متزايدة تشير إلى أن استخدام ILE في عكس التخدير الموضعي الناجم عن السمية الجهازية شديدة، والسمية القلبية التي تهدد الحياة، على الرغم من أن النتائج متناقضة. وقد أثبتت كفاءة ILE في الدراسات الحيوانية في علاج الضعف الشديد في وظائف القلب، عن طريق آلية لمحاكاة أدوية الدهون في جزء بلازما الدم الشحمي (a.k.a) للمرضى الذين يعانون من انخفاض الدورة الدموية و / أو انهيار القلب والأوعية الدموية بسبب عوامل قابلة للذوبان في الدهون، ويمكن اعتبار ILE للإنعاش في الأماكن الحادة من قبل أطباء الطوارئ. تشمل الآثار السلبية الأكثر شيوعاً ILE القياسية زيادة شحوم الدم، والانسداد الدهون، والعدوى، وتهيج الوريد، والتهاب البنكرياس، واضطرابات الكهارل وردود الفعل التحسسية. وتشمل مزايا ILE زيادة السلامة، وتكلفة منخفضة نسبياً، وعمر افتراضي طويل، وسهولة استخدام.

The use of intravenous lipid emulsion (ILE) therapy as antidote in systemic toxicity of certain agents has gained widespread support. There are increasing data suggesting use of ILE in reversing from local anesthetic-induced systemic toxicity severe, life-threatening cardiotoxicity, although findings are contradictory. Efficiency of ILE was demonstrated in animal studies in the treatment of severe impairment of cardiac functions, via a mechanism for trapping lipophilic drugs in an expanded plasma lipid compartment ("lipid sink"). In patients with hemodynamic compromise and/or cardiovascular collapse due to lipid-soluble agents, ILE may be considered for resuscitation in the acute setting by emergency physicians. The most common adverse effects from standard ILE include hypertriglyceridemia, fat embolism, infection, vein irritation, pancreatitis, electrolyte disturbances and allergic reactions. The advantages of ILE include an apparent wide margin of safety, relatively low cost, long shelf-life, and ease of administration.

Saudi Med J 2017; Vol. 38 (10): 985-993
doi: 10.15537/smj.2017.10.20525

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Lipid injectable emulsions have been in the market since the 1960s and used clinically with certain benefits. Originally, these were lipid-rich formulations used to provide intravenous calorific and nutritional support. The main difference after these ancestor products took place in the oil composition-triglycerides of plant and marine oil origin. Of note, lipid emulsions containing fish oil have less proinflammatory characteristics, which exerts beneficial effects on immune system and organ functions.¹ Widely used lipid solutions mainly contain soybean oil, which is composed of linoleic acid, alpha linolenic acid, alpha tocopherol, and phyosterols.² Linoleic acid constitutes almost 50% of the total fatty acid profile. The soybean oil-based IV fat emulsions contain a substantial amount of nonessential ω-9 fatty acid oleic acid, which accounts for approximately 25% of the fatty acid content. Nearly 85% of the fatty acid profile in soybean oil is composed of 3 18-carbon, long-chain unsaturated fatty acids and the remaining 15% is composed of saturated fatty acids such as palmitic and stearic acids.²

The first case report on the use of intravenous lipid emulsion (ILE) therapy as a rescue or antidotal therapy for acute drug poisoning was published in 2006.³ In recent years, this therapy has become one of the most commonly recommended treatment modalities by most US poison control centers for patients who have suffered cardiac arrest or with hemodynamic compromise following xenobiotic toxicity.⁴ Intravenous lipid emulsion therapy has also been beneficial in neonates and children. Presley and Chyka accumulated findings on pediatric applications of ILE and proposed that a vast majority of the pediatric cases exhibited a positive response to the procedure, despite being unresponsive to

standard resuscitation methods.⁵ The case and anecdotal reports reveal that ILE therapy holds promise in the management of toxicity induced by various lipophilic agents, including drugs and pesticides. Furthermore, some trials assessed the safety of ILE in the treatment of acute poisoning.

The purpose of this review was to examine significant advances in our understanding of the efficacy and safety of ILE, with specific emphasis on its use in local anesthetic toxicity.

Mechanisms of effect and clinical use. The mechanism of action of ILE in the management of poisoning is not completely understood. Nonetheless, numerous mechanisms are believed to contribute to its effectiveness. The emulsion acts as a lipid sink, surrounding a lipophilic drug molecule and rendering it ineffective. Various *in vitro* and *in vivo* studies have confirmed the benefits of the lipid sink effect.⁶⁻⁸ *In vitro* models suggested that the mechanism underlying ILE binding to a drug is mostly dependent on the drug's lipid partition constant and volume of distribution.⁹ It is highly likely that mechanisms other than the lipid sink contribute to the beneficial action of ILE.

The second theory postulates that local anesthetics interrupt the transport of fatty acids to the cardiac mitochondria, thereby reducing energy supply. The fatty acids from the ILE provide the myocardium a ready energy source and thus improve cardiac function.¹⁰

In recent years, some studies proposed a novel mechanism to eliminate toxic agents using poly(N-isopropylacrylamide)-based functional nanogels for effectively scavenging compounds.¹¹ Acid-functionalized nanogels bind to cationic drugs, such as local anesthetics, and thus have the potential to treat overdose. The cell-based assay facilitates reliable drug uptake for nanogels compared with conventional centrifugation-based assays.

Another proposed mechanism involves drug-induced disruption of cellular calcium transport and the restoration of the function through the activation of calcium channels by ILE, which helps in increasing intracellular calcium.⁵ Mechanisms underlying the effects of ILE are primarily based on droplet formation as well as changes in cell metabolism involving survival cell pathway, on functional properties, and on direct hemodynamic parameters.¹² Secondary insults to

cellular metabolism, such as hypoxia and acidosis, can modify the effects of ILE on local anesthetic-induced systemic toxicity (LAST). Finally, there is evidence that ILE protects against ischemia-reperfusion injury and decreases the myocardial infarct size when it is administered at the beginning of reperfusion.¹³

To date, ILE has been used fairly late in the resuscitative procedure and commonly as a last gasp intervention. Cave et al¹⁴ pointed out that in case of immediate threat to life where other treatments have failed, it is reasonable to use an agent when there is an established rationale for use in "all or nothing" cases such as those described above. There are limited randomized clinical trials due to ethical and feasibility issues. Three clinical trials have been conducted with local anesthetics; all showed a redistribution effect but did not significantly alter symptoms from low doses.¹⁵⁻¹⁷ A single randomized controlled trial with non-local anesthetic drugs demonstrated an improvement in coma scale.¹⁸ Recently, a clinical trial was conducted to assess the benefit of ILE as a postconditioning agent.¹⁹ Zhou et al¹⁹ randomized patients undergoing aortic or mitral valve surgery into intralipid postconditioning or control group to determine whether the administration of intralipid immediately before aortic cross-clamping would reduce myocardial injury. They concluded that the protective effect of postischemic administration of ILE before aortic cross-clamping against reperfusion injury could be determined only by biomarkers of injury and not by cardiac function or other clinical outcomes in these groups. In another recent study, Wu et al²⁰ investigated the effect of ILE on local anesthetic induced central nervous system toxicity with special regard to pre- and post conditioning effects of lipid emulsions. The authors concluded that lipid emulsion post conditioning can mitigate central nervous system toxicity associated with LAST while pre conditioning can prevent this toxicity in poisoned rats. Fettiplace et al²¹ who used a physiological pharmacokinetic-pharmacodynamic model, demonstrated the rapid recovery of hemodynamic stability after LAST (bupivacaine overdose) in rodents to be dependent on a direct cardiotoxic action, coupled with volume and sink effects acting in tandem. They rendered the most comprehensive explanation for the effect of triglyceride microemulsion on bupivacaine toxicity by combining physiological parameters with pharmacokinetic data obtained from bupivacaine-intoxicated rats in an *in silico* computational model.²² The authors demonstrated a rapid detoxifying effect of lipid emulsion, acting primarily on key end organs, including the heart and brain, dependent on the partitioning

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

effect of the introduced lipid. The emulsion produced a cardiostimulant effect through the combined actions of volume expansion and direct inotropy.²¹ Fettiplace et al²² proposed a multi-modal therapeutic paradigm for colloidal biodegradation, wherein a microemulsion improves cardiac output as well as rapidly ferries the drug away from organs subject to toxicity. In vivo and in silico models of toxicity were combined to test the contribution of individual mechanisms and reveal the multimodal role of the cardiostimulant and scavenging actions of the triglyceride suspension. The findings demonstrated the critical importance of a cardiostimulant effect independent of cardiac drug concentration, the undisputable scavenging of drug by the lipid compartment, and the acceleration of microsomal (namely liver) metabolism to increase processing and excretion of the drug.

Animal studies. The evidence on the efficacy of ILE in reversing acute toxicity of numerous substances (local anesthetics and other lipophilic compounds) consists mainly of case reports and animal studies. Animal studies show efficacy of ILE in the treatment of severe cardiotoxicity associated with local anesthetics, clonidine, and verapamil, possibly by trapping such lipophilic drugs in an expanded plasma lipid compartment (lipid sink).

In 2010, Jamaty et al³ reviewed 23 animal and 50 human trials involving the use of ILE in the management of poisoning. Intravenous lipid emulsion has certain benefits against poisoning by bupivacaine, verapamil, chlorpromazine, some tricyclic antidepressants, and beta-blockers. In a systematic review, Levine et al²³ analyzed 40 animal experiments involving LAST. Despite the use of ILE in the treatment of patients with poisoning and overdose, the effect of ILE in various non-local anesthetic poisonings is heterogeneous and the quality of evidence is poor.

In a recent systematic review, Hoegberg et al²⁴ concluded that although ILE appears to be effective in the reversal of cardiovascular or neurological consequences of LAST, there is no plausible finding that supports that ILE should be preferred over vasopressors as the first line therapy in severe LAST. In 2011, Mauch et al²⁵ postulated that epinephrine was more useful than ILE in the treatment of severe hemodynamic failure associated with bupivacaine toxicity in piglets, with special regard to survival as well as normalization of hemodynamic parameters and capnography. In contrast, authors of a more recent comparison study demonstrated that ILE with or without epinephrine or epinephrine alone was equally effective in achieving a return of spontaneous circulation (ROSC) in a piglet model of toxicity with levobupivacaine.²⁶ Epinephrine

alone or in combination with lipid was associated with a higher rate of ECG abnormalities compared with ILE alone. In another rat model, Li et al²⁷ reported that late intervention (10 min after administration) with epinephrine plus ILE improved hemodynamics but failed to reduce hypoxemia and acidemia.²⁷

A dose-response relationship was demonstrated by Fettiplace et al²¹ in a rat non-lethal bupivacaine overdose model to produce transient cardiovascular toxicity. Intravenous lipid emulsion resulted in faster recovery (with regard to rate-pressure product) when used in 30% solutions compared with 20%. The authors concluded that this dose-dependent model shows that the cardiostimulant effect is more dominant than the lipid sink in rendering a rapid cardiovascular normalization from cardiovascular toxicity following bupivacaine administration.

Use of intravenous lipid emulsion. Dosing. The dosing protocol most widely reported consists of an intravenous bolus of 1-1.5 mL/kg of 20% ILE solution administered over one minute.^{28,29} If there is no response, the same dose may be repeated in case of cardiac arrest every 3-5 min (maximum total of 3 boluses). Although the maximum duration of ILE therapy has not been specified in the literature, the treatment mostly takes 30-60 minutes. Following the bolus administration, an infusion is started at 0.25-0.5 mL/kg/minute until hemodynamic variables return to normal levels. The infusion rate can be decided to avoid hypotension. A maximum of 12.5 mL/kg of 20% ILE over 24 hours in adults and 15 mL/kg over 24 hours in children is the regimen suggested by the United States Food and Drug Administration.³⁰

Few data on dosing recommendations for children with local anesthetic toxicity have been published. The typical bolus doses published in Presley & Chyka's⁵ review of pediatric series of lipid emulsion for resuscitation ranged from 0.8 to 3 mL/kg of a 20% lipid emulsion, which are well below the doses previously reported³¹ in the acute overdoses of 20% lipid emulsion. The use of ILE is recommended by the American College of Medical Toxicology (ACMT) for intoxicated patients with hemodynamic compromise not responding to conventional resuscitative treatment.³² Table 1 demonstrates the dosing scheme recommended by ACMT in 2011. The optimal dosage, timing, and administration of ILE should be determined in detail as a resuscitative measure.

In the context of resuscitative efforts, intravenous lines for drug administration, flow rates, and doses should be double-checked for appropriateness to ensure drug safety.

Untoward effects. Commonly encountered adverse effects following ILE administration comprise hypertriglyceridemia, fat embolism, hypersensitivity and allergic reactions, infection, local vein irritation, acute pancreatitis, and electrolyte imbalance. A broad literature survey pointed out that the untoward effects are not few and can include kidney injury, cardiac arrest, ventilation perfusion mismatch, acute lung injury, venous thromboembolism, fat overload syndrome, extracorporeal circulation machine circuit obstruction, and increased susceptibility to infections.³³ Nonetheless, it should be noted that most complications are associated with high doses of lipid emulsion, mostly beyond the recommended dosing. Adverse effects are rarely encountered with appropriate dosing (<12.5 mL/kg in 24 hours).

Intravenous lipid emulsion interferes with some laboratory measurements and may affect therapeutic drug monitoring. The analyses of creatinine, amylase and lipase, phosphate, total protein, alanine-aminotransferase, creatine kinase, and bilirubin can become impractical following ILE. Moreover, serine glucose and magnesium levels analyzed using standard laboratory processes would be inaccurate.^{34,35} Whenever possible, blood samples should be collected before ILE therapy. Interferences can be reduced by low-speed brief centrifugation.

In vitro and clinical evidence suggests that the combined use of ILE and extracorporeal membrane oxygenation (ECMO) may be associated with fat deposition in the venoarterial-ECMO circuits and increased blood clot formation.³⁶ Adverse effects appear to be proportional to the rate of infusion as well as total dose received. Further safety studies in humans and reporting of adverse events associated with ILE administration at the conventional doses are required.³⁷

Despite many untoward effects being attributed to ILE therapy, more in-depth data are necessary to identify the risk of complications from ILE therapy in patients with acute toxicity.

Local anesthetic overdoses. In 2013, five of the 1218 poisoning cases that resulted in mortality (recorded by poison control centers) were caused by local anesthetics.³⁷ Intravenous lipid emulsion is beneficial in treating local anesthetic overdose. In humans, ILE was first reportedly used for the treatment of drug toxicity in the setting of LAST, specifically in systemic toxicity due to bupivacaine.³⁸ Intravenous lipid emulsion is known to be useful against toxicity induced by almost all local anesthetics including bupivacaine, mepivacaine, ropivacaine, levobupivacaine, prilocaine, lignocaine, and lidocaine.³⁰ Up-to-date, laboratory and clinical data indicate that ILE therapy can reverse poisoning caused by local anesthetics as well as nonlocal anesthetics, calcium channel blockers, beta-blockers, and tricyclic antidepressant drugs, among others.

Local anesthetic-induced systemic toxicity is a potentially lethal complication in anesthesia (regional or local), which is not easily reversible by a single treatment. It is associated with neural excitation and can cause refractory cardiac dysfunction and collapse. The development of ILE for the treatment of LAST is based on observations of studies on potent, lipophilic local anesthetic bupivacaine, and its associated clinical risk of intransigent cardiac toxicity in healthy individuals.³⁹ Intravenous lipid emulsion was found to be useful in experiments where cardiac compressions and ventilation were started immediately upon cardiac arrest and continued throughout the experiment. In a rabbit model, ILE did not achieve ROSC in rabbits after a hypoxic cardiac arrest.⁴⁰

Findings on the practical efficacy of ILE in LAST in different clinical settings are contradictory. In a

Table 1 - The dosing scheme recommended by The American College of Medical Toxicology (ACMT) in 2011.³²

Step #	Dosing and instructions	Explanation - Notes
1	20% lipid emulsion should be administered as a 1.5-ml/kg bolus.	draw the right volume of 20% lipid emulsion into 50 ml syringes and infuse it through an indwelling catheter over 2–3 min.
2	The bolus should be followed immediately by an infusion of 20% lipid emulsion at a rate of 0.25 ml/kg/min.	All hemodynamic parameters (blood pressure, heart rate, and other available ones) should be recorded every 15 min during the infusion.
3	For asystolic patients, or those with pulseless electrical activity, who do not respond to the bolus, the abovementioned dose may be repeated.	
4	If there is an initial response to the bolus followed by the re-emergence of hemodynamic instability, the infusion rate could be increased or, in severe cases, the bolus could be repeated.	
5	Where possible, ILE can be stopped after 1 h, or less, in accord with the patient's clinical status.	Longer periods of infusion may be necessary, should the patient's stability be dependent on continued lipid infusion.

Table 2 - Main characteristics of the studies which investigate the efficacy of intravenous lipid emulsion therapy in local anesthetic-induced systemic toxicity.

Investigator	Title	Date	Sample size	Objectives	Results
Presley et al ⁵	Intravenous lipid emulsion to reverse acute drug toxicity in pediatric patients.	2013	14 case reports	To identify and summarize published cases in which ILE was used to treat pediatric patients with acute drug toxicities.	13 cases demonstrated a beneficial response in reversing systemic toxicity; 1 of these patients developed hypertriglyceridemia and pancreatitis.
Nouette-Gaulain et al ¹²	[Intravenous lipid emulsion and local anesthetic-induced systemic toxicity: mechanisms and limits]	2014		To describe mechanisms involved in the interaction between ILE and local anesthetic factors influencing this interaction and the limits associated with the use of ILE.	ILE treatment is recommended by published guidelines on LAST resuscitation. ILE cannot substitute to the standard resuscitation protocol. It should be added to that protocol.
Cave et al ¹⁴	Should we consider the infusion of lipid emulsion in the resuscitation of poisoned patients?	2014	Two clinical trials and five case series	to examine recent literature on the mechanism of ILE, and to evaluate the evidence supporting ILE administration, and thereby establish whether any changes to present recommendations for utilisation are warranted.	The present evidence supports use of ILEs only in LAST and in lipophilic cardiotoxin intoxication when there is an immediate threat to life, and other therapies have proven ineffective.
Heinonen et al ¹⁶	Intravenous lipid emulsion given to volunteers does not affect symptoms of lidocaine brain toxicity.	2015	8 healthy volunteers	To identify the exact mechanism of action of ILE as treatment for LAST.	Lidocaine was only minimally entrapped in the plasma by ILE, but the mean un-entrapped lidocaine concentration (AUC) was clearly smaller during lipid than Ringer infusion. ILE did not influence subjective toxicity symptoms nor affect the EEG changes caused by lidocaine.
Dureau et al ¹⁷	Effect of intralipid® on the dose of ropivacaine or levobupivacaine tolerated by volunteers: a clinical and pharmacokinetic study.	2016	16 volunteers	To determine the effect of Intralipid® administration on the time to neurologic symptoms.	Peak concentration was decreased by 26 to 30% in the subjects receiving Intralipid®. Simulations showed that Intralipid® might prevent the rapid increase of local anesthetic concentration after extravascular administration.
Fettiplace et al ²¹	Resuscitation with lipid emulsion: dose-dependent recovery from cardiac pharmacotoxicity requires a cardiotoxic effect.	2014	28 rats	To test the dose-dependent response to ILE during reversal of bupivacaine-induced cardiovascular toxicity in vivo	ILE accelerates cardiovascular recovery from bupivacaine toxicity in a dose-dependent manner, driven by a cardiotoxic response that complements the previously reported sequestration effect.
Hoegberg et al ²⁴	Lipid Emulsion Workgroup. Systematic review of the effect of intravenous lipid emulsion therapy for local anesthetic toxicity.	2016	76 human and 38 animal studies	A collaborative lipid emulsion workgroup was therefore established by the American Academy of Clinical Toxicology to review the evidence on the effect of ILE for LA toxicity.	ILE appears to be effective for reversal of cardiovascular or neurological features in some cases of LA toxicity, but there is currently no convincing evidence showing that ILE is more effective than vasopressors or to indicate which treatment should be given as 1st line therapy in severe LAST.
Li et al ²⁷	Association of sustained cardiovascular recovery with epinephrine in the delayed lipid-based resuscitation from cardiac arrest induced by bupivacaine overdose in rats.	2012	32 rats	To explore the effect of epinephrine on delayed lipid-based treatment for bupivacaine-induced cardiac arrest in rats.	Late intervention with epinephrine plus ILE contributed to sustained improvement in haemodynamic profile, but failed to alleviate deterioration of hypoxaemia and acidaemia.
Lam et al ³⁰	Use of intravenous fat emulsion in the emergency department for the critically ill poisoned patient.	2016	Systematic review of 85 trials	To conduct literature search from 1996 to 2015 and limited to human studies written in English and articles with relevant keywords and to review of the results.	In critically ill patients with refractory shock or cardiac arrest after a suspected LAST, ILE may be considered as a potentially beneficial adjunctive treatment.
Bern et al ⁴¹	Local anesthetic toxicity and lipid resuscitation in pregnancy.	2011	Review	To discuss clinical reports, relevant laboratory studies, and future directions for the development of an optimal protocol for ILE in pregnancy.	ILE appears to be an effective treatment for toxicity induced by lipophilic medications and may be useful in treating systemic toxicity in the pregnant patient.
Ozcan et al ⁴²	Intravenous lipid emulsion for the treatment of drug toxicity.	2014	Review	To summarize the experimental evidence as well as the clinical experience in using ILE as an antidote.	In scenarios where ILE has shown clear benefit (eg, LAST), we believe that earlier administration is preferred since it might prevent, interrupt, or reverse a physiological vicious cycle that can progress to cardiovascular collapse.

Table 2 - Main characteristics of the studies which investigate the efficacy of intravenous lipid emulsion therapy in local anesthetic-induced systemic toxicity (continuation)

Gosselin et al ⁴³	Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning	2016	Systematic review of the literature (22 toxin categories and 3 clinical situations).	To appraise the literature and provide evidence-based recommendations for the use of ILE in poisoning.	Clinical recommendations regarding the use of ILE in poisoning were only possible in a small number of scenarios and were based on very low quality of evidence. If other therapies fail, ILE is recommended for bupivacaine toxicity and also for other LAs.
Harvey et al ⁴⁵	Lipid emulsion in local anesthetic toxicity	2017	Review	To analyze published literature to determine the value of ILE in the treatment of LAST	ILE remains first-line therapy (in conjunction with standard resuscitative measures) in LAST.
Fettiplace et al ⁴⁶	Lipid emulsion improves survival in animal models of local anesthetic toxicity: a meta-analysis	2017	Meta-analysis of 16 trials	Efficacy of ILE as a treatment for local anesthetic toxicity on survival in animal models	ILE reduced the odds of death in resuscitative models. Data supports the use of ILE for the treatment of LAST, specifically from bupivacaine.
Mithani et al ⁴⁷	A cohort study of unstable overdose patients treated with intravenous lipid emulsion therapy	2017	36 non-LAST poisoning	to examine a cohort of poisoned patients to identify the change in blood pressure in the 1st hr after ILE infusion and to highlight survival, length of stay, and the effect of drug class on outcome.	The study did not find a clinically important improvement in blood pressure after ILE. Until future research is done, ILE should remain an option for hemodynamically unstable patients only after conventional therapy fails.
Cao et al ⁴⁸	Intravenous lipid emulsion in the emergency department: a systematic review of recent literature	2015	systematic review of 94 articles and 40 conference abstracts	To identify literature on the use of ILE in humans as an antidote and to familiarize caregivers with the indications, dosing, and adverse reactions associated with ILE use	In the setting of severe hemodynamic compromise by lipid-soluble xenobiotics, ILE may be considered for resuscitation. As such, ILE may be stocked in EDs.
Cave et al ⁴⁹	Intravenous lipid emulsion as antidote: a summary of published human experience	2011	42 cases of ILE use (19 LAST, 23 non-LAST)	to report a comprehensive literature search of all human reports of ILE application in drug poisoning	Data suggest a possible benefit of ILE in potentially life-threatening cardio-toxicity from bupivacaine, mepivacaine, ropivacaine, haloperidol, tricyclic antidepressants, lipophilic cardiac agents.
Chai et al ⁵⁰	Intravenous lipid emulsion in the resuscitation of cocaine-induced cardiovascular arrest in a rat model	2016	12 Sprague-Dawley rats	to determine if ILE would reverse cocaine-induced cardiac arrest in a rat model.	ILE administration did not affect outcome of cocaine-induced cardiac arrest compared with control in this model.
Di Gregorio et al ⁵¹	Lipid emulsion is superior to vasopressin in a rodent model of resuscitation from toxin-induced cardiac arrest	2009	24 Sprague-Dawley rats	To compare the efficacy of resuscitation from bupivacaine-induced asystole using ILE vs. vasopressin, alone and with epinephrine.	Lipid emulsion in this rat model provides superior hemodynamic and metabolic recovery from bupivacaine-induced cardiac arrest than do vasopressors.
Liu et al ⁵²	The comparative effects of lipid, epinephrine, and their combination in the reversal of bupivacaine-induced asystole in the isolated rat heart	2012	30 rats	To compare the effects of lipid, epinephrine, and the combination of the two in reversing bupivacaine-induced asystole in the rat model.	Lipid combined with epinephrine resulted in better recovery of cardiac function than either drug alone in reversal of bupivacaine-induced asystole in the rat heart.
Heinonen et al ⁵³	Intravenous lipid emulsion for levobupivacaine intoxication in acidotic and hypoxaemic pigs	2016	20 pigs	To investigate whether hypoxaemia and acidosis following LAST influences the effects of ILE on drug concentrations and cardiovascular recovery in levobupivacaine intoxication in pigs.	Administration of lipid emulsion did not improve cardiovascular recovery from levobupivacaine toxicity exacerbated by acidosis and hypoxaemia. ILE did not entrap levobupivacaine or affect levobupivacaine pharmacokinetics.

ILE - intravenous lipid emulsion, LAST - local anesthetic-induced systemic toxicity.

recent study where modestly toxic doses of ropivacaine or levobupivacaine was infused intravenously in 16 volunteers, the authors did not observe any effect of ILE during the time early signs of neurological toxicity are expected.¹⁷ Peak concentration declined by up to 30% in the subjects who received ILE. Simulations showed that ILE can prevent a rapid increase in local anesthetic concentration after extravascular administration.

Increased physician awareness and training as well as optimized treatment protocols may significantly decrease the observed rate of morbidity and mortality attributed to LAST.³⁹ Current guidelines and case reports suggest that treatment with a large bolus of lipid at the earliest signs of toxicity may prevent cardiovascular collapse.⁴¹ When used with ILE, high doses of vasopressors (epinephrine and/or vasopressin)

did not improve ROSC following systemic toxicity caused by bupivacaine.⁴² Similarly, Gosselin et al⁴³ reported a broad group of toxicological associations and recommended the use of ILE in the management of bupivacaine toxicity, followed by cardiac arrest. However, their opinion regarding its use in cardiac arrest due to other local anesthetics was neutral.

In a recent study, Rosenthal et al⁴⁴ queried the number of German hospitals that were equipped to treat LAST with ILE and identify the frequency and type of toxic reactions as well as determine the success of the treatment. They reported that the majority of German hospitals are equipped to treat LAST and published guidelines for improving this preparedness. A vast majority of the hospitals that use ILE in the treatment of LAST found this therapeutic approach to be successful. Intravenous lipid emulsion therapy was used on encountering prodromal symptoms.

More studies in children will help determine the optimal use and safety profile of ILE in the treatment of acute poisoning. Intravenous lipid emulsion is mostly administered if conventional resuscitation is unsuccessful and the response has been markedly positive, as pointed out in most reports. Therefore, the use of ILE is likely to continue. Although ILE cannot substitute the standard resuscitation protocol in LAST, it should be added to the protocol. The treatment modality is recommended in conjunction with standard resuscitation therapies in poisoned patients who are hemodynamically compromised.³⁰

Table 2 summarizes main characteristics of the studies that investigate the efficacy of ILE therapy in LAST.

Directions for future use. Considering that most concrete data on ILE in clinical toxicity are obtained from case reports and the scarcity of blinded controlled studies, there is still substantial skepticism with regard to its generalizability to the whole community. It should also be noted that ILE could effectively protect against uninvestigated xenobiotics. A recent systematic review conducted by Gosselin et al³⁶ stressed that dose-finding and controlled studies reflecting poisoning scenarios in humans are mandatory to highlight limitations, adverse effects, indications, effectiveness, and best regimen for the treatment modality.

In conclusion, ILE is postulated to reverse untoward effects of local anesthetic agents not only by extracting lipophilic compound from the tissues, but also by counteracting the inhibition of myocardial fatty acid oxygenation by the poison. Lipid therapy for cardiac arrest associated with drug toxicity, and in particular LAST, has been strongly advocated in the recent years.

Literature describing animal studies and human case reports suggests that lipid emulsion is effective in the reversal of LAST. Despite the lack of unequivocal data on the outcome of the patients, ILE therapy can be considered for those with severe LAST when conventional treatments have failed. The treatment modality is recommended in conjunction with standard resuscitation therapies in poisoned patients who are hemodynamically unstable. Thus, a higher level of training of clinicians with regard to the beneficial and changing value of ILE in different clinical settings is warranted. As potentially lethal toxic reactions to local anesthetics are common, it is recommended that lipid emulsions be accessible in routine clinical practice. Well-designed population-based studies are required to highlight its optimal indications, timing, and dose.

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