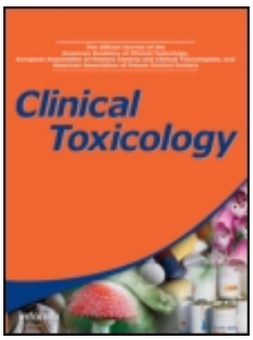

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REVIEW

Systematic review of the effect of intravenous lipid emulsion therapy for local anesthetic toxicity

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ABSTRACT

Background: Following national and regional recommendations, intravenous lipid emulsion (ILE) has become established in clinical practice as a treatment for acute local anesthetic (LA) toxicity, although evidence of efficacy is limited to animal studies and human case reports. 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. **Methods**: We performed a systematic review of the literature published through 15 December 2014. Relevant articles were determined based on pre-defined inclusion and exclusion criteria. Pre-treatment experiments, pharmacokinetic studies not involving toxicity and studies that did not address antidotal use of ILE were excluded. **Results**: We included 113 studies and reports. Of these, 76 were human and 38 animal studies. One publication included both a human case report and an animal study. Human studies included one randomized controlled crossover trial involving 16 healthy volunteers. The subclinical LA toxicity design did not show a difference in the effects of ILE versus saline. There was one case series and 73 case reports of ILE use in the context of toxicity (83 patients) including CNS depression or agitation ($n = 45$, 54%), seizures ($n = 49$, 59%), hypotension, hypertension, EKG changes, arrhythmias ($n = 39$, 47%), cardiac arrest ($n = 18$, 22%), cardiopulmonary resuscitation, and/or requirement for endotracheal intubation and/or mechanical ventilation ($n = 35$, 42%). There were 81 (98%) survivors including 63 (76%) with no reported sequelae from the LA poisoning or ILE, although the presence or absence of sequelae was not reported in 15 (18%) cases. Animal studies included 29 randomized controlled studies, three observational studies, five case series, and one case report; bupivacaine was used in 29 of these reports (76%). Of 14 controlled experiments in animals, eight showed improved survival or time to return of spontaneous circulation and five no benefit of ILE versus saline or non-ILE treatments. Combining ILE with epinephrine improved survival in five of the six controlled animal experiments that studied this intervention. The studies were heterogeneous in the formulations and doses of ILE used as well as the doses of LA. The body of the literature identified by this systematic review yielded only a very low quality of evidence. **Conclusion**: 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 instituted as first line therapy in severe LA toxicity.

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Intravenous lipid emulsion; local anesthetics; systematic review

Introduction

There has been increasing interest in the use of intravenous lipid emulsion (ILE) for the treatment of acute local anesthetic (LA) poisoning following the publication of a case report in 2006.[1] Since then, national and regional anesthesiology societies have published recommendations for use of ILE in the treatment of LA toxicity after iatrogenic overdose.[2–4] However, evidence supporting the use of ILE in the context of toxicity involving local anesthetics or other toxins reported by previous reviews consists primarily of human case reports and

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controlled animal experiments that cannot necessarily be extrapolated to human clinical settings.[5–8]

The American Academy of Clinical Toxicology (AACT) initiated a collaboration between the European Association of Poison Centres and Clinical Toxicologists (EAPCCT), the Asia Pacific Association of Medical Toxicology (APAMT), the Canadian Association of Poison Control Centres (CAPCC), the American College of Medical Toxicology (ACMT) and the American Association of Poison Control Centers (AAPCC) to create the Lipid Emulsion Therapy in Clinical Toxicology Workgroup, which included clinical experts in clinical toxicology, anesthesiology, emergency medicine, critical care, and pharmacy with assistance of medical librarians and epidemiologists. This workgroup was tasked to review all appropriate evidence pertaining to the use of lipid emulsion in toxicology, with the ultimate goal of providing a comprehensive evaluation of the published evidence and consensus-based recommendations.[9] Here, we present the results of our systematic review of human and animal studies regarding the effect of ILE in the treatment of LA toxicity. Use for treating toxicity from other substances and adverse effects of ILE will be presented in other systematic reviews.

Methods

A working subgroup (the authors) of the lipid emulsion therapy workgroup [9] was formed to gather and review the evidence on the effect of ILE in the treatment of LA toxicity. This subgroup was formed based on the best possible match to represent the clinical experts and various stakeholders and involved in the workgroup. It also included two medical librarians who assisted in conducting the systematic searches and the retrieval of potentially eligible publications, as well as an epidemiologist with specific methodological expertise in conducting systematic reviews. Subgroup members divulged all potential conflicts of interests prior to inclusion in the workgroup. All communication was performed by email exchanges and by telephone conferences.

Two medical librarians created a systematic search strategy for Medline (Ovid), which is provided in the Appendix. The strategy comprised a combination of Medical Subject Headings, title/abstract key words, truncations, and Boolean operators, and included the concepts of ILE and toxicology (including but not limited to local anesthetics). It was subsequently translated for Embase (via Ovid), CINAHL (via EBSCO), BIOSIS Previews (via Ovid), Web of Science, Scopus, and the Cochrane Library/DARE. All databases were searched from inception to 15 December 2014. Subsequently, articles were triaged into local anesthetics and non-local anesthetics for review by each designated groups.

In addition, conference abstracts from the European Association for Poison Centers and Clinical Toxicologists, and the North American Congress of Clinical Toxicology (both from 2000 to 2014) and previous reviews were hand-searched by various group members. Abstracts from the Asia Pacific Association of Medical Toxicology were searched in the same way from 2007 to 2014. Group members also performed cross-referencing of full-text articles. No limits were applied for language, and candidate studies in languages not known to any of the authors were translated.

In summary, the criteria for publication inclusion in the evaluation of the effect of ILE include studies in humans and animals to whom ILE was given for the purpose of treating poisoning, and exclusion criteria are non-original data, animal studies with methods and results that cannot be extrapolated or are uninterpretable to humans, pre-treatment models, and experimental *in vitro* or *ex vivo* models. A complete methodology of the larger project of which this systematic review is one part was previously published, and describes in detail all relevant methodological aspects such as clinical questions, search strategies, eligibility of publications, data extraction and summary, and assessment of the risk of bias.[9]

The log *D*, which is based on the partition coefficient, and is a measure of lipophilicity, is reported for each local anesthetic. The degree of lipophilicity directly corresponds with the log D; as the log *D* increases, so does the lipophilicity of a substance.

Results

Our combined search for the effect of ILE retrieved 838 full text articles that were subsequently analyzed for their pertinence to LA. Of these, 113 publications were included in our systematic review. Among the included publications, 76 were conducted in a human setting and 38 in an animal setting. One article included both a case report and an animal experiment. One human study was published as two publications. The flow diagram of study selection is presented in Figure 1.

Human studies

Randomized controlled trials

One phase-II randomized controlled trial (unpublished, available as conference abstract at the time of writing) evaluated the efficacy of ILE on the pharmacokinetic properties of LA in 16 healthy volunteers (8 female and 8 male) aged 18–40 years (Table 1).[10,11] This was a double-blind crossover study consisting of a first phase of habituation to LA with an infusion of lidocaine, followed by a second phase of either a continuous infusion of ropivacaine or levobupivacaine at 8 mg/min treated with either a bolus of 120 mL of 20% ILE or of 0.9% saline, administered 2 min after the start of the LA infusion. The primary outcome of interest was the duration of drug infusion (expressed as total dose) required to induce early clinical signs of neurotoxicity such as paresthesiae and a sensation of inebriation, as evaluated by an examiner blinded to the treatment. Secondary outcome measures were detection of sub-clinical seizure activity based on electroencephalogram (EEG), duration of PR, QRS intervals based on electrocardiogram (EKG), and pharmacokinetics of local anesthetics [maximum concentration (C_{max}) and area under the plasma concentration versus time curve (AUC)].

No significant difference in the total LA dose given to reach early signs of clinical toxicity was observed between ILE and control groups: Ropivacaine/ILE (75.7 mg ± 29.1 mg) or saline (81.7 mg ± 22.3 mg) and Levobupivacaine/ILE (69.4 mg ± 26.2 mg) or saline (80.8 mg ± 31.7 mg; $p = 0.61$). The LA dose

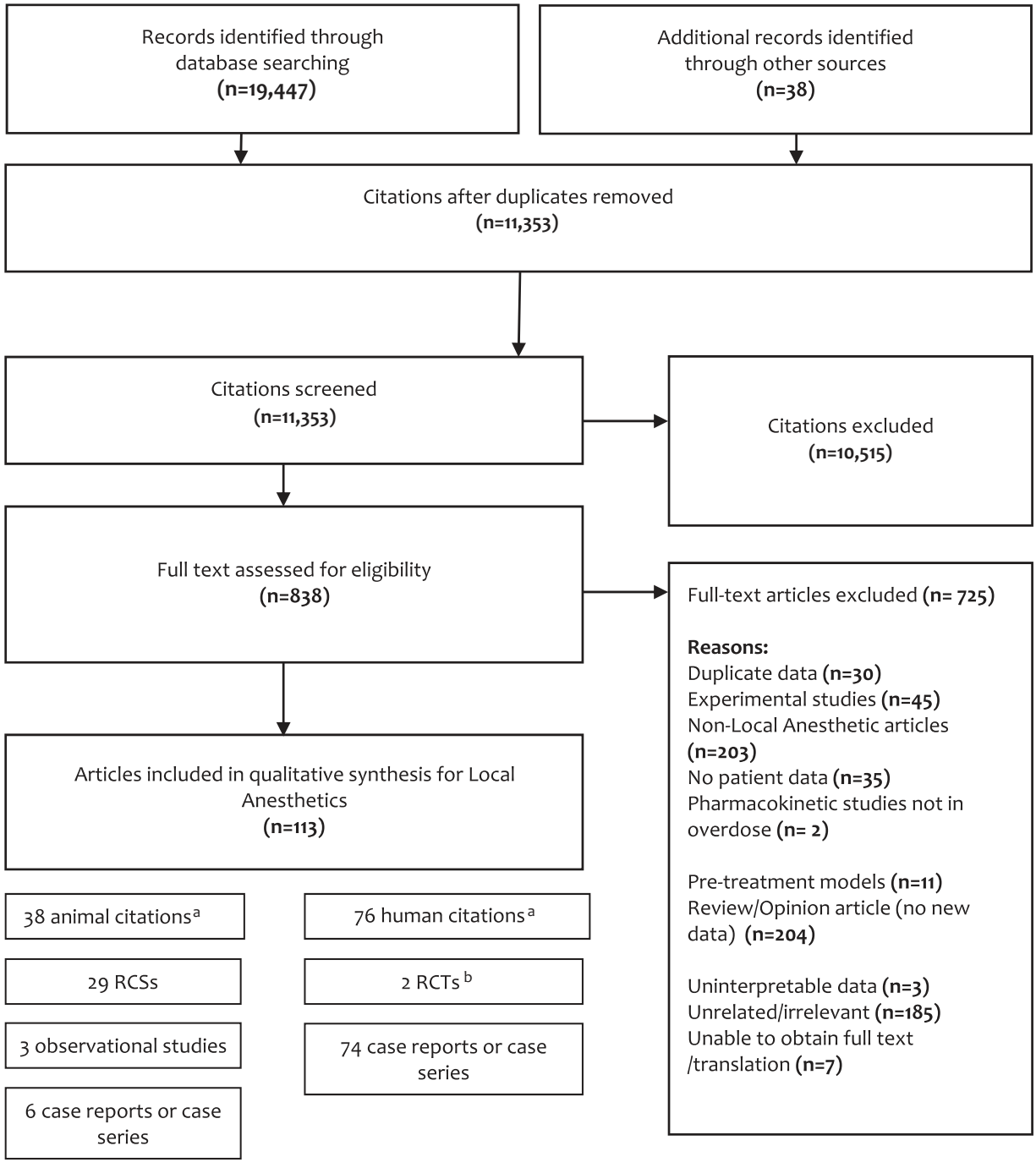

Figure 1. Selection of articles flow diagram. Search date 15 December 2014.
[a]One citation included both one animal study and one human case report.
[b]2 citations for abstracts of a single experiment with 2 parts thus counted as one experiment.
RCS: randomized controlled study; RCT: randomized controlled trial.

was provided at 8 mg/min, and maximum allowed dose was 120 mg. Four of the 16 volunteers received the maximum dose of LA allowed in the protocol. No EEG abnormalities were seen. QRS prolongation was present at the end of the LA infusion as compared to baseline ($p < 0.001$), but no significant difference was observed between the ILE and control groups ($p = 0.68$).[11] Small pharmacokinetic differences between groups, including a 25–30% reduction in C_{max} and a 20% increase in volume of distribution of the LA at a comparable mean dose, were not statistically significant and disappeared after 45 min [10]. The authors concluded that their study confirmed the lipid sink hypothesis in humans, but that no clinical efficacy of ILE could be observed in this systemic toxicity model, where a 3.8 ms prolongation in QRS was induced by the LA perfusion. No obvious risk of bias was identified from the research protocol (https://clinicaltrials.gov/ct2/show/NCT01602250?term=toxalip&rank=1), but concerns remain regarding indirectness (use of surrogate markers and uncertain generalizability to a poisoning context) and imprecision of the reported results due to the small sample size (potentially underpowered study).

No published peer-reviewed clinical controlled or observational studies were retrieved by our search.

Table 1. Summary of the 16 volunteers from a crossover randomized controlled trial, and 83 patients from 73 case reports and one case series included in the systematic review.

References	Study type	Age/sex, weight	Local anesthetic and dose	Log *D* [129]	Route of administration	Symptoms	ILE used	ILE dose[a]	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
RCT												
Dureau et al. (2014) R010 + R011 [10,11][b]	RCT, cross-over	Age 18–40 years/ 8 F + 8 M	Ropivacaine or Levobupivacaine; Continued infusion doses 8 mg/min, maximum 120 mg or until early signs of toxicity such as paresthesias or inebriation sensation reached.	4.21 2.68	Infusion	Neurologic impregnation (paresthesia, inebriation) QRS broadening at LA cessation	20%, Intralipid	120 mL bolus	Yes	Saline (120 ml) on two study days (Control group)	Study confirms the Lipid Sink hypothesis in humans, but unable to demonstrate any clinical benefit of ILE	4 out of 16 volunteers reached maximum dose. Mean dose to reach mild toxicity threshold was not different in ILE versus control groups (75.7 =/ − 29.1 mg versus 81.7 =/- 22.3 mg for ropivacaine and 69.4 =/- 26.2 mg versus 80.8 =/- 31.7 mg for levobupivacaine
Case reports/series												
Admani & Essajee (2010) [12]	Case report	3 months/ M, 5.9 kg	Bupivacaine 25 mg, Lidocaine 100 mg	2.68 1.26	Subcutaneous	Seizure. bradycardia with block then Ventricular fibrillation and Ventricular tachycardia	20%, Intralipid	9 mL (0.31 g/kg) bolus then 0.25 mL/ kg/min (0.51 g/kg/h)	No	Dexamethasone 2 mg, hydrocortisone 20 mg, thiopental 5 mg Mechanical ventilation	Probably no effect required benzodiazepine after seizures restarted in ICU	Survival, no sequelae
Al-Alami (2011) [13]	Case report	16 years/M, 58 kg	Ropivacaine 300 mg	4.21	Nerve block	Confusion, visual hallucinations slurred speech tremor Sinus tachycardia and hypertension	20%, Intralipid	0.0015 g/kg bolus then 0.015 g/kg/h in 3 h	No	Midazolam 0.5 mg	ILE was safe and successful in reversing LA-induced early CNS and cardiac abnormalities	Survival, no sequelae
Aveline et al. (2010) [14]	Case report	52 years/F, 57 kg	Lidocaine 400 mg, Ropivacaine 112.5 mg	1.26 4.21	Nerve block	GCS 7, agitated, confused, jerking arms/ head	20%, Intralipid	100 mL (0.35 g/ kg) × 2 bolus	No	Midazolam 3 mg, thiopental 300 mg and suxamethonium 80 mg Intubation	ILE not effective	Survival, no sequelae
Bazerbachi et al. (2014) [15]	Case report	57 years/M, weight NR	Ropivacaine 1540 mg	4.21	Nerve block	Lethargic, hallucinations Bradycardia, wide QRS, prolonged QT, ejection fraction 20% Cardiac arrest Tinnitus, dysgeusia	20%, Intralipid	Total dose 2480 mL	No	Plasmapheresis	Suggest the failure of ILE rescue	Died from cardiac arrest
Bilotta et al. (2012) [16]	Case report	53 years/M, weight NR	Lidocaine 500 mg, Ropivacaine 3000 mg	1.26 4.21	Nerve block	AV block, HR 28/min, MAP 40 mmHg	20%, Intralipid	100 mL bolus (<5 min) then 100 mL in 20 min	No	Atropine 0.5 mg, phenylephrine 10 mg	Rapid beneficial effect	Survival, no sequelae
Buckenmaier et al. (2012) [17]	Case report	29 years/M, weight NR	Ropivacaine, Mepivacaine. Bolus and continued infusion doses of both, total dose NR	4.21 1.40	Nerve block	Unresponsive, cardiac arrest	Intralipid	1 mL/kg × 3 bolus	No	Epinephrine, atropine, amiodarone, calcium, sodium bicarbonate, magnesium, thrombolytic therapy CPR	NR	Died from blast injuries complicated by LA toxicity resulting in a fatal cardiac arrhythmia
Calenda & Dinescu (2009) [18]	Case report	72 years/M, 60 kg	Mepivacaine 300 mg, Ropivacaine 112.5 mg	1.40 4.21	Nerve block	Numb mouth/tongue Seizures Tachycardia (130/ min)	20%, Intralipid	250 mL (0.83 g/kg) bolus	No	Midazolam 5 mg, propofol 150 mg (first seizure); Thiopental 125 mg (second seizure) Mechanical ventilation	ILE not effective in stopping second seizure	Survival, no sequelae
Cave et al. (2014) (Lipid Registry) [19]	Case series, No 1	Age NR/M, weight NR	Lidocaine 560 mg	1.26	Nerve block	Hypertension Drowsy	NR	NR	NR	NR	NR	Survival, sequelae NR

(continued)

Table 1. Continued

References	Study type	Age/sex, weight	Local anesthetic and dose	Log *D* [129]	Route of administration	Symptoms	ILE used	ILE dose[a]	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Cave et al. (2014) (Lipid Registry) [19]	Case series, No 2	67 years/F, 49 kg	Lidocaine 200 mg, Bupivacaine 75 mg	1.26 2.68	Nerve block	Seizure	20%, Intralipid	1.5 mL/kg (0.30 g/kg) bolus then 400 mL (4.9 g/kg/h) in 20 min. Total dose 500 mL (2.04 g/kg)	No	Midazolam	ILE was thought to have prevented death	Survival, sequelae NR
Cave et al. (2014) (Lipid Registry) [19]	Case series, No 3	NR	Mepivacaine 900 mg, Bupivacaine 100 mg	1.40 2.68	Nerve block	Decreased level of consciousness	NR	NR	NR	NR	NR	Survival, sequelae NR
Cave et al. (2014) (Lipid Registry) [19]	Case series, No 4	68 years/M, 75 kg	Ropivacaine 200 mg	4.21	Nerve block	Seizure Cardiac arrest	20%, Intralipid	100 mL (0.27 g/kg) × 3 bolus. Total dose 300 mL (0.80 g/kg)	No	Midazolam, epinephrine, sodium bicarbonate, magnesium, and hydrocortisone	NR	Survival, sequelae NR
Cave et al. (2014) (Lipid Registry) [19]	Case series, No 5	69 years/F, 80 kg	Bupivacaine 150 mg	2.68	Nerve block	Seizure Cardiovascular collapse	20%, Intralipid	1.5 mL/kg (0.30 g/kg) bolus then 400 mL/h (1.0 g/kg/h) Total dose 500 mL (1.25 g/kg)	NR	NR	ILE was thought to have prevented death	Survival, sequelae NR
Cave et al. (2014) (Lipid Registry) [19]	Case series, No 6	NR	Bupivacaine 50 mg	2.68	Nerve block	Seizure	NR	NR	NR	NR	NR	Survival, sequelae NR
Cave et al. (2014) (Lipid Registry) [19]	Case series, No 7	NR	Bupivacaine 100 mg	2.68	Nerve block	Seizure	NR	NR	NR	NR	NR	Survival, sequelae NR
Cave et al. (2014) (Lipid Registry) [19]	Case series, No 8	30 years/M, 81 kg	Bupivacaine 100 mg	2.68	Nerve block	Seizure	20%, Lipofundin	1.5 mL/kg (0.30 g/kg) bolus then 15 mL/min (2.22 g/kg/h) Total dose 640 mL 1.58 g/kg)	NR	NR	ILE was thought to have prevented death	Survival, sequelae NR
Cave et al. (2014) (Lipid Registry) [19]	Case series, No 9	47 years/F, 60 kg	Bupivacaine 187.5 mg	2.68	Subcutaneous	Decreased level of consciousness	20%, Intralipid	1.5 mL/kg (0.30 g/kg) bolus then 13 mL/min (2.58 g/kg/h) Total dose 900 mL (3.0 g/kg)	NR	NR	NR	Survival, sequelae NR
Cave et al. (2014) (Lipid Registry) [19]	Case series, No 10	75 years/F, 57 kg	Bupivacaine 1595 mg	2.68	Nerve block	Seizure	20%, Intralipid	1.5 mL/kg (0.30 g/kg) bolus then 870 mL/h (3.05 g/kg/h) Total dose 587 mL 1.95 g/kg)	NR	NR	NR	Survival, sequelae NR
Charbonneau et al. (2009) [20]	Case report	19 years/sex NR, 67 kg	Mepivacaine 1000 mg	1.40	Nerve block	Dysarthria, myoclonia, confusion	20%, Medialipid	100 mL (0.30 g/kg) bolus	No	Midazolam 1 mg, clonazepam 1 mg	Efficacy was immediate and complete	Survival, no sequelae
Contargyris et al. (2012) [21]	Case report	26 years/F, 34 weeks pregnant, 51/58 kg	Bupivacaine 7 mg, Ropivacaine 90 mg	2.68 4.21	Nerve block	Headache, metallic taste, hallucinations	20%, Intralipid	200 mL (0.78 g/kg mother) bolus	Yes	NR	Resolution of symptoms	Survival, sequelae NR
Cordell et al. (2010) [22]	Case report	17 years/F, weight NR	Bupivacaine 75 mg	2.68	Nerve block	Seizure Tachycardia (180/min)	20%, brand NR	100 mL × 3 bolus, then infusion. Total dose NR	No	Midazolam 2 mg, propofol 100 mg and epinephrine 1 mg CPR, intubation	Resolution of cardiac and neurologic symptoms	Survival, no sequelae
Dacosta (2009) [23][b]	Case report	44 years/F, 104 kg	Lidocaine 150 mg Bupivacaine 200 mg	1.26 2.68	Nerve block	Metallic taste Sinus bradycardia (34/min), hypotension (80/45 mmHg)	NR	100 ml in 10 min	No	Atropine 2 mg, ephedrine 5 mg, saline 500 mL	Resolution of cardiac symptoms in 15 min	Survival, no sequelae
Diaz et al. (2012) [24]	Case report	Adult/F, 75 kg	Levobupivacaine 34.25 mg, Lidocaine 340 mg	2.68 1.26	Nerve block	Somnolent, developed tremor, nystagmus and became comatose Decrease in blood pressure Nausea	20%, Medialipid (MCT/LCT)	100 mL (0.27 g/kg) bolus then 400 mL (0.53 g/kg/h) in 2 h	No	Phenylephrine, ondansetron 4 mg, sufentanil 20.5 mcg, clonidine 138 mcg	Resolution of cardiac and neurologic symptoms	Survival, no sequelae

(continued)

Table 1. Continued

References	Study type	Age/sex, weight	Local anesthetic and dose	Log *D* [129]	Route of administration	Symptoms	ILE used	ILE dose[a]	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Dix et al. (2011) [25]	Case report	57 years/M, weight NR	Lidocaine 120 mg + 2 mg/min infusion, total dose NR	1.26	Intravenous	Somnolent, confused, unresponsive QRS widening, Suffered from cardiovascular disease already. Pulseless, electromechanical dissociation Tremor, difficulty performing cerebellar testing	20%, Intralipid	1 mL/kg bolus then 0.25 mL/kg/min in 30 min	No	Epinephrine, amiodarone, magnesium sulfate, calcium gluconate, and sodium bicarbonate, dopamine 7 mcg/kg/min CPR	Resolution of cardiac symptoms	Survival, no sequelae
Egan (2013) [26][b]	Case report	38 years/F, 62 kg	Ropivacaine 100 mg, Lidocaine 200 mg	4.21 2.26	Nerve block	Grand mal seizures 1 min post-injection Coma	20%, Intralipid	100 mL (0.32 g/kg) bolus then 0.25 mg/kg/h infusion, duration NR	No	Midazolam >2 mg Intubation	Resolution of seizure unclear timing Resolution of coma 30 minutes later	Survival, no sequelae
Espinet & Emmerton (2009) [27]	Case report	36 years/M, 80 kg	Bupivacaine 100 mg, Lidocaine 100 mg	2.68 1.26	Nerve block	Perioral tingling, headache, dizziness, light headedness, diplopia Tachycardia (153/min), BP 180/110 mmHg, ST depression	20%, Intralipid	100 mL (0.25 g/kg) × 2 bolus then 100 mL (0.25 g/kg/h) in 1 h	No	Crystalloid (Hartmann's solution) 1 L Oxygen	Resolution of cardiac and neurologic symptoms	Survival, no sequelae
Etesse et al. (2011) [28]	Case report	23 years/F, 38 weeks pregnant, weight NR	Ropivacaine 46 mg	4.21	Nerve block	Visual hallucination, nausea 7 hour prior to development of status epilepticus Hypertension	NR	100 mL	No	Midazolam 2 mg, magnesium sulfate 1 g in 20 min and then 1 g/h Oxygen	Resolution of neurologic symptoms	Survival, no sequelae
Fenten et al. (2014) [29]	Case report	67 years/F, weight NR	Ropivacaine 400 mg	4.21	Intra-articular/ Subcutaneous	Chest pain Coma Seizure	20%, brand NR	Infusion Unknown duration	No	Nitroglycerin (spray), metoprolol 5 mg, midazolam 1 mg boluses Oxygen	Resolution of initial seizure but recurrence of seizures and twitching for 5.5 h after	Survival, no sequelae
Foxall et al. (2007) [30]	Case report	75 years/F, 85 kg	Levobupivacaine 100 mg	2.68	Nerve block	Unresponsiveness Seizures QRS widening; Suffered from cardiovascular disease already Groaned	20%, Intralipid	100 mL (0.24 g/kg) bolus in 5 min	No	Metaraminol 0.5 mg, propofol 80 mg, suxamethonium 100 mg Oxygen, intubation	Resolution of cardiac symptoms	Survival, no sequelae
French et al. (2012) [31][b]	Case report	11 months/M, 9.9 kg	Lidocaine 100 mg	1.26	Intraosseous	Status epilepticus	20%, Intralipid	12 mL (0.24 g/kg) bolus	No	Lorazepam 0.1 mg/kg	NR	Survival, no sequelae
Fuzaylov et al. (2010) [32]	Case report	13 years/F, 50 kg	Bupivacaine 25 mg	2.68	Intravenous	Decreased BP (from 90 to 60 mmHg) and broad complex ventricular tachycardia	20%, Intralipid	100 mL (0.4 g/kg) bolus	No	Saline 500 mL. Epinephrine 10 mcg × 2 bolus + 0.1 mcg/kg/min infusion, dopamine 10 mcg/kg/min infusion CPR	Possible effect in resolution of symptoms	Survival, pulmonary edema, resolved day 4

(continued)

Table 1. Continued

References	Study type	Age/sex, weight	Local anesthetic and dose	Log *D* [129]	Route of administration	Symptoms	ILE used	ILE dose[a]	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Gallagher et al. (2010) [33]	Case report	28 years/M 55.8 kg	Lidocaine 2%, Bupivacaine 0.5%, 50 mL mixture LA ratio NR	1.26 2.68	Subcutaneous	Dizziness then coma Apnea Generalized seizure activity with severe tonic-clonic activity Sudden cardiac arrest	20%, brand NR	2 units (mL not reported)	No	Sodium bicarbonate 200 mEq, saline bolus Epinephrine 4 mg, vasopressin 40 U, atropine 4 mg, midazolam 1 mg, lorazepam 2 mg CPR	Resolution of cardiac symptoms	Survival, no sequelae
Gnaho et al. (2009) [34]	Case report	82 years/F, 45 kg	Ropivacaine 100 mg	4.21	Nerve block	Lost consciousness Generalized tonic-clonic seizure Ventricular fibrillation, no pulse Difficulties in speaking	20%, Intralipid	70 mL (0.31 g/kg) bolus	No	Thiopental 325 mg, suxamethonium 100 mg, propofol 30 mg, epinephrine 0.3 mg Oxygen, intubation, CPR	Rapid beneficial effect on cardiac resuscitation	Survival, no sequelae
Goyal et al. (2011) [35]	Case report	26 years/M, 75 kg	Bupivacaine 25 mg	2.68	Nerve block	Tachycardia (244–250/min) and BP 50–56/30–36 mmHg	10%, Intralipid	150 mL (0.20 g/kg) in 15 min	Yes	NA	Resolution of cardiac symptoms	Survival, no sequelae
Grenc et al. (2011) [36][b]	Case report	84 years/F, weight NR	Lidocaine 20 mg, Triamcinolone 80 mg	1.26 0.92	Nerve block	Generalized tonic-clonic seizures Cardiac arrest	20%, Intralipid	100 mL × 2 bolus	No	Epinephrine 2 mg, atropine 3 mg Intubation, CPR	Resolution of cardiac symptoms; bolus ILE repeated due to persistent hypotension	Survival, no sequelae
Hartley et al. (2012) [37]	Case report	46 years/F, 46 kg	Bupivacaine 37.5 mg + 18.75 mg/h, total dose NR	2.68	Nerve block	Coma Seizures	20%, Intralipid	NR	Yes	Intubation	Unclear if effect is related to ILE	Survival, sequelae NR
Harvey et al. (2011) [38]	Case report	69 years/F, 80 kg	Lidocaine 50 mg, Bupivacaine 150 mg	1.26	Nerve block	Unresponsiveness, GCS 3 Seizure HR 50/min, AV block, BP 51/29 mmHg	20%, Intralipid	100 mL (0.25 g/kg) bolus then 400 mL 1.33 g/kg/h) in 45 min	No	Midazolam 5 mg, atropine, 600 mcg, epinephrine 100 mcg, metaraminol 4 mg Intubation, mechanical ventilation	Resolution of cardiac symptoms	Survival, no sequelae
Heavner & Heavner (2012) [39][b]	Case report	60 years/F, weight NR	Lidocaine 1500 mg	1.26	Intrapleural	Seizure Cardiac arrest	20%, brand NR	500 mL bolus then 50 mL/h	No	Unspecified conventional therapy	Resolution of cardiac symptoms	Survival, no sequelae
Hurley & Hanlon (2009) [40][b]	Case report	54 years/M, weight NR	Bupivacaine, dose NR	2.68	NR	Cardiac arrest Asystole	NR	NR	NR	NR	Resolution of toxicity within a few minutes	Survival, no sequelae
Jensen & Borglum (2011) [41][b]	Case report	41 years/M, weight NR	Ropivacaine 600 mg	4.21	Nerve block	Loss of consciousness Seizure	20%, Intralipid	100 mL bolus	No	Diazepam 2.5 mg	Resolution of neurologic symptoms	Survival, no sequelae
Landy et al. (2012) [42, p. 463]	Case report	59 years/sex NR, weight NR	Ropivacaine 2250 mg	4.21	Nerve block	Seizures	20%, Intralipid	200 mL bolus	Yes	NR	Resolution of neurologic symptoms	Survival, no sequelae
Landy et al. (2012) [43, p. 701]	Case report	74 years/F, 60 kg	Lidocaine 380 mg	1.26	Nerve block	Tonic-clonic movements	20%, Intralipid	200 mL (3 mL/kg (0.60 g/kg)) bolus	No	Flecainide	Resolution of symptoms	Survival, no sequelae

(continued)

Table 1. Continued

References	Study type	Age/sex, weight	Local anesthetic and dose	Log *D* [129]	Route of administration	Symptoms	ILE used	ILE dose[a]	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Lange et al. (2012) [44]	Case report	31 years/M, 61 kg	Lidocaine 1600 mg	1.26	Subcutaneous/ Intraperitoneal	Visual hallucinations, dysarthria, lower level of consciousness and became non-verbal	20%, Intralipid	100 mL (0.33 g/kg) in 10 min	Yes	NR	Resolution of neurologic symptoms	Survival, no sequelae
Larson et al. (2013) [45]	Case report	4 months/F, 6.54 kg	Lidocaine 1500 mg, Prilocaine 1500 mg	1.26 1.33	Topical	Single seizure Tachycardia (147/min) Methemoglobin level was 22.8%	20%, brand NR	1 g/kg bolus	No	Lorazepam 0.2 mg/kg i.m. and 0.2 mg/kg i.o., fosphenytoin 20 mg PE/kg. Methylene blue 10 mg (1.5 mg/kg) Topical decontamination Intubation, mechanical ventilation	Unclear if effect is related to ILE	Survival, no sequelae
Levine et al. (2014) [46]	Case report	20 years/F, weight NR	Bupivacaine, dose NR	2.68	Nerve block	Seizure	20%, brand NR	20 mL/kg bolus then 0.25 mL/kg/min for 3 h	Yes	NR	NR	Survival, increased lipase 185 IU/L suggesting pancreatitis, resolved after 14 days
Li & Wardhan (2013) [47][b]	Case report	57 years/F, weight NR	Ropivacaine 75 mg, Lidocaine 400 mg	4.21 1.26	Nerve block	Severe pain, somnolent, pinpoint pupils	Intralipid, conc. NR	75 mL bolus then infusion, dose and duration NR	No	Naloxone 80 mcg, midazolam 1 mg, propofol 30 mg	Resolution of symptoms, but confused and agitated	Survival, no sequelae
Lin & Aronson (2010) [48]	Case report	2 days/M, 3.2 kg	Bupivacaine 8 mg	2.68	Nerve block	ST-segment elevation, QRS widening Bradycardia	20%, Intralipid	1 mL/kg (0.2 g/kg) bolus	Yes	No pharmaceuticals Intubation, CPR	Resolution of cardiac symptoms	Survival, no sequelae
Litz et al. (2006) [49]	Case report	84 years/F, 50 kg	Ropivacaine 400 mg	4.21	Nerve block	Dizziness, drowsiness Seizures Asystole	20%, Intralipid	100 mL (2 mL/kg (0.40 g/kg)) bolus, then 10 mL/min (2.4 g/kg/h) Total dose 200 mL (0.8 g/kg)	No	Thiopental 150 mg, epinephrine 3 × 1 mg Intubation, CPR	Resolution of cardiac symptoms	Survival, no sequelae
Litz et al. (2008) [50]	Case report	91 years/M, 57 kg	Mepivacaine 300 mg, Prilocaine 100 mg	1.40 1.33	Nerve block	Dizziness, agitation and developed unresponsiveness Bigeminy and PVCs	20%, Intralipid	100 mL (0.35 g/kg) bolus then 0.25 mL/kg/min (3 g/kg/h) Total dose 200 mL (0.70 g/kg)	No	Dolastrone 12.5 mg	Resolution of cardiac and neurologic symptoms	Survival, no sequelae
Liu et al. (2012) [51][b]	Case report	NR	Bupivacaine 200 mg	2.68	Intravenous	Unclear symptoms	Intralipid, conc. NR	110 mL (1.5 mL/kg) bolus then 'low dose' infusion in 2 h	Yes	NR	Unclear if any symptoms developed or were reversed	Survival, sequelae NR
Ludot et al. (2008) [52]	Case report	13 years/F, 55 kg	Lidocaine 200 mg, Ropivacaine 150 mg	1.26 4.42	Nerve block	Ventricular tachycardia with wide QRS	20%, Medialipid	150 mL (3 mL/kg (0.60 g/kg)) bolus	Yes	No pharmaceuticals Manual ventilation	Resolution of cardiac symptoms	Survival, no sequelae
Markowitz & Neal (2009) [53]	Case report	17 years/M, 61 kg	Bupivacaine 100 mg	2.68	Nerve block	Coma Status epilepticus Ventricular fibrillation	20%, Intralipid	500 mL (8 ml/kg (1.6 g/kg)), dose regimen NR	No	Midazolam 3 mg Intubation	Unclear if effect is related to ILE	Survival, no sequelae
Marraffa & Stork (2013) [54][b]	Case report	66 years/F, weight NR	Bupivacaine 420 mg	2.68	Subcutaneous	CNS depression, declining mental status Generalize tonic-clonic seizure activity Systolic hypotension to 60 mmHg	20%, brand NR	500 mL × 2 bolus	No	Hydromorphone 60 mg with the LA. Bicarbonate empirically given, dopamine. Naloxone 0.4 mg × 2, icepacks were applied every 2 h at the injection site, lorazepam 0.2 mg Intubation	Resolution of cardiac symptoms	Survival, no sequelae

(continued)

Table 1. Continued

References	Study type	Age/sex, weight	Local anesthetic and dose	Log *D* [129]	Route of administration	Symptoms	ILE used	ILE dose[a]	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Marwick et al. (2009) [55]	Case report	33 years/M, 72 kg	Bupivacaine 112.5 mg	2.68	Nerve block	Seizure Wide QRS Cardiac arrest Dry mouth, apnea	20%, Intralipid	150 mL (0.43 g/kg) bolus then 350 mL (1.94 g/kg/h) in 30 min	No	Epinephrine 1 mg + 0.06 mcg/kg/min infusion, total time NR. Thiopental 250 mg, sodium bicarbonate, insulin, potassium, amiodarone 300 mg in 30 min Oxygen, intubation, CPR	Resolution of cardiac symptoms	Survival, amylase 608 IU/L
Mazoit (2013) [56]	Case report	44 years/M, weight NR	Ropivacaine 260 mg	4.21	Nerve block	Metallic taste, myoclonic movement Seizure Cardiac arrest with asystole	20%, Intralipid	100 mL bolus	No	Epinephrine 100 mcg Manual ventilation, CPR	Resolution of cardiac symptoms	Survival, no sequelae
McCutchen & Gerancher (2008) [57]	Case report	82 years/F, weight NR	Bupivacaine 150 mg	2.68	Nerve block	Seizures × 2 VT at 200/min	20%, Intralipid	100 mL bolus then 400 mL over 15 min	No	Midazolam 3 mg, amiodarone 150 mg, unspecified ACLS drugs Oxygen, defibrillation	Unclear if effect is related to ILE	Survival, no sequelae
Mizutani et al. (2011) [58]	Case report	24 years/M, 66 kg	Ropivacaine 200 mg	4.21	Nerve block	Disappearance of motor response to stimulation	20%, brand NR	100 mL (0.30 g/kg) bolus	No	Propofol (titrated), fentanyl 100 μg Mechanical ventilation during general anesthesia	Resolution of neurologic symptoms, but unclear if effect is related to ILE	Survival, no sequelae
Nguyen & White (2012) [59]	Case report	19 years/M, 72 kg	Ropivacaine 75 mg	4.21	Nerve block	Visual hallucinations Sinus tachycardia and hypertension Myoclonic movements of the head and neck	20%, Intralipid	100 mL (0.28 g/kg) bolus	No	Midazolam 2 mg × 2 Oxygen	Resolution of neurologic symptoms	Survival, no sequelae
Ogugua et al. (2009) [60][b]	Case report	47 years/F, weight NR	Bupivacaine 165 mg	2.68	Nerve block	Seizure Asystole	20%, brand NR	160 mL bolus then 200 mL infusion, duration NR	No	Midazolam 2 mg, epinephrine 9 mg, ACLS protocol to ROSC Intubation	Apparent improvement in cardiac output	Survival, no sequelae
Reddy & Lahm (2010) [61][b]	Case report	59 years/M, weight NR	Mepivacaine, Ropivacaine 50 mL 50/50 mixture, conc. NR	1.40 4.21	Nerve block	Agitation Seizures Tachycardia (160–170/min) Slurred speech	20%, Intralipid	1.5 mL/kg bolus then 0.25 mL/kg/min in 60 min	Yes	No pharmaceuticals Oxygen	Resolution of cardiac and neurologic symptoms	Survival, no sequelae
Rosenblatt et al. (2006) [1]	Case report	58 years/M, 82 kg	Bupivacaine 100 mg, Mepivacaine 300 mg	2.68 1.40	Nerve block	Incoherent Repeated seizures Apneic Asystole	20%, Intralipid	100 mL (0.24 g/kg) bolus then 0.5 mL/kg/min (6.0 g/kg/h) in 60 min	No	Epinephrine 3 mg, atropine 2 mg, arginine vasopressin 40 U, amiodarone 300 mg, propofol 150 mg Mechanical ventilation, CPR, defibrillation	Resolution of cardiac symptoms	Survival, no sequelae
Sakai et al. (2010) [62]	Case report	40 years/F, 40 kg	Ropivacaine 150 mg	4.21	Nerve block	Lowered responsiveness, paleness, peripheral coldness, restlessness, hypotension, shallow irregular breathing, clonic convulsions in the limbs	20%, Intralipos	5 × 10 ml (0.25 g/kg) bolus, then 100 ml (0.5 g/kg) in 50 min, then 20 ml/h (0.1 g/kg/h). Total dose 230 ml	No	Etilefrine (dose NR), diazepam 5 mg	Resolution of symptoms	Survival, no sequelae

(continued)

Table 1. Continued

References	Study type	Age/sex, weight	Local anesthetic and dose	Log *D* [129]	Route of administration	Symptoms	ILE used	ILE dose[a]	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Schaeffer et al. (2010) [63]	Case report	74 years/F, 60 kg	Lidocaine 400 mg	1.26	Nerve block	Confused, disoriented, had loss of consciousness and myoclonus of the face	20%, Intralipid	200 mL (0.67 g/kg) bolus	Yes	NR	Apparent improvement of symptoms, but unclear if effect is related to ILE	Survival, no sequelae
Schellhammer & Milde (2011) [64]	Case report	54 years/F, weight NR	Mepivacaine 1000 mg	1.40	Nerve block	Dysphagia, dyspnea, PVC with bigeminy, ventricular tachycardia 145 bpm, perioral automatisms, dysarthria, hallucinations, progressive loss of consciousness and finally seizure	20%, Lipofundin	Infusion, specific dose and duration NR	No	Amiodarone 5 mg/kg, midazolam, propofol Oxygen	Transient improvement in level of consciousness	Survival, no sequelae
Scherrer et al. (2013) [65][b]	Case report	25 years/F, weight NR	Ropivacine 450 mg	4.21	Intraperitoneal/ nerve block	Seizure, ventricular arrhythmia	20%, brand NR	Infusion, specific dose and duration NR	Yes	NR	Ventricular arrhythmia converted to sinus rhythm	Survival, sequelae NR
Schwarzkopf et al. (2011) [66][b]	Case report	NR	Prilocaine 300 mg, Bupivacaine 50 mg	1.33 2.68	Nerve block	Seizures Hypertension	20%, brand NR	1.5 mL/kg bolus then 0.1 mL/kg in 30 min	No	Midazolam 10 mg Manual ventilation	Unclear if effect is related to ILE	Survival, sequelae NR
Shah et al. (2009) [67]	Case report	40 days/M, 4.96 kg	Bupivacaine 10 mg	2.68	Nerve block	BP 31/19 mmHg; tachycardia (170/min); The ST segment was noted to be elevated 2–3 mm and the T-wave was inverted	20%, Intralipid	10 mL (2 mL/kg (0.4 g/kg)) bolus	No	Epinephrine 2 mcg/kg × 2, albumin 5% 20 mL. Mechanical ventilation during general anesthesia	Resolution of cardiac symptoms	Survival, no sequelae
Shenoy et al. (2014) [68]	Case report	3 years/sex NR, 11 kg	Bupivacaine 25 mg	2.68	Nerve block	Pulseless ventricular tachycardia	20%, brand NR	15 mL (0.27 g/kg) bolus then 150 mL/h (2.73 g/kg/h) in 15 min, then 5 mL (0.091 g/kg) bolus. Total dose 170 mL (3.1 g/kg)	No	Epinephrine 0.03 mg Oxygen, CPR	Beneficial effect with resolution of cardiac symptoms together with other treatments.	Survival, no sequelae
Shih et al. (2011) [69]	Case report	69 years/F, 48.5 kg	Lidocaine 225 mg, Bupivacaine 37.5 mg	1.26 2.68	Nerve block	Bradycardia, reduced blood pressure Obtunded, unable to fully arouse	20%, Lipovenoes	50 mL (0.21 g/kg) bolus	No	Atropine 0.5 mg × 3, ephedrine 10 mg	Resolution of cardiac and neurologic symptoms	Survival, no sequelae
Smith et al. (2008) [70]	Case report	83 years/M, 75 kg	Bupivacaine 130 mg	2.68	Nerve block	Loss of consciousness Seizure Pulseless wide complex tachycardia and asystole	20%, brand NR	250 mL (3 mL/kg (0.60 g/kg)) bolus then 0.2 mL/kg/min (2.4 g/kg/h)	No	Epinephrine 1 mg, atropine 1 mg (dosed after lipid emulsion), midazolam 2 mg. Oxygen, manual ventilation, CPR; then intubation, mechanical ventilation	Resolution of cardiac symptoms, but unclear if effect is related to ILE	Survival, no sequelae
Sonsino & Fischler (2009) [71]	Case report	92 years/F, weight NR	Ropivacaine 150 mg	4.21	Nerve block	Generalized tonic-clonic seizure × 1 Asystole	Kabiven 2000, conc. NR	50 mL bolus	No	Propofol 30 mg, epinephrine 0.3 mg (ACLS). Intubation, mechanical ventilation	Resolution of cardiac symptoms	Survival, no sequelae (died from bronchopneumonia 10 days after)
Sorrenti et al. (2014) [72][b]	Case report	46 years/M, weight NR	Mepivacaine 360 mg	1.40	Nerve block	Dysarthria, confusion, loss of verbal contact, agitation, tachycardia, hypertension	20%, Intralipid	150 mL bolus then 0.25 mL/kg/min. Total dose 250 mL	No	Midazolam 2.5 mg	Resolution of neurological and cardiac symptoms	Survival, no sequelae
Spence (2007) [73]	Case report	18 years/F, 38 weeks pregnant, 86 kg	Lidocaine 80 mg, Bupivacaine 65 mg	1.26 2.68	Nerve block	Restless, agitated, did not obey commands, unresponsive. Fetal heart rate decelerating	20%, Intralipid	50 mL (0.12 g/kg) × 2 bolus	No	General anesthesia for delivery Neonatal intubation	Resolution of neurologic symptoms	Survival, no sequelae

(continued)

Table 1. Continued

References	Study type	Age/sex, weight	Local anesthetic and dose	Log *D* [129]	Route of administration	Symptoms	ILE used	ILE dose[a]	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Sturini et al. (2010) [74][b]	Case report	NR	Mepivacaine 750 mg	1.40	Intravenous	Numbness, light headedness dizziness slurred speech	20%, Intralipid	100 mL bolus	Yes	NR	Possibly prevented cardiac symptoms from LA toxicity	Survival, no sequelae
Süzer et al. (2011) [75]	Case report	71 years/M, 78 kg	Bupivacaine 50 mg, Lidocaine 200 mg	2.68 1.26	Nerve block	Loss of consciousness, dyspnea, hypotension 65/40 mmHg, ventricular extra systoles, tachycardia 140 bpm, seizures	20%, Intralipid	0.5 mL/kg/min (6.0 g/kg/h) infusion. Total dose 500 mL (1.3 g/kg)	No	Midazolam 5 mg, epinephrine 10 mg, amiodarone 150 mg Intubation	Resolution of cardiac symptoms within 3 min, resolution of neurological symptoms within total dose administered	Survival, no sequelae
Ter Horst et al. (2010) [76]	Case report	27 years/F, weight NR	Ropivacaine 300 mg	4.21	Nerve block	Decreased level of consciousness Seizure	20%, Intralipid	100 mL (1.5 mL/kg) bolus then 400 mL in 1.5 h	No	Midazolam 5 mg × 2. Mechanical ventilation until resolution of respiratory symptoms	Rapid beneficial effect on neurologic symptoms	Survival, no sequelae
Varela & Bums (2010) [77]	Case report	83 years/F, 70 kg	Bupivacaine 150 mg, Ropivacaine 300 mg	2.68 4.21	Nerve block	Repeated seizures Bradycardia, hypotension, first degree heart block, multifocal PVC, VT	20%, Liposyn	250 mL (1.43 g/kg/h) × 2 infusion, each in 30 min	No	Atropine 1 mg, midazolam 4 mg. ACLS protocol). Intubation, oxygen, manual ventilation	Resolution of cardiac symptoms	Survival, no sequelae
Warren et al. (2008) [78]	Case report	60 years/M, 83 kg	Mepivacaine 450 mg, Bupivacaine 50 mg	1.40 2.68	Nerve block	Unresponsiveness Cardiac arrest Labored respiration	20%, Liposyn III	250 mL (1.2 g/kg/h) infusion in 30 min	No	Sodium bicarbonate 8.4% 100 mL, atropine 1 mg, epinephrine 1 mg × 3, vasopressin 40 U, magnesium sulfate 6 g CPR, defibrillation × 11	Longer intervals of sustained cardiac rhythm during defibrillation	Survival, no sequelae
Whiteman & Kushins (2014) [79]	Case report	32 years/F, 62 kg	Bupivacaine 870 mg	2.68	Nerve block	Confusion, agitation, combative then seizures, cardiac arrhythmia	20%, Intralipid	1.5 mL/kg (0.3 g/kg) bolus then 0.25 mL/kg/min (3.0 g/kg/h) for 60 min	No	Unspecified medical therapy, cardiac defibrillation × 2, surgery with evacuation of 60 mL fluid from the right rectus sheath CPR	ROSC and normocardia after 45 min Resolution of cardiac arrhythmia the following day	Survival, no sequelae
Whiteside (2008) [80]	Case report	Elderly/F, 74 kg	Levobupivacaine 21.65 mg	2.68	Nerve block	Seizure	20%, Intralipid	100 mL (1.5 mL/kg (0.30 g/kg)) bolus	Yes	No pharmaceuticals Oxygen, manual ventilation	Unclear of effect is related to ILE	Survival, no sequelae
Widfeldt & Kolmodin (2014) [81]	Case report	62 years/F, weight NR	Ropivacaine 150 mg	4.21	Nerve block	Unconsciousness, nystagmus, muscle twitching	20%, Intralipid	100 mL (1.5 mL/kg) × 2 bolus – 10 min interval, then 50 mL/h for 10 h	No	Diazepam, few doses (specific dose NR)	Resolution of neurologic symptoms	Survival, no sequelae
Wong et al. (2010) [82]	Case report	6 years/M, 24 kg	Bupivacaine, dose NR	2.68	Nerve block	Sinus bradycardia (60/min) that rapidly proceeded to a wide complex ventricular arrhythmia at 40/min and hypotension to BP 65 / 35 mmHg and tachycardia 120/min	20%, Intralipid	20 mL (0.17 g/kg) bolus	No	Crystalloid fluid boluses 20 mL/kg, atropine 0.4 mg, epinephrine 0.2 mg then continued 0.1 mg boluses to maintain a systolic pressure > 60 mmHg then 0.2 μg/kg/min infusion. Packed red cells (300 mL) + 5% albumin (250 mL) CPR	Resolution of cardiac symptoms	Survival, no sequelae for 3 days. After 8 days, brain stem death from cerebral ischemia not related to ILE treatment

(continued)

Table 1. Continued

References	Study type	Age/sex, weight	Local anesthetic and dose	Log *D* [129]	Route of administration	Symptoms	ILE used	ILE dose[a]	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Zhurda et al. (2010) [83]	Case report	78 years/M, 62 kg	Bupivacaine 100 mg	2.68	Nerve block	Perioral numbness, muscle twitching, agitation, difficult accommodation HR 38/min which became wide complex and hypotension to 75/35 mmHg	20%, Intralipid	60 mL (0.19 g/kg) bolus	No	Midazolam 3 mg, atropine Oxygen	Resolution of cardiac symptoms	Survival, no sequelae
Zimmer et al. (2007) [84]	Case report	84 years/F, 53 kg	Bupivacaine 43 mg	2.68	Nerve block	Agitation, confusion, restless. Seizure. Supraventricular tachycardia (150/min) ventricular extra systole, hypertension (170/85 mmHg) Heat sense in feet	20%, Lipofundin	100 mL (0.38 g/kg) bolus then 0.5 mL/kg/h (0.1 g/kg/h)	No	Clonidin 150 mcg, midazolam 5 mg, lidocain 100 mg, propofol 1% 50 mg × 2	Resolution of cardiac and neurologic symptoms	Survival, no sequelae

ACLS: Advanced cardiac life support; AV: Atrio-ventricular; BP: Blood Pressure; CNS: Central nervous system; CPR: Cardiopulmonary resuscitation; ICU: Intensive care unit; GCS: Glasgow coma score; HR: Heart rate; ILE: Intravenous lipid emulsion; LA: Local anesthetic; LCT: Long-chain triglyceride; MAP: Mean arterial pressure; MCT: Medium-chain triglyceride; NR: Not reported; PVC: Premature ventricular contractions; RCT: Randomized controlled trial; ROSC: Return of spontaneous circulation; VT: Ventricular tachycardia.

Note: Lidocaine and lignocaine are synonyms for the same compound, and the name lidocaine is used in the table.

[a]The total dose in g/kg was infrequently available, and could only be calculated if bodyweight was reported.

[b]Available as abstracts only at the time of writing.

Human case reports

There were 73 case reports and one case series, including 10 cases not individually reported elsewhere, that described the effect of ILE for treating LA toxicity.[1,12–84] These articles involved 83 patients, aged from 2 days to 91 years, of whom two died and 81 (98%) survived (Table 1). The local anesthetics involved, often in combination, are shown in Tables 1 and 2.

The most common lipid concentration administered in these publications was 20% (71 cases; 86%), while a 10% concentration was used in one case,[35] and the lipid concentration used was not reported in the remaining 11 cases (Table 1).[17,19,23,28,40,47,51,71] Lipid emulsion was administered as a bolus in 30 (36%) cases, as a bolus followed by infusion in 34 (41%) cases, and as an infusion without bolus in eight cases (10%). The dose regimen used was not specified or not reported in 11 (13%) cases. The median bolus dose was 0.30 g/kg (range: 0.0015–0.83 g/kg) and the median infusion dose was 1.9 g/kg/h (range: 0.015–6.0 g/kg/h). Overall, the total volume of lipid emulsion administered ranged from 9 to 2480 mL (Table 1). The bolus dose in infants up to the age of 1 year was 1–2 mL/kg (Table 1).

In 52 cases (63%), the lipid emulsion used was Intralipid™; other formulations used were Medialipid™ ($n = 3$, 4%), Lipofundin™ ($n = 3$, 4%), Liposyn™ ($n = 2$, 2%), Lipovenoes™ ($n = 1$, 1%), Kabiven™ ($n = 1$, 1%), and Intralipos™ ($n = 1$, 1%). In 20 cases (24%), the lipid emulsion formulation was not reported (Table 1).

Sixty-nine (83%) patients experienced toxicity following the use of local anesthetics for nerve blocks (Table 1), including 10 cases described in the single case series (Table 1).[19] Toxicity was also reported after intravenous ($n = 4$; 5%),[25,32,51,74] subcutaneous ($n = 6$; 7%),[12,19,29,33,44,54] intraosseous ($n = 1$; 1%),[31] topical ($n = 1$; 1%),[45] intraperitoneal ($n = 2$; 2%),[44,65] intraarticular ($n = 1$; 1%),[29] and intrapleural administration ($n = 1$; 1%).[39] Two routes of administration were involved in three cases (4%) [29,44,65] and the route was not reported in one case (1%) (Table 1).[40]

The most frequent toxic effects from LA reported were central nervous system (CNS) features including (but not limited to) CNS depression/coma or agitation ($n = 45$; 54%) and seizures ($n = 49$; 59%). Cardiovascular features included hypotension, hypertension, EKG changes and arrhythmias ($n = 39$; 47%), and cardiac arrest ($n = 18$; 22%); other non-cardiovascular symptoms ($n = 22$; 27%) were also common (Table 1).

In 14 cases (17%),[21,35,37,42,44,46,48,51,52,61,63,65,74,80] ILE was the only treatment used for reversal of toxic effects and in 10 (12%) of these resolution of symptoms was reported.[21,35,42,44,46,48,52,61,65,74] In four (5%) cases, the authors reported that it was unclear if effects were related to ILE.[37,51,63,80] One case report did not comment on ILE effects [46] (Table 1).

Sixty case reports (72%) described the use of ILE in combination with additional treatments. In 35 (42%) cases, lipid emulsion was used after failure of other treatments, in six (7%) cases before other treatment, and in 16 (19%) cases lipid emulsion was used concomitantly. The sequence of treatment was not reported in three (4%) cases (Table 1).

Table 2. Reported local anesthetics in the 16 volunteers from the randomized controlled study and the 83 patients from case reports and case series included in the systematic review.

Local anesthetic	Reported cases, *n*	Combination local anesthetics	Reported cases, *n*
Lidocaine[b]	8	Mepivacaine/Prilocaine	1
Bupivacaine	26	Mepivacaine/Ropivacaine	3
Mepivacaine	4	Lidocaine[b]/Ropivacaine	5
Ropivacaine	33[a]	Lidocaine[b]/Levobupivacaine	1
Levobupivacaine	18[a]	Lidocaine[b]/Prilocaine	1
		Bupivacaine/Lidocaine[b]	9
		Bupivacaine/Mepivacaine	3
		Bupivacaine/Ropivacaine	2
		Bupivacaine/Prilocaine	1

[a]The 16 volunteers received ropivacaine and levobupivacaine on each occasion, both are included in the table.
[b]Note: Lidocaine and lignocaine are synonyms: lidocaine is used in the table.

Other treatments used included benzodiazepines or other sedatives ($n = 41$; 49%), vasopressors ($n = 29$; 35%), sodium bicarbonate ($n = 7$; 8%), anti-arrhythmic drugs ($n = 9$; 11%), intravenous fluids ($n = 5$; 6%), and/or other treatments ($n = 20$; 24%). Three studies (4%) reported other but unspecified treatments. Cardiopulmonary resuscitation (CPR) and/or intubation and/or ventilation were initiated in 35 (42%) cases. In three (4%) cases, the patient was already intubated when features of LA toxicity appeared. Oxygen supply by mask was initiated in nine cases (11%). Cardiac defibrillation was reported in four cases (5%). CPR and/or intubation were not required in 19 (23%) cases and use of these procedures was not reported in 16 studies (19%; Table 1). Nine case reports did not state if any other treatments were performed (Table 1).

The authors of these case reports observed that ILE had a possible beneficial effect or was the cause of resolution of toxic features in 59 of cases (71%). Four case reports (5%) suggested no benefit from ILE. In 10 case reports (12%), it was unclear whether benefits were related to ILE or not; the effect of ILE was not described in 10 other cases (12%; Table 1).

Animal studies

Among the 38 publications using animal models, 29 (76%) were randomized controlled studies (11 studies on rats, 14 on pigs, 2 on dogs, and 2 on rabbits) [17,85–112], three (8%) were observational studies (1 study on pigs, 1 on rats, and 1 on rabbits) [113–115], five (13%) were case series (1 study on rabbits and 4 on rats), [116–120] and one (3%) was a case report (cat). [121] The animal studies are summarized in Table 3.

The local anesthetics used the 38 publications included bupivacaine ($n = 29$ studies, 76%) levobupivacaine ($n = 5$, 13%), lidocaine ($n = 1$, 3%), mepivacaine ($n = 1$, 3%), and ropivacaine ($n = 4$, 11%). Two studies combined two local anesthetics, bupivacaine/mepivacaine and levobupivacaine/ropivacaine (Table 3).

Lipid concentrations used were 20% ($n = 22$, 58%), 30% ($n = 8$, 21%), or not described ($n = 2$, 5%). A bolus dose was used in 29 (76%) studies and was followed by an infusion in 22 studies (58%). In three (8%) studies, an infusion was used without an initial bolus. The median bolus dose was 0.80 g/kg or 4 mL/kg of 20% ILE (range: 0.20–3.0 g/kg) and median infusion dose was 6.0 g/kg/h (range: 0.60–54 g/kg/h). In 22 studies (58%), the lipid emulsion used was Intralipid™ while two studies used the medium chain/long chain triglyceride preparations Lipovenos™ MCT ($n = 2$, 5%) or Medialipid™ ($n = 1$, 3%). Other products used in one study each (3%) were Lipovenos™, Ivelip™, SMOFLipid™, ClinOleic™, and Liposyn II™; an un-named Soybean oil emulsion was used in one study and the ILE formulation used was not reported in five studies (Table 3).

Animal randomized controlled studies

In 12 of the 29 randomized controlled studies, ILE was compared to the vasopressors epinephrine and/or vasopressin, either alone or in combination, or with vasopressors combined with ILE (Table 3).[88,89,91,92,97,102–105,107,110,111]

The ILE versus epinephrine studies [88,89,91,102–104,107,110,111] showed therapeutic benefit on survival or return to spontaneous circulation for ILE compared to epinephrine in four studies (14% of the animal RCS) [102–104,107] and for epinephrine + vasopressin in one study (3% of the animal RCS).[105] There were comparable efficacy of ILE and epinephrine in five studies (17% of the animal RCS). [88,89,91,110,111]

Combining epinephrine + ILE gave a better survival outcome compared to ILE alone in six studies (21% of the animal RCS),[88,89,97,102,104,111] and of these, two studies concluded comparable efficacy of epinephrine and epinephrine + ILE.[102,104]

In two studies (7% of the animal RCS), the combination vasopressin + ILE did not improve survival over ILE alone and was not as effective as epinephrine or epinephrine + ILE treatment.[102,104] ILE was superior in one study (4% of the animal RCS) comparing ILE with vasopressin alone or epinephrine + vasopressin.[92]

Lipid infusion was compared to crystalloids, either saline [17,85–87,90,91,94,96,97,106–111] or Ringer's acetate [101] in 15 of the 29 randomized controlled studies (Table 3). Nine (31% of the animal RCS) studies showed therapeutic benefit [85,87,90,91,94,97,106,109,110] and six (21%) no benefit if ILE.[17,86,96,101,107,111] In one study comparing ILE and saline, the control groups were different (electrically initiated ventricular fibrillation versus LA induced venticular fibrillation); this study was therefore considered not useful for evaluating the efficacy of ILE.[108]

Various LA doses were evaluated in the included studies, and these doses were provided in varying units. These doses depended on the type of LA and the secondary outcome symptom severity. For bupivacaine, used in 22 (76%) out of the 29 studies,[86,87,90–97,100–106,108–112] the dose ranged from 1 mg/kg/min to 10 mg/kg/min given over 10 s or 4–30 mg/kg (Table 3). Levobupivacaine was used in four studies (14%),[88,89,98,99] with a dose of 500 mg/h,[88] 10 mg/kg,[99] or 3–8.3 mg/kg/min.[89,98] Mepivacaine was used in one study (3%) at an infusion rate of 6 mg/kg/min.[101] Ropivacaine was used in three studies (10%),[17,85,107] at 1.5 mg/kg/min as lowest infusion dose up to a maximum of 14.9 ± 2.8 mg/kg given as a bolus (Table 3).

Table 3. Summary of the 38 animal studies included in the systematic review on the effect of ILE.

References (Species)	Model	Local anesthetic (dose)	Log D [129]	Symptoms	ILE used	ILE bolus[a]	ILE infusion[a]	Study arms	Timing of rescue, time from LA termination	Other treatments received[b]	Parameter measured	Outcome	Support therapeutic effect of ILE alone
RCS													
Bonfim et al. (2012) [85] (Pig)	RCS; compared LCT and MCT/LCT	Ropivacaine (7 mg/kg in 30 s)	4.21	Decrease in mean arterial pressure	20%, Lipovenos MCT and Lipovenos	4 mL/kg (0.8 g/kg)	No	MCT/LCT ILE versus LCT ILE versus Saline	Other treatment and study treatment at 1 min	Vasopressors: 0.8 g/kg	At 30 min increase MAP (LCT = MCT/LCT), CI (only MCT/LCT), SVRI (LCT = MCT/LCT), PVRI (only MCT/LCT); no effect HR, CVP, mPAP, PCP	Survival: All	Yes; for both LCT and MCT/LCT
Buckenmaier et al. (2012) [17] (Pig)	RCS; post-mortem distribution study	Ropivacaine (1.5 mg/kg/min)	4.21	Asystole	20%, Intralipid	1 mL/kg (0.2 g/kg)	No	ILE versus No ILE	LA and study treatment were dosed simultaneously	Saline 1–2 mL/kg/h	Asystole; Earlier onset of death (asystole) in ILE compared to non-ILE	Survival: ILE 0/6, No ILE 0/6	No; post-mortem study
Bushey et al. (2011) [86] (Pig)	RCS; resuscitation model	Bupivacaine (5 mg/kg)	2.68	Cardiovascular collapse	20%, Intralipid	4 mL/kg (0.8 g/kg)	0.5 mL/kg/min (6 g/kg/h) for 10 min	ILE versus Saline	Other treatments at 4 min, then study treatment	ACLS resuscitation and closed chest compression	ROSC (unsupported systolic BP of 60 mmHg or greater for 10 min)	Survival: ILE 6/12, Saline 4/12	No; suggest that the addition of ILE to ACLS intervention does not improve survival
Candela et al. (2010) [87] (Pig)	RCS; resuscitation model	Bupivacaine (4 mg/kg)	2.68	Lengthening of HV, QRS, AH and PQ intervals, no alteration in RR and JTc intervals. Hemodynamics: decrease in LVdP/dtmax, increase in LVEDP, no change in MAoP	20%, Medialip and Ivelip	1.5 mL/kg (0.3 g/kg)	0.25 mL/kg/min (3 g/kg/h)	(MCT/LCT and LCT) ILE + Saline versus Saline	Study treatment at 30 s	No	Hemodynamics: LCT and MCT/LCT – MAoP and LVdP/dTmax were increased by ILE therapy when comparing AUC; QRS width: LCT and MCT/LCT – Effects on QRS duration was reversed	Survival: LCT 7/7, MCT/LCT 8/8, Saline 9/9	Yes
De Queiroz et al. (2012) [88][b] (Pig)	RCS; resuscitation model	Levobupivacaine (500 mg/h until symptoms)	2.68	MAP decrease by 50% for 15 s	20%, brand NR	4 mL/kg (0.8 g/kg)	0.25 mL/kg/min (3 g/kg/h)	ILE versus ILE + EPI versus EPI versus Control (no additional drugs)	NR	EPI 10 mg/kg every 3 min	Hemodynamics: Cardiovascular collapse defined by a decrease in MAP by 50%; EPI alone or in combination with ILE was associated with rhythmic or conduction cardiac disturbances	Survival: ILE 7/9, ILE + EPI 10/10, EPI 6/7, Control 1/7	Yes
De Queiroz et al. (2014) [89] (Pig)	RCS; resuscitation model	Levobupivacaine (8.3 mg/min)	2.68	MAP decreased to 50% of its baseline value	20%, Intralipid	4 mL/kg (0.8 g/kg)	0.25 mL/kg/min (3 g/kg/h)	ILE versus EPI versus ILE + EPI versus Saline	Std CPR immediately, then study treatment	Std CPR (chest compressions and manual ventilation)	Time to ROSC in survivors: ILE 460 s, EPI 296 s, ILE + EPI 304 s, Saline 720 s ECG abnormalities (arrhythmia; conduction) number, after ROSC in survivors: ILE (0;0), EPI (11;3), ILE + EPI (10;7)	Survival: ILE 7/9, EPI 6/7, ILE + EPI 10/10, Saline 1/7	Yes; ILE, EPI, and ILE + EPI provided similar ROSC. ECG abnormalities from EPI or ILE + EPI increased compared to ILE
de Simone et al. (2012) [90][b] (Pig)	RCS; resuscitation model	Bupivacaine (5 mg/kg)	2.68	Fall in arterial BP, cardiac index, ventricular systolic work index mainly and no important changes in vascular resistances	20%, SMOFLipid	4 mL/kg (0.8 g/kg)	No	ILE versus Saline	Study treatment at 1 min	No	Hemodynamics: ILE improved BP by increasing vascular resistance compared to saline; QRS width: No improvement in 'cardiac index'	Survival: NR	Yes; ILE is an option for reversing hypotension in cases of intoxication by bupivacaine

(continued)

Table 3. Continued

References (Species)	Model	Local anesthetic (dose)	Log D [129]	Symptoms	ILE used	ILE bolus[a]	ILE infusion[a]	Study arms	Timing of rescue, time from LA termination	Other treatments received[b]	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Di Gregorio et al. (2008) [91][b] (Rats)	RCS; resuscitation model	Bupivacaine (20 mg/kg)	2.68	Cardiac arrest	30%, Soy bean oil emulsion	5 mL/kg (1.5 g/kg)	0.5 mL/kg/min (9 g/kg/h)	ILE versus EPI versus Saline	NR	Cardiac resuscitation	QRS width: Bupivacaine-induced QRS prolongation reverted to normal in both ILE and EPI groups but persisted in Saline group at 10 min	ROSC: ILE 5/5, EPI 4/5, Saline 2/5	Yes
Di Gregorio et al. (2009) [92] (Rats)	RCS; resuscitation model	Bupivacaine (20 mg/kg)	2.68	Cardiac arrest	30%, Intralipid	5 mL/kg (1.5 g/kg), repeated at 2.5 and 5 min	1 mL/kg/min (18 g/kg/h)	ILE versus VASO versus VASO + EPI	Other treatment and study treatment immediately after LA	VASO 0.4 U/kg, EPI 30 g/kg, chest compression, mechanical ventilation	Hemodynamics: Rate pressure product higher in ILE versus VASO and VASO + EPI; QRS width: ILE group returned to baseline	Survival: NR	Yes; ILE resuscitation was superior to vasopressors (VASO and VASO + EPI) in treating bupivacaine-induced asystole. Adverse events higher in vasopressor group
Fettiplace et al. (2014) [93] (Rats)	RCS; resuscitation model	Bupivacaine (10 mg/kg)	2.68	Transient cardiovascular toxicity	20% and 30%, Intralipid	4 mL/kg (0.8 g/kg and 1.2 g/kg)	No	30% ILE versus 20% ILE versus 0.9% Saline versus Control (no treatment)	Study treatment after 10 s	Mechanical ventilation	Time to 50% recovery of cardiovascular parameters rate-pressure product (RPP), MAP, Carotid flow (flow), HR; All animals returned to 50% RPP. Order of mean recovery times: ILE30 < ILE20 < Saline < Null. HR recovered faster than other measures parameters	Survival: ILE30 7/7, ILE20 7/7, Saline 7/7, Control 7/7	Not studied
Fettiplace et al. (2014) [94] (Rats)	RCS; resuscitation model	Bupivacaine (10 mg/kg in 10 s)	2.68	Asystole	30%, Intralipid	IO 10 mL/kg (3.0 g/kg) in 180 s; IV 10 mL/kg (3.0 g/kg) in 90 s	0.5 mL/kg/min (9 g/kg/h)	ILE (IO) versus ILE(IV) versus Saline (IO)	Study treatment at 10 s.	No	Hemodynamics: ECG, aortic pressure, carotid blood flow; Return of 50% flow; Comparable recovery of hemodynamic variables in ILE (IO) and ILE (IV). Faster recovery in ILE (IO) and ILE (IV) compared to Saline and no treatment	Survival: All	Yes
Gokahmetoglu et al. (2014) [95] (Rabbit)	RCS; resuscitation model	Bupivacaine (10 mg/kg)	2.68	Asystole	20%, Intralipid	1.5 mL/kg (0.3 g/kg), additional bolus × 3, 5 min interval if absence of ROSC	0.25 mL/kg/min (3 g/kg/h), increased in the absence of ROSC after additional boluses	ILE versus Levosimendan 3 mcg/kg/min versus ILE + Levosimendan 3 mcg/kg/min versus 0.9% Saline	30 s non-intervention period, then study treatment	Mechanical ventilation, manual chest compression, EPI 100 mcg/kg every 5 min	Time to ROSC, min: Saline NA, ILE 7, Levosimendan 10, ILE + Levosimendan 2. Arrests while alive, number: Saline NA, ILE 1, Levosimendan 1, ILE + Levosimendan 2. Duration of arrest, min: Saline 20, ILE 7.5, Levosimendan 20, ILE + Levosimendan 4	ROSC: ILE 8/12, Levosimendan 4/12, ILE + Levosimendan 11/12, Saline 0/12	No; suggest preferred coadministration of EPI + ILE + Levosimendan compared to EPI + ILE or Levosimendan + EPI
Hicks et al. (2009) [96] (Pig)	RCS; resuscitation model	Bupivacaine (10 mg/kg in 10 s)	2.68	Cardiac arrest, then wide QRS complex, premature ventricular contractions, and premature atrial contractions	20%, Intralipid	4 mL/kg (0.8 g/kg)	0.5 mL/kg/min (6 g/kg/h)	ILE versus Saline	Other treatments immediately after LA for 5 min, then study treatment	EPI (100 g/kg) and VASO (1.5 U/kg) cardiac resuscitation	Hemodynamics: MAP: 82.9 + ± 12.2 (base line), 83.9 ± + 10.4 (15 min), 83.6 ± + 8.9 (30 min), 80.2 ± + 13.7 (45 min), 69.5 + ± 7.8 (60 min)	Survival: ILE 3/10, Saline 4/9	No; adding ILE resuscitation to EPI and VASO did not improve outcomes

(continued)

Table 3. Continued

References (Species)	Model	Local anesthetic (dose)	Log D [129]	Symptoms	ILE used	ILE bolus[a]	ILE infusion[a]	Study arms	Timing of rescue, time from LA termination	Other treatments received[b]	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Hiller et al. (2009) [97] (Rats)	RCS; resuscitation model	Bupivacaine (20 mg/kg)	2.68	Asystole	30%, Intralipid	5 mL/kg (1.5 g/kg) × 2	1 mL/kg (9 g/kg/h) for 2 min	ILE versus ILE + EPI versus Saline	Other treatment immediately after LA, study treatment at 3 min	Saline or ILE or ILE + EPI 1, 2.5, 10 or 25 mcg/kg	Hemodynamics: Manual chest compressions to achieve a rate-pressure product (=systolic pressure HR) of at least 50% of baseline; EPI (up to 2.5 mcg/kg) improved initial ROSC but few animals sustained by 15 min. ILE alone resulted in slower but more sustained recovery	Survival: All	No; ILE alone compared to ILE + EPI (1, 2.5, 10, 25 mcg/kg). ILE alone resulted in ROSC, ILE + EPI doses below 10 had faster and more sustained ROSC
Karci et al. (2009) [98][b] (Rats)	RCS; resuscitation model	Levobupivacaine (3 mg/kg/min)	2.68	Decrease of 50% in mean BP. Asystole	20%, brand NR	No	1.5 mL/kg (0.6 g/kg/h) for 30 min (one group) time NR for other groups	Post-treatment ILE or Simultaneous-treatment ILE versus no ILE versus No LA + ILE	Other treatment and study treatment immediately after LA	Standard resuscitation (unspecified)	Hemodynamics: No hemodynamic changes were observed in rats receiving only ILE emulsion; Time to development of asystole was longer compared to other levobupivacaine dosed groups	Survival: ILE at 50% MAP + std resusc 4/7, ILE + std resusc 1/7, std resusc 0/7, No LA + ILE 7/7	Yes; simultaneous treatment and post-treatment parts suggest that administration of ILE may prevent cardiac arrest and ILE infusion along with standard resuscitation in cardiac arrest may improve survival
Karcioğlu et al. (2014) [99] (Rabbit)	RCS; resuscitation model	Levobupivacaine (10 mg/kg)	2.68	Asystole	20% Intralipid	1.5 mL/kg (0.3 g/kg), additional boluses, 5 min interval if absence of ROSC	No	ILE versus Saline	30 s non-intervention period, then study treatment	Mechanical ventilation, manual chest compression, EPI 100 mcg/kg every 5 min	ROSC (MAP > 50 mmHg and HR > 120 bpm): ILE > Saline	Survival: ILE 3/7, Saline 1/7	Not studied; ILE + EPI superior to EPI alone
Li et al. (2011) [100] (Rats)	RCS; resuscitation model	Bupivacaine (20 mg/kg)	2.68	Cardiac arrest	20%, Lipovenos MCT and Intralipid	5 mL/kg (1 g/kg)	1 mL/kg/min (12 g/kg/h) for 3 min	MCT/LCT ILE versus LCT ILE	Other treatment and study treatment immediately after LA	EPI 40 mcg/kg (LCT), 50 mcg/kg (MCT/LCT), chest compression, mechanical ventilation	Hemodynamics: RPP more than 20% of baseline value for 1 min = ROSC	Mortality after resusc lower in LCT (2/30) versus MCT/LCT (8/30)	Not studied; supports LCT over a MCT/LCT. Did not have a control without ILE resuscitation
Litonius et al. (2012) [101] (Pig)	RCS; resuscitation model	Bupivacaine (2 mg/kg/min) or Mepivacaine (6 mg/kg/min)	2.68 1.40	MAP decreased to 50% of its baseline value	20%, ClinOleic and Intralipid	1.5 mL/kg (0.3 g/kg)	0.25 mL/kg/min (3 g/kg/h) for 29 min	ILE versus Ringer acetate	Other treatment and study treatment immediately after LA	EPI 0.5 mg repeated doses, chest compression, mechanical ventilation, electrical defibrillation.	Hemodynamics: Comparison of MAP and HR among treatment groups at each measured time point revealed no overall effect of ILE in comparison with Ringer's acetate solution; No difference in effect between the two ILE's tested	Survival: Bupi + ILE 10/10, Bupi + Ringer 8/10, Mepi + ILE 9/10, Mepi + Ringer 10/10	No; ILEs did not improve hemodynamic parameters
Mauch et al. (2012) [102] (Pig)	RCS; compared ILE effect with EPI and vasopressin	Bupivacaine (1 mg/kg/min)	2.68	Cardiac arrest	20%, Intralipid	4 mL/kg (0.8 g/kg)	No	ILE versus ILE + EPI versus ILE + VASO versus EPI	Other treatment immediately after LA, study treatment at 1 min	Vasopressors 2IU, EPI 10 mcg/kg chest compression	ROSC was regained after one EPI rescue dose in EPI and EPI + ILE. ILE and VASO + ILE ROSC achieved after secondary EPI rescue dose	Survival: ILE 2/7, ILE + EPI 6/7 ILE + VASO 4/7, EPI 5/7	No; supports using EPI and EPI + ILE resuscitation over ILE resuscitation alone and ILE + VASO

(continued)

Table 3. Continued

References (Species)	Model	Local anesthetic (dose)	Log D [129]	Symptoms	ILE used	ILE bolus[a]	ILE infusion[a]	Study arms	Timing of rescue, time from LA termination	Other treatments received[b]	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Mauch et al. (2011) [103] (Pig)	RCS; compare effectiveness of EPI and ILE	Bupivacaine (1 mg/kg/min until symptoms)	2.68	LA infused at a rate of 1 mg/kg min until invasively measured MAP dropped to 50% of the initial value	20%, Intralipid	2 mL/kg (0.4 g/kg) and 4 mL/kg (0.8 g/kg)	No	ILE 2 ml/kg versus ILE 4 ml/kg versus EPI	Other treatment and study treatment immediately after LA	EPI rescue doses, 3 mcg/kg, every 5 min if MAP < 75%	Hemodynamics: EPI bolus + resusc – HR (beats/min): baseline 127 (101–154), 6–7 pigs reached baseline at 1–5 min. MAP (mmHg): baseline 51 (48-52), 6-7 pigs reached baseline at t1-5 min. ILE 2 + EPI resusc – HR (beats/min): baseline 122 (107–130), 1 pig reached baseline at t4–5 min. MAP (mmHg): baseline 50 (48-52), 1 pig reached baseline at t5 min. ILE 4 + EPI resusc – HR (beats/min): baseline 113 (107-142), 1 pig reached baseline at t5 min. MAP (mmHg): baseline 51 (50-54), 3–4 pigs reached baseline at t4-5 min	Survival: ILE 2 + EPI resusc 4/7, ILE 4 + EPI resusc 4/7, EPI bolus + resusc 7/7	Yes; but EPI may be better first line therapy
Mauch et al. (2011) [104][b] (Pig)	RCS; resuscitation model	Bupivacaine (1 mg/kg/min until symptoms)	2.68	Pulseless electrical activity, $n = 23$ Asystole, $n = 2$. LA infused until cardiac arrest (pulseless electrical activity was defined as MAP 25% of initial value, corresponding to 12-13 mmHg)	20%, Intralipid	4 mL/kg (0.8 g/kg)	No	ILE versus EPI versus ILE + EPI versus ILE + VASO	Other treatment immediately after LA, study treatment at 1 min	EPI bolus 10 mcg/kg. Followed by rescue doses every 5 min if necessary, 10 mcg/kg in case of cardiac arrest, or 3 mcg/kg if MAP ≤ 75%, chest compressions, mechanical ventilation	Hemodynamics: EPI + std resusc - Secondary high dose EPI was not needed in surviving pigs; low dose EPI for hemodynamic support was given in 3 of 5 surviving pigs; ILE – Secondary high dose EPI was needed in all surviving pigs; low dose EPI for hemodynamic support was given in 1 surviving pig; ILE + EPI – Secondary high dose EPI was not needed in surviving pigs; ILE + VASO – Secondary high dose EPI was needed in all surviving pigs	Survival: ILE 1/6, EPI 5/7, ILE + EPI 5/6, ILE + VASO 3/6	No; EPI and EPI + ILE resuscitation was superior to ILE alone

(continued)

Table 3. Continued

References (Species)	Model	Local anesthetic (dose)	Log D [129]	Symptoms	ILE used	ILE bolus[a]	ILE infusion[a]	Study arms	Timing of rescue, time from LA termination	Other treatments received[b]	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Mayr et al. (2008) [105] (Pig)	RCS; compare resuscitation with ILE and VASO/EPI	Bupivacaine (5 mg/kg)	2.68	Aortic blood pressure decreasing to hydrostatic pressure; Asystole	20%, Intralipid	4 mL/kg (0.8 g/kg)	0.5 mL/kg/min (6 g/kg/h) for 10 min	ILE versus VASO + EPI	Other treatment at 1 min, study treatment at 2 min	Ringer's solution, gelatine solution, saline (one group); VASO, EPI (saline group); Azaperone 4 mg/kg IM, atropine 0.1 mg/kg IM; Anesthesia, ketamine 20 mg/kg IM, piritramid 30 mg IV, maintained with isoflurane 1–2% end-tidal; Heparin; Oxygen	Hemodynamics: ILE + Saline – none of the ILE-pigs had restoration of spontaneous circulation, coronary perfusion pressure <20-30 mmHg. EPI + VASO + Saline – coronary perfusion pressure as a decisive predictor of spontaneous circulation was significantly higher 90 s after the first and second VASO/EPI injection compared to ILE, >20–30 mmHg	Survival: ILE + Saline 0/5, EPI + VASO + Saline 5/5	No; supports use of Vasopressors + EPI over ILE resuscitation
Shi et al. (2003) [106] (Rats)	RCS; evaluation of the effect on hemodynamics and LA pharmaco kinetics	Bupivacaine (2 mg/kg/min for 4 min)	2.68	Hypotension, bradycardia	30%, Intralipid	No	3 ml/kg/min (54 g/kg/h for 5 min)	ILE versus Saline	Study treatment or other treatment immediately after LA	No	HR, MAP: Comparable Plasma-bupivacaine: distribution constant, elimination half-life ($t_{1/2}\beta$) decreased in ILE groups, elimination half-life($t_{1/2}\alpha$), clearance increased in ILE groups. Bupivacaine tissue (brain, myocytes, lung, kidney, spleen, muscle) content reduced in ILE group; increased in liver ILE group compared to saline	Survival: All	Yes; ILE accelerated the elimination of bupivacaine. The lipid sink phenomenon was observed
Wat et al. (2009) [107][b] (Pig)	RCS; resuscitation model	Ropivacaine (14.9 ± 2.8 mg/kg)	4.21	Cardiovascular collapse	20%, Intralipid	4 mL/kg (0.8 g/kg)	0.5 mL/kg/min (6 g/kg/h)	ILE versus EPI versus Saline	Other treatment immediately, study treatment NR	Cardiac massage	Failed to regain 50% of baseline systolic blood pressure and HR 10 min after iv treatment commenced. myocardial ATP content were not different between groups	Survival: ILE 0/5, EPI 5/5, Saline 0/5	No; Ropivacaine induced cardiac toxicity responded well to standard resuscitation with cardiac massage and intravenous adrenaline
Weinberg et al. (2004) [108] (Dogs)	RCS; evaluation of the effect of bupivacaine on myocardial acidosis induced by ventricular fibrillation	Bupivacaine (10 mg/kg)	2.68	Ventricular fibrillation or myocardial pH 7.0	20%, Intralipid	4 mL/kg (0.8 g/kg)	0.5 mL/kg/min (6 g/kg/h) for 10 min	LA + ILE versus Saline + Fibrillation (no LA, fibrillation until same symptoms as LA group)	Defibrillation at 20 min or at myocardial pH $\leq$ 7.0	Fibrillation in non-ILE group	PmO2 was comparable in saline versus LA + ILE group; Tissue pH decreased 4 times faster in saline compared to LA group during ventricular fibrillation; Time to normal sinus rhythm was comparable in Saline versus LA + ILE group	Survival: LA + ILE 8/8, Saline 8/8	Not studied
Weinberg et al. (2003) [109] (Dogs)	RCS; resuscitation model	Bupivacaine (10 mg/kg in 10 s)	2.68	Cardiac arrest	20%, Intralipid	4 mL/kg (0.8 g/kg)	0.5 mL/kg/min (6 g/kg/h) for 10 min	ILE versus Saline	Other treatment immediately, study treatment at 10 min	Mechanical ventilation, internal cardiac massage	Hemodynamics: P_mO_2, and pHm were improved during resuscitation with ILE compared with saline treatment in which dogs did not recover. Data are compared between baseline and after recovery	Survival: ILE 6/6, Saline 0/6	Yes

(continued)

Table 3. Continued

References (Species)	Model	Local anesthetic (dose)	Log D [129]	Symptoms	ILE used	ILE bolus[a]	ILE infusion[a]	Study arms	Timing of rescue, time from LA termination	Other treatments received[b]	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Weinberg et al. (2008) [110] (Rats)	RCS; resuscitation model	Bupivacaine (20 mg/kg)	2.68	Asystole	30%, Intralipid	5 mL/kg (1.5 g/kg)	0.5 mL/kg/min (9 g/kg/h)	ILE versus EPI versus Saline	Other treatment and study treatment immediately after LA	Chest compressions, mechanical ventilation	QRS width: ILE – comparative EPI – Significantly prolonged at 2.5 min compared to ILE; But shorter than saline control. Recovered to baseline at 5 min. Saline – Significantly prolonged at 2.5 min compared to ILE, stayed elevated throughout the experiment	Survival: ILE 5/5, EPI 5/5, Saline 5/5	Yes
Yan et al. (2012) [111] (Rats)	RCS; resuscitation model	Bupivacaine (30 mg/kg)	2.68	Asystole	20%, Intralipid	5 mL/kg (1 g/kg)	0.5 mL/kg/min (6 g/kg/h)	ILE versus ILE + EPI versus EPI versus Saline	Other treatment immediately, study treatment at 10 min	No	Hemodynamic parameters at 25 min, coronary perfusion. Post-mortem myocardial LA content	Survival: ILE 3/8, EPI + ILE 5/8, EPI 2/8, Saline 0/8	No; EPI + ILE had improved hemodynamics compared to ILE alone
Yoshimoto et al. (2014) [112][b] (Rats)	RCS; resuscitation model	Bupivacaine (hyperbaric, 2 mg/kg/min)	2.68	Cardiac arrest	20%, brand NR	5 mL/kg (1 g/kg)	0.5 mL/kg/min (6 g/kg/h)	ILE versus Saline	CPR, then study treatment	Glucose with LA. Immediate ventilation and chest compressions	MAP and HR values at 2, 3, 4, 5, and 10 min: ILE = Saline	Survival rate unclear	No; suggests glucose reduces the ILE effect on reversal of LA-induced cardiac arrest
Observational													
Callejo et al. (2014) [113][b] (Pig)	Observational; compare ILE with saline	Bupivacaine (4 mg/kg)	2.68	150% increase in QRS duration	Conc. NR, Intralipid	1.5 mL/kg	0.25 mL/kg/min	ILE versus Saline	NR	NR	QRS widening was reversed after ILE	Survival NR. ILE:?/6, Saline?/3	No; suggests concomitant resuscitation measures
Cave et al. (2010) [114] (Rabbit)	Observational; compared to 21% saline	Bupivacaine (10 mg/kg)	2.68	Asystole	20%, Intralipid	1.5 mL/kg (0.3 g/kg)	0.25 mL/kg/min (3 g/kg/h)	ILE versus ILE + Hypertonic saline (21%)	Other treatment at 30 s, study treatment at 1 min	Hypertonic saline (one group); Adrenaline ketamine Chest compressions and mechanical ventilation, with 100% oxygen	Hemodynamics: ILE + Saline – Return of spontaneous circulation in 9/10 animals in median (IQR [range]) time 2.5 (2.0–5.0 [1.0–6.0]) min (No difference between groups); Number of adrenaline doses 1.5 (1.0–3.0 [1–4]) (No difference between groups) ILE – Return of spontaneous circulation in 7/10 animals in median (IQR [range]) time 2.0 (2.0–3.0 [2.0–3.0]) min (No difference between groups); Number of adrenaline doses 2.5 (1.8–3.0 [1–4]) (No difference between groups) QRS width: ILE + Saline – QRS duration at 4 min 0.10 ms, 9 min 0.090 ms, 14 min 0.095 ms, 19 min 0.090 ms ILE – QRS duration significant longer at 4 min and 9 min; QRS duration at 4 min 0.19 ms, 9 min 0.18 ms, 14 min 0.095 ms, 19 min 0.090 ms	Survival: ILE 5/10, ILE + 21% saline 6/10	Not studied

(continued)

Table 3. Continued

References (Species)	Model	Local anesthetic (dose)	Log D [129]	Symptoms	ILE used	ILE bolus[a]	ILE infusion[a]	Study arms	Timing of rescue, time from LA termination	Other treatments received[b]	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Weinberg et al. (1998) [115] (Rats)	Observational; resuscitation model	Bupivacaine (various dose)	2.68	Asystole	30%, Intralipid	7.5 ml/kg (2.25 g/kg)	3 mL/kg/min (54 g/kg/h) for 2 min Total dose 4 g/kg	ILE versus Saline	Other treatment and study treatment immediately after LA	Bicarbonate: 2 min IV fluids: 2.5 min Vasopressors: 3.05 g/kg	ILE increased the dose required to cause death in 50% of animals	LD50 study	Yes; increase LD50 dose from 12.5 to 18.5 mg/kg
Case Series													
Harvey et al. (2010) [116] (Rabbit)	Case series; resuscitation model	Bupivacaine (10 mg/kg)	2.68	Asystole	20%, Intralipid	5 mL/kg (1 g/kg) x2	No	ILE versus ILE + EPI	Other treatment at 30 s, study treatment at 1 min	Control group received late dosing of EPI 100 mcg/kg (1 mL/kg)	Hemodynamics: Time to ROSC after chest compressions and mechanical ventilation. High-dose EPI administration was associated with a significant increase in coronary perfusion pressure before ROSC	Survival: None; Failure of animals from any group to maintain effective circulation	No; ILE alone was compared to ILE with 3 doses of EPI. Only high dose EPI + ILE had ROSC
Partownavid et al. (2012) [117, p. 2431] (Rats)	Case series; resuscitation model	Bupivacaine (10 mg/kg)	2.68	Asystole	NR	5 mL/kg	0.5 mL/kg/min	ILE versus Pre-treatment + ILE	Other treatment immediately	Pre-treatment with naloxone 1 mg/kg, 10 mcg/kg, 5 mcg/kg, 1 mcg/kg	HR, ejection fraction and fractional shortening measures by ECG at baseline, 1, 5, and 10 min	Survival rate unclear	Not studied; Naloxone abolishes ILE rescue of bupivacaine-induced cardiotoxicity in a dose dependent manner
Partownavid et al. (2010) [118][b] (Rats)	Case series; resuscitation model	Bupivacaine (10 mg/kg)	2.68	Asystole	20%, Intralipid	5 mL/kg (1 g/kg)	0.5 mL/kg/min (6 g/kg/h)	ILE versus Pre-treatment + ILE	Other treatment immediately	Cardiac massage (LA groups); Fatty-acid oxidation inhibitor CVT (one group); Phosphate buffered saline (one group)	Oxygen consumption, membrane potential and calcium-retention capacity (in response to Ca^{2+} overload)	Survival rate unclear	Not studied; fatty-acid oxidation is required for successful rescue of bupivacaine-induced cardiotoxicity by ILE
Partownavid et al. (2012) [119][b] (Rats)	Case series; resuscitation model	Bupivacaine (10 mg/kg)	2.68	Asystole	NR	5 mL/kg	0.5 mL/kg/min	ILE versus Pre-treatment + ILE	Other treatment immediately	Pre-treatment with fatty-acid oxidation inhibitor CVT (one group)	HR, ejection fraction and fractional shortening measures by ECG at baseline, 1, 5, and 10 min	Survival rate unclear	Not studied; ILE rescue of bupivacaine-induced cardiotoxicity is abolished by fatty acid oxidation Inhibitor CVT-4325
Yoshimoto et al. (2012) [120][b] (Rats)	Case series; compared ILE effect between 2 LA, no control	Levobupivacaine (2 mg/kg/h) or Ropivacaine (2 mg/kg/h)	2.68 4.21	Pulse pressure decrease to zero (0 mmHg, MAP 6.8–7.6 ± 1.3 mmHg, HR 40–47 ± 15 bpm)	30%, brand NR	5 mL/kg (1.5 g/kg)	0.5 mL/kg/min (9 g/kg/h)	Levobupivacaine + ILE versus Ropivacaine + ILE	Other treatment and study treatment immediately after LA	Chest compressions and mechanical ventilation	Hemodynamics: Levobupivacaine – HR at t5 min 302 ± 84; MAP (mmHg) at t2min 22 ± 6, t3min 11 ± 7, t4min 31 ± 5, t5min 16 ± 6, t10min 38 ± 13; Ropivacaine – HR at t5 min 152 ± 75; MAP (mmHg) at t2min 16 ± 5, t3min 54 ± 32, t4min 16 ± 4, t5min 184 ± 15, t10min 77 ± 60	Survival: Levobupi + ILE 6/6, Ropi + ILE 6/6	Not studied

(continued)

Table 3. Continued

References (Species)	Model	Local anesthetic (dose)	Log D [129]	Symptoms	ILE used	ILE bolus[a]	ILE infusion[a]	Study arms	Timing of rescue, time from LA termination	Other treatments received[b]	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Case report													
O'Brien et al. (2010) [121] (Cat)	Case report	Lidocaine (20 mg/kg)	1.26	Lethargy, Erratic, poor-quality pulses with severe hypotension, Almost cardiac arrest, Respiratory distress, pulmonary edema	20%, Liposyn II	No	1.5 mL/kg (0.6 g/kg/h) for 30 min	NA	Other treatment immediately, ILE treatment at 15 min	Lactate ringer oxygen	Hemodynamics: improvement in cardiovascular variables; CNS: Improvement in behavioural variables (more responsive to stimuli, could hold its head up without assistance)	Survived	Yes; 15 min after initiation of the ILE emulsion, the cat was more responsive to stimuli

ACLS: Advanced cardiac life support; AH: Atrial-His interval; ATP: Adenosine triphosphate; AUC: Area under the curve; BP: Blood pressure; CI: Cardiac index; CVP: Central venous pressure; CVT: CVT-4325; ECG: electrocardiogram; EPI: Epinephrine; HR: Heart rate; HV: His-ventricle interval; ILE: Intravenous lipid emulsion; IO: Intraosseous; IV: Intravenous; LA: Local anesthetic; LCT: Long chain triglyceride; LVdP/dtmax: maximal first derivative of left ventricular pressure; LVEDP: Left ventricular end-diastolic pressure; MAoP: Mean aortic pressure; MAP: Mean arterial pressure; MCT: Medium chain triglyceride; mPAP: Mean pulmonary artery pressure; NA: Not applicable; NR: Not reported; PCP: Pulmonary capillary pressure; pHm: Myocardial pH; P_mO_2: Myocardial tissue oxygen pressure; PVRI: Pulmonary vascular resistance index; RCS: Randomized controlled studies; ROSC: Return of spontaneous circulation; RPP: Rate pressure product; RR: Cardiac cycle length; std CPR: Standard cardio-pulmonary resuscitation; std resusc: Standard resuscitation; SVRI: Systemic vascular resistance index; VASO: Vasopressin.

[a]The bolus dose in g/kg and infusion dose in g/kg/h could only be calculated if lipid concentration was reported.

[b]Available as abstracts at the time of writing.

[c]Drugs used for general anesthesia or euthanasia are not included.

Resuscitation treatments were generally initiated immediately or within 3 min of the termination of LA administration (Table 3). Intravenous lipid emulsion was initiated immediately or within one minute in 19 studies [17,85,87,90,92,94,96,98, 100–104,106,110,116–119] or less commonly up to 3 min (two studies),[97,105] 4 min (one study),[86] 10 min (two studies),[109,111] or 20 min (one study) [108] after termination of LA administration. The timings of administration of study treatments were not reported in three studies (10%).[88,91,107] Three studies (10%) were not designed to evaluate the therapeutic effects of ILE alone, and either compared the use of ILE for toxicity caused by two different local anesthetics,[101] compared two types of ILE (long-chain triglyceride versus long-chain and medium-chain triglyceride [100]) or evaluated the myocardial tissue pH.[108] These studies were not considered generalizable to human poisoning and were therefore excluded from further analysis.

Animal observational studies

The three observational studies included in this review measured the LA dose required to cause death in 50% of the animals dosed (LD50),[115] compared the effect of ILE or saline on QRS widening using ILE or saline,[113] or compared ILE to hypertonic saline in combination with ILE.[114]

Intravenous lipid emulsion was initiated immediately or within 2 min of the termination of LA administration (Table 3). Bupivacaine was used at 4 mg/kg,[113] 10 mg/kg,[114] or at several different doses.[115] A benefit of ILE use was supported by the demonstration that lipid infusion increased the bupivacaine LD50 in rats by 48%, from 12.5 to 18.5 mg/kg,[115] and by reversing the lengthening of QRS interval induced by the injection of bupivacaine in pigs (Table 3).[113]

Animal case reports and case series

Only one animal case report was retrieved from our literature search, describing a cat suffering from toxicity after administration of lidocaine 140 mg (20 mg/kg).[121] The ILE infusion regimen was derived from clinical human studies, but the dose was reduced due to concerns about fluid overload. The authors reported a pronounced clinical response within 15 min of ILE initiation, with the cat becoming more responsive to stimuli and being able to hold its head up without assistance.

Five studies were included in this review as case series as the studies did not include a control group without ILE or included ILE in both study groups.[116–120] Thus, one study compared ILE plus the addition of three different doses of epinephrine,[116] one study compared the effect of ILE for either levobupivacaine or ropivacaine toxicity,[120] and three studies evaluated if the protective action of lipid emulsion was mediated through the fatty acid oxidation pathway [117,118] or involved the opioid receptor.[119]

Bupivacaine 10 mg/kg was the LA used in four of these five studies,[116–119] and levobupivacaine and ropivacaine were used in the other study each at a dose of 2 mg/kg/h.[120] Intravenous lipid emulsion was initiated immediately or up to 1 min after LA administration.

Assessment of the quality of evidence

Table 4 presents the summary estimates with associated Grading of Recommendations Assessment, Development and Evaluation (GRADE) ratings for the two human controlled studies reporting the efficacy of ILE on LA cardiotoxicity and neurotoxicity. All other evidence retrieved in this systematic review was rated as of very low quality; the human studies were seriously limited by their study designs (all uncontrolled studies preventing comparison with a control group, such as case series and case reports) and by the high likelihood of publication bias (especially with case reports), while animal studies were seriously limited by indirectness (resuscitation model lacking generalizability to humans) and imprecision (systematically underpowered studies).[122–128]

Discussion

In our systematic review on the effect of ILE for acute LA toxicity, we identified animal and clinical studies that yielded a very low quality of evidence. Most randomized studies were conducted in animal settings with limited observation of test subjects after treatment and where no autopsies were performed or drug concentration measured. The human publications presenting the effect of ILE in severe LA toxicity were mainly case reports. Data from these studies and reports showed inconsistent benefits of ILE for the treatment of acute LA intoxication. Many also employed several treatments and, although this reflects what often happens in clinical practice, it makes the assessment of the specific effects of ILE difficult if not impossible.

A possible beneficial effect was reported in 71% of the human case reports, although this estimate of benefit is questionable due to the high risk of publication bias usually associated with this specific study design and due to the indirectness of the results caused by the absence of comparison to a control group. Furthermore, the only human controlled study showed no effect of ILE on mild LA toxicity. Thus, most of the useful evidence supporting a beneficial effect of ILE relies on animal studies. In controlled animal experiments and animal observational studies, the effects of ILE were mainly based on cardiovascular variables, which are the most frequently observed adverse events with bupivacaine, the LA most often studied. Neurological symptoms could not be fully evaluated as the animals used were anesthetized during the experimental procedures. Results suggested improved efficacy for the reversal of LA cardiovascular toxicity with ILE alone compared to other treatments received alone in 48% of the controlled animal studies, but reduced efficacy was seen in 28% of the these studies. The dose of LA given to induce toxicity in animals may not be comparable to the toxic dose known in humans and the amount of ILE given bolus often exceeded current recommendations.

When ILE was compared to other active treatments (vasopressors), inconsistent results were observed. There were 13

controlled animal studies favoring ILE alone, six studies favoring vasopressors and seven studies favoring the combination of vasopressors and ILE. These studies are too heterogeneous to allow a pooled analysis. The limited results of the available observational studies also suggested a possible clinical benefit from ILE alone or in combination with other resuscitative treatments with the same limitations to the human poisoning context as stated previously.

From the eight animal experiments using vasopressors and ILE, results appears to be conflicting and in particular with the use of epinephrine. On the one hand, ILE appears to be associated with better hemodynamic outcomes in one study.[110] On the other hand, epinephrine alone, or the association of epinephrine and ILE, was better than ILE alone for survival or hemodynamic outcomes in five other studies in pigs and rats.[102–104,107,111] It is worth noting that the amount of epinephrine and ILE given were quite heterogeneous and the formulation of ILE was not reported in one publication. Finally, two studies demonstrated that no differences between epinephrine and ILE for mortality.[88,97]

Thus, data from the human case reports and the animal studies provides weak evidence that that ILE may be effective in some cases of LA toxicity. However, there is no convincing evidence that this treatment is more effective than the use of vasopressors. These results also do not offer evidence to support which treatment should be instituted as first line therapy when cardiovascular toxicity arises after LA anesthetic administration.

Limitations

We performed a very broad search of the literature using appropriate eligibility criteria by considering all types of study design, including preclinical studies, but we may not have uncovered all studies reported in abstract form. A further potential limitation of our review is the inclusion of animal studies, which may not be generalizable to human cases of LA poisoning. The consideration of animal studies to support clinical practice may be perceived as inappropriate by some. However, several editorials and reviews used animal data to support the concept of ILE as an antidote. Our decision to consider such methodology was driven by our intention to be as exhaustive as possible in a field where very little research is conducted, and when it is done, this is often in a non-optimal context.

The human cases described were also heterogeneous regarding the LA involved, the severity of symptoms, the ILE dose, and the use of other treatments before ILE and we could not explore the potential impact of these discrepancies on the effect of the intervention. As stated in our methodology paper,[9] the primary outcome of interest was survival. The included case reports showed 98% survival. However, the validity of this finding is questionable due to reporting and publication bias. In most of the case reports, the reversal of toxicity was thought to be related to ILE, however, some uncertainty remains as other treatments were often provided at the same time and effects could not be specifically distinguished. Furthermore, it is likely that cases that described negative outcome after ILE administration are underreported.

Table 4. Summary estimates with associated GRADE ratings for human controlled studies reporting the effect of ILE on LA toxicity.

		Comparison		Summary of finding		Quality of evidence	
No. of Studies	Population	Intervention (No. of patients)	Comparator (No. of patients)	Summary estimate[a]	Interpretation	Quality assessment[b]	GRADE rating
Cardiotoxicity $N = 1$ [11]	Healthy volunteers receiving lidocaine infusion followed by either Ropivacaine or Levobupivacaine in continued infusion (8 mg/min)	20% Intralipid 120 mL bolus 2 min after the start of LA infusion ($n = 16$ for each LA infusion)	Saline ($n = 16$ for each LA infusion)	Prolong QRS was present at the end of the LA infusion when compared with baseline, but no difference in PR, QTc or QRS duration between groups ($p = 0.68$)	No difference in EKG between groups	RCT cross-over; Downgrade: Indirectness due to surrogate marker (−1) and subclinical toxicity design (−1), Imprecision due to small sample size (−1)	Very low
Neurotoxicity $N = 1$ [11]	Healthy volunteers receiving lidocaine infusion followed by either Ropivacaine or Levobupivacaine in continued infusion (8 mg/min)	20% Intralipid 120 mL bolus 2 min after the start of LA infusion ($n = 16$ for each LA infusion)	Saline ($n = 16$ for each LA infusion)	MD Ropivacaine = −6.0 (−24.7; + 12.7) MD Levobupivacaine = −11.4 (−32.4; 9.6) No EEG abnormalities observed	No difference in LA doses needed to reach neurotoxicity or in EEG changes between groups	RCT cross-over; Downgrade: Indirectness due to surrogate marker (−1) and subclinical toxicity design (−1), Imprecision due to small sample size (−1)	Very low

[a]Summary estimate is expressed in difference between the 'group intervention – group comparator'. Either a risk difference (RD), a mean difference (MD) or weighted mean difference (WMD) was reported.
[b]Quality assessment according to the GRADE methodology. Of note, since no controlled studies were pooled together to answer a specific clinical question, inconsistency and publication bias were not evaluable.

Our inability to deliver some of the results as intended in our methodology paper [9], was principally due to unreported data, insufficient data, or the nature of the data, and also included the units used to specify the dose. Our intention was to extract or calculate the total amount of ILE in g/kg, but in many articles the information was insufficient, and therefore different units appears in Tables 1 and 3. As mentioned in the 'Results' section, most of the included studies and reports used 20% ILE, but a limitation to this review is that in 11 human case reports and two animal studies, the actual concentration of the ILE used was not reported.

A further limitation of the data was that it was not easy to obtain information if reported sequelae in human case reports referred to adverse effects from local anesthetics or from ILE. The details of sequelae that we were able to extract from data are included in Table 1.

Conclusions

The currently available published evidence concerning the effect of ILE in severe LA toxicity is limited to very low quality studies such as small animal experiments and human and animal case reports or series. It is possible that ILE may be effective for reversal of cardiovascular or neurological features in some cases of LA toxicity. However, there is currently no consistent evidence that ILE is more effective than vasopressors. The available evidence is insufficient to judge the combined effects of ILE and vasopressors and to determine whether one drug should precede the other in treating severe LA toxicity.

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Disclosure statement

All members completed a conflict of interest form for AACT and received no honoraria. Webcast conference and rooms for meeting were provided by AACT. No member with a financial or academic conflict of interest preventing neutral assessment of the literature participated in the review (i.e. no committee member's livelihood or academic career is depending on a grant studying lipid emulsion in poisoning). Dr Lavergne and Dr Turgeon are recipients of salary support awards from the Fonds de la Recherche du Québec - Santé (FRQS).

References

[1] Rosenblatt MA, Abel M, Fischer GW, et al. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. Anesthesiology. 2006;105:217–218.

[2] AAGBI. AAGBI Safety Guideline – Management of Severe Local Anaesthetic Toxicity 2010. [cited 2015 May 20]. Available from: http://www.aagbi.org/sites/default/files/la_toxicity_2010_0.pdf.

[3] American College of Medical Toxicology. ACMT position statement: interim guidance for the use of lipid resuscitation therapy. J Med Toxicol. 2011;7:81–82.

[4] ASRA. Checklist for treatment of local anesthetic systemic toxicity 2011. [cited 2015 May 20]. Available from: https://www.asra.com/advisory-guidelines/article/3/checklist-for-treatment-of-local-anesthetic-systemic-toxicity.

[5] Cao D, Heard K, Foran M, et al. Intravenous lipid emulsion in the emergency department: a systematic review of recent literature. J Emerg Med. 2015;48:387–397.

[6] Cave G, Harvey M, Graudins A. Intravenous lipid emulsion as antidote: a summary of published human experience. Emerg Med Australas. 2011;23:123–141.

[7] Corman SL, Skledar SJ. Use of lipid emulsion to reverse local anesthetic-induced toxicity. Ann Pharmacother. 2007;41:1873–1877.

[8] Jamaty C, Bailey B, Larocque A, et al. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin Toxicol (Phila). 2010;48:1–27.

[9] Gosselin S, Morris M, Nesbitt-Miller A, et al. Methodology for AACT evidence-based recommendations on the use of lipid emulsion therapy in poisoning. Clin Toxicol (Phila). 2015;53:557–564.

[10] Dureau P, Charbit B, Benhamou D, et al. La toxicité systémique des anesthésiques locaux peut-elle être prévenue par l'Intralipide®? Une étude pharmacocinétique [Abstract]. Ann Fr Anesth Reanim. 2014;33(suppl 2): A7.

[11] Dureau P, Mazoit JX, Navarro V, et al. La toxicité systémique des anesthésiques locaux peut-elle être prévenue par l Intralipide®? [Abstract]. Ann Fr Anesth Reanim. 2014;33(suppl 2):A7–A8.

[12] Admani B, Essajee F. Successful resuscitation of a three month old child with intralipid infusion, presumed to have bupivacaine induced seizures and cardiovascular complications: case report. East Afr Med J. 2010;87:354–356.

[13] Al-Alami AA. Successful treatment of early ropivacaine toxicity with intralipid in a patient with attention deficit hyperactivity disorder. Middle East J Anesthesiol. 2011;21:427–429.

[14] Aveline C, Cognet F, Bonnet F. Ineffectiveness of intralipid infusion for central nervous toxicity following ultrasound-guided sciatic nerve block with lidocaine-ropivacaine solution: interaction between carbamazepine, local anaesthetic and intralipid? Eur J Anaesthesiol. 2010;27:1070–1072.

[15] Bazerbachi F, Rank K, Chan A. Intravenous lipid rescue and ropivacaine systemic toxicity. J Anesth. 2014;28:139.

[16] Bilotta F, Titi L, Rosa G. Local anesthetic-induced complete atrioventricular block during awake craniotomy. J Neurosurg Anesthesiol. 2012;24:238.

[17] Buckenmaier ICC, Capacchione J, Mielke AR, et al. The effect of lipid emulsion infusion on postmortem ropivacaine concentrations in swine: endeavoring to comprehend a soldier's death. Anesth Analg. 2012;114:894–900.

[18] Calenda E, Dinescu SA. Failure of lipid emulsion to reverse neurotoxicity after an ultrasound-guided axillary block with ropivacaine and mepivacaine. J Anesth. 2009;23:472–473.

[19] Cave G, Harvey M, Willers J, et al. LIPAEMIC report: results of clinical use of intravenous lipid emulsion in drug toxicity reported to an online lipid registry. J Med Toxicol. 2014;10:133–142.

[20] Charbonneau H, Marcou TAP, Mazoit JX, et al. Early use of lipid emulsion to treat incipient mepivacaine intoxication. Reg Anesth Pain Med. 2009;34:277–278.

[21] Contargyris C, Bourgoin A, Guilhaumou R, et al. Local anesthetics toxicity during a post caesarian transverse abdominis plane block. Prat Anesth Reanim. 2012;16:308–310.

[22] Cordell CL, Schubkegel T, Light TR, et al. Lipid infusion rescue for bupivacaine-induced cardiac arrest after axillary block. J Hand Surg. 2010;35:144–146.

[23] Dacosta WP. Subcutaneous bupivacaine intoxication managed with lipid emulsion [Abstract]. Anestesia en Mexico. 2009;21:143–144.

[24] Diaz J, Bernasinski M, Malinovsky JM. Reversal of neurologic symptoms related to lidocaine toxicity with a lipid emulsion administration [French]. Ann Fr Anesth Reanim. 2012;31:647.

[25] Dix SK, Rosner GF, Nayar M, et al. Intractable cardiac arrest due to lidocaine toxicity successfully resuscitated with lipid emulsion. Crit Care Med. 2011;39:872–874.

[26] Egan T. Seizure post brachial plexus block in patient with remote history of seizures with non toxic dose of local anaesthetic [Abstract]. Reg Anesth Pain Med. 2013;38.

[27] Espinet AJ, Emmerton MT. The successful use of intralipid for treatment of local anesthetic-induced central nervous system

toxicity: some considerations for administration of intralipid in an emergency. Clin J Pain. 2009;25:808–809.
[28] Etesse B, Letouzey V, Roger C, et al. Epidural analgesia is not the only cause of peripartum central neurologic symptoms. Report of one case of posterior reversible encephalopathy syndrome [French]. Ann Fr Anesth Reanim. 2011;30:57–60.
[29] Fenten MGE, Rohrbach A, Wymenga AB, et al. Systemic local anesthetic toxicity after local infiltration analgesia following a polyethylene tibial insert exchange: a case report. Reg Anesth Pain Med. 2014;39:264–265.
[30] Foxall G, McCahon R, Lamb J, et al. Levobupivacaine-induced seizures and cardiovascular collapse treated with Intralipid®. Anaesthesia. 2007;62:516–518.
[31] French LK, Kusin S, Hendrickson RG. Pediatric lidocaine toxicity following intraosseous injection: a case series. Clin Toxicol (Phila). 2012;50:329–330.
[32] Fuzaylov G, Ying B, Tang Y, Sethna NF. Successful resuscitation after inadvertent intravenous injection of bupivacaine in an adolescent. Paediatr Anaesth. 2010;20:958–959.
[33] Gallagher C, Tan JM, Foster CG. Lipid rescue for bupivacaine toxicity during cardiovascular procedures. Heart Int. 2010;5:20–21.
[34] Gnaho A, Eyrieux S, Gentili M. Cardiac arrest during an ultrasound-guided sciatic nerve block combined with nerve stimulation. Reg Anesth Pain Med. 2009;34:278.
[35] Goyal R, Shukla RN, Kumar G, et al. Supraventricular tachycardia after an intercostal nerve block with bupivacaine treated with 10% intralipid. J Anaesthesiol Clin Pharmacol. 2011;27:564–565.
[36] Grenc D, Sarc L, Knafelj R, et al. Successful lipid emulsion treatment for generalized seizures and cardiac arrest following epidural lidocaine administration. Clin Toxicol (Phila). 2011;49:268.
[37] Hartley RA, Foster PN, Moore JA. Local anaesthetic toxicity with continuous local anaesthetic infusion following hepatic resection. Eur J Anaesthesiol. 2012;29:455–456.
[38] Harvey M, Cave G, Chanwai G, et al. Successful resuscitation from bupivacaine-induced cardiovascular collapse with intravenous lipid emulsion following femoral nerve block in an emergency department. EMA. 2011;23:209–214.
[39] Heavner J, Heavner M. Cardiac arrest following pleurodesis: lipid rescue for lidocaine overdose [Abstract]. Chest. 2012;142:291A.
[40] Hurley WT, Hanlon P. Lipid emulsion as an antidote at the Washington Poison Center; use in carbamazepine, flecanide, hydroxychloroquine, bupivacaine, and bupropion. Clin Toxicol (Phila). 2009;47:729–730.
[41] Jensen K, Borglum J. High volume nerve blocks and systemic toxicity of local anaesthetics. A case report [Abstract]. Reg Anesth Pain Med. 2011;36:E213.
[42] Landy C, Gagnon N, Boulland P, et al. Seizures associated with local anaesthetic intoxication. Br J Anaesth. 2012;109:463–464.
[43] Landy C, Schaeffer E, Raynaud L, et al. Convulsions after normal dose of lidocaine: a probable drug interaction. Br J Anaesth. 2012;108:701.
[44] Lange DB, Schwartz D, DaRoza G, et al. Use of intravenous lipid emulsion to reverse central nervous system toxicity of an iatrogenic local anesthetic overdose in a patient on peritoneal dialysis [Erratum appears in Ann Pharmacother 2013;47:139]. Ann Pharmacother. 2012;46:e37.
[45] Larson A, Stidham T, Banerji S, et al. Seizures and methemoglobinemia in an infant after excessive EMLA application. Pediatr Emerg Care. 2013;29:377–379.
[46] Levine M, Skolnik AB, Ruha AM, et al. Complications following antidotal use of intravenous lipid emulsion therapy. J Med Toxicol. 2014;10:10–14.
[47] Li J, Wardhan R. Local anesthetic systemic toxicity (LAST) in an ESKD patient upon receiving an axillary brachial plexus block along with blocks of the musculocutaneous & intercostobrachial nerves [Abstract]. Reg Anesth Pain Med. 2013;38:A218.
[48] Lin EP, Aronson LA. Successful resuscitation of bupivacaine-induced cardiotoxicity in a neonate. Paediatr Anaesth. 2010;20:955–957.
[49] Litz RJ, Popp M, Stehr SN, et al. Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. Anaesthesia. 2006;61:800–801.
[50] Litz RJ, Roessel T, Heller AR, et al. Reversal of central nervous system and cardiac toxicity after local anesthetic intoxication by lipid emulsion injection. Anesth Analg. 2008;106:1575–1577.
[51] Liu SK, Ou Yang HH, Chen KB, et al. Successful treatment of highly potential local anesthetic systemic toxicity by ''staged prevention strategy'' with intravenous lipid emulsion [Abstract]. Eur J Anaesth. 2012;29:129.
[52] Ludot H, Tharin JY, Belouadah M, et al. Successful resuscitation after ropivacaine and lidocaine-induced ventricular arrhythmia following posterior lumbar plexus block in a child. Anesth Analg. 2008;106:1572–1574.
[53] Markowitz S, Neal JM. Immediate lipid emulsion therapy in the successful treatment of bupivacaine systemic toxicity [Abstract]. Reg Anesth Pain Med. 2009;34:276–277.
[54] Marraffa JM, Stork CM. Delayed cardiovascular toxicity after inadvertent subcutaneous injection of bupivacaine successfully treated with intravenous fat emulsion. Clin Toxicol (Phila). 2013;51:652–653.
[55] Marwick PC, Levin AI, Coetzee AR. Recurrence of cardiotoxicity after lipid rescue from bupivacaine-induced cardiac arrest. Anesth Analg. 2009;108:1344–1346.
[56] Mazoit JX. Cardiac arrest and local anaesthetics. [French]. Presse Med. 2013;42:280–286.
[57] McCutchen T, Gerancher JC. Early intralipid therapy may have prevented bupivacaine-associated cardiac arrest. Reg Anesth Pain Med. 2008;33:178–180.
[58] Mizutani K, Oda Y, Sato H. Successful treatment of ropivacaine-induced central nervous system toxicity by use of lipid emulsion: effect on total and unbound plasma fractions. J Anesth. 2011;25:442–445.
[59] Nguyen VH, White JL. Further support for the early administration of lipid emulsion in the treatment of ropivacaine-induced central nervous system toxicity. J Anesth. 2012;26:479–480.
[60] Ogugua CS, Savel RH, Keene A, et al. Prevention of catastrophic outcomes in systemic bupivacaine toxicity: early recognition and aggressive management [Abstract]. Chest. 2009;136:38S–39S.
[61] Reddy JG, Lahm T. Intravenous lipid emulsion rescue for severe central nervous system local anesthetic toxicity [Abstract]. Chest. 2010;138:76A.
[62] Sakai T, Manabe W, Kamitani T, et al. Ropivacaine-induced late-onset systemic toxicity after transversus abdominis plane block under general anesthesia: successful reversal with 20% lipid emulsion. Masui. 2010;59:1502–1505.
[63] Schaeffer E, Rayaud L, Landy C, et al. Local anaesthetics intoxication, during ultrasound-guided axillary plexus block, treated by Intralipide®. Ann Fr Anesth Reanim. 2010;29:929–930.
[64] Schellhammer F, Milde A. Lipid rescue therapy of toxic effects from local anesthetics in interventional radiology. RöFo. 2011;183:73–74.
[65] Scherrer V, Compere V, Loisel C, et al. Cardiac arrest from local anesthetic toxicity after a field block and transversus abdominis plane block: a consequence of miscommunication between the anesthesiologist and surgeon. A A Case Rep. 2013;1:75–76.
[66] Schwarzkopf P, Ruffert H, Pracht K. Psoas compartment block: how to limit systemic side effects? [Abstract]. Reg Anesth Pain Med. 2011;36:E261.
[67] Shah S, Gopalakrishnan S, Apuya J, et al. Use of Intralipid in an infant with impending cardiovascular collapse due to local anesthetic toxicity. J Anesth. 2009;23:439–441.
[68] Shenoy U, Paul J, Antony D. Lipid resuscitation in pediatric patients – need for caution? Paediatr Anaesth. 2014;24:332–334.
[69] Shih YH, Chen CH, Wang YM, et al. Successful reversal of bupivacaine and lidocaine-induced severe junctional bradycardia by lipid emulsion following infraclavicular brachial plexus block in a uremic patient. Acta Anaesthesiol Taiwan. 2011;49:72–74.
[70] Smith HM, Jacob AK, Segura LG, et al. Simulation education in anesthesia training: a case report of successful resuscitation of bupivacaine-induced cardiac arrest linked to recent simulation training. Anesth Analg. 2008;106:1581–1584.
[71] Sonsino DH, Fischler M. Immediate intravenous lipid infusion in the successful resuscitation of ropivacaine-induced cardiac arrest after infraclavicular brachial plexus block. Reg Anesth Pain Med. 2009;34:276–277.

[72] Sorrenti D, Peverini M, Casalena S, et al. Late onset local anaesthetic systemic toxicity (last) after ENS guided axillary brachial plexus block with mepivacaine 1.5%: successful reversal with early 20% lipid emulsion therapy [Abstract]. Reg Anesth Pain Med. 2014;39:e260.
[73] Spence AG. Lipid reversal of central nervous system symptoms of bupivacaine toxicity. Anesthesiology. 2007;107:516–517.
[74] Sturini E, Saporito A, Tomasetti R, et al. Mepivacaine neurologic toxicity after an erroneous administration for intravenous regional anesthesia treated with lipid emulsion: new solutions for old mistakes [Abstract]. Reg Anesth Pain Med. 2010;35:E179–E180.
[75] Süzer MA, Özhan MO, Eşkin MB, et al. Local anesthetic toxicity managed successfully with lipid infusion (case report). Türk Anest Rean Der Dergisi. 2011;39:159–163.
[76] Ter Horst MT, Tjiang GCH, Luitwieler RL, et al. Antidote for intoxication due to local anesthetics: new application of fat emulsion for intravenous administration. Ned Tijdschr Geneeskd. 2010;154:1822–1825.
[77] Varela H, Bums SM. Use of lipid emulsions for treatment of local anesthetic toxicity: a case report. AANA J. 2010;78:359–364.
[78] Warren JA, Thoma RB, Georgescu A, et al. Intravenous lipid infusion in the successful resuscitation of local anesthetic-induced cardiovascular collapse after supraclavicular brachial plexus block. Anesth Analg. 2008;106:1578–1580.
[79] Whiteman DM, Kushins SI. Successful resuscitation with intralipid after marcaine overdose. Aesthet Surg J. 2014;34:738–740.
[80] Whiteside J. Reversal of local anaesthetic induced CNS toxicity with lipid emulsion Anaesthesia. 2008;63:203–204.
[81] Widfeldt N, Kolmodin L. CNS symptoms of ropivacaine in bloodless field disappeared with Intralipid. [Norwegian]. Lakartidningen. 2014;111:742–743.
[82] Wong GK, Joo DT, McDonnell C. Lipid resuscitation in a carnitine deficient child following intravascular migration of an epidural catheter. Anaesthesia. 2010;65:192–195.
[83] Zhurda T, Muzha D, Caushi GJ, et al. Usefulness of lipidic solution for the treatment of systemic toxicity related to bupivacaine injected in a sub-coracoid brachial plexus block. [French]. Ann Fr Anesth Reanim. 2010;29:592–593.
[84] Zimmer C, Piepenbrink K, Riest G, et al. Cardiotoxic and neurotoxic effects after accidental intravascular bupivacaine administration. Therapy with lidocaine propofol and lipid emulsion [German]. Anaesthesist. 2007;56:449–453.
[85] Bonfim MR, De Simone Melo M, Dreyer E, et al. Lipid therapy with two agents in ropivacaine-induced toxicity: experimental study in swine. Rev Bras Anestesiol. 2012;62:685–695.
[86] Bushey BA, Auld VH, Volk JE, et al. Combined lipid emulsion and ACLS resuscitation following bupivacaine- and hypoxia-Induced cardiovascular collapse in unanesthetized swine. AANA J. 2011;79:129–138.
[87] Candela D, Louart G, Bousquet PJ, et al. Reversal of bupivacaine-induced cardiac electrophysiologic changes by two lipid emulsions in anesthetized and mechanically ventilated piglets. Anesth Analg. 2010;110:1473–1479.
[88] De Queiroz M, Rhondali O, Leveneur O, et al. Resuscitation with lipid or with epinephrine in levobupivacaine-induced cardiac toxicity in piglets. Br J Anaesth. 2012;108:ii292–ii293.
[89] de Queiroz Siqueira M, Chassard D, Musard H, et al. Resuscitation with lipid, epinephrine, or both in levobupivacaine-induced cardiac toxicity in newborn piglets. Br J Anaesth. 2014;112:729–734.
[90] de Simone Melo M, Bonfm MR, Dreyer E, et al. Hemodynamic changes in lipid emulsion therapy (SMOFlipid) for bupivacaine toxicity in swines. Acta Cir Bras. 2012;27:318–324.
[91] Di Gregorio G, Kessler C, Weinberg G. Lipid emulsion in treatment of sodium channel blocker overdose. Ann Emerg Med. 2008;51:489.
[92] Di Gregorio G, Schwartz D, Ripper R, et al. Lipid emulsion is superior to vasopressin in a rodent model of resuscitation from toxin-induced cardiac arrest [Erratum appears in Crit Care Med 2009;37:2329]. Crit Care Med. 2009;37:993–999.
[93] Fettiplace MR, Akpa BS, Ripper R, et al. Resuscitation with lipid emulsion: dose dependent recovery from cardiac pharmaco toxicity requires a cardiotonic effect. Anesthesiology. 2014;120:915–925.
[94] Fettiplace MR, Ripper R, Lis K, et al. Intraosseous lipid emulsion: an effective alternative to IV delivery in emergency situations. Crit Care Med. 2014;42:e157–e160.
[95] Gokahmetoglu G, Aksu R, Bicer C, et al. The effect of levosimendan combined with 20% lipid emulsion treatment on survival from bupivacaine induced toxicity in experiment. Bratisl Lek Listy. 2014;115:275–279.
[96] Hicks SD, Salcido DD, Logue ES, et al. Lipid emulsion combined with epinephrine and vasopressin does not improve survival in a swine model of bupivacaine-induced cardiac arrest. Anesthesiology. 2009;111:138–146.
[97] Hiller DB, Gregorio GD, Ripper R, et al. Epinephrine impairs lipid resuscitation from bupivacaine overdose: a threshold effect. Anesthesiology. 2009;111:498–505.
[98] Karci A, Aykac Ibisoglu A, Oransay K, et al. The effects of lipid treatment on levobupivacaine induced cardiotoxicity in rats [Abstract]. Eur J Anaesthesiol. 2009;26:108.
[99] Karcioğlu M, Tuzcu K, Sefil F, et al. Efficacy of resuscitation with intralipid in a levobupivacaine-induced cardiac arrest model. Turk J Med Sci. 2014;44:330–336.
[100] Li Z, Xia Y, Dong X, et al. Lipid resuscitation of bupivacaine toxicity: long-chain triglyceride emulsion provides benefits over long-and medium-chain triglyceride emulsion. Anesthesiology. 2011;115:1219–1228.
[101] Litonius ES, Niiya T, Neuvonen PJ, et al. Intravenous lipid emulsion only minimally influences bupivacaine and mepivacaine distribution in plasma and does not enhance recovery from intoxication in pigs. Anesth Analg. 2012;114:901–906.
[102] Mauch J, Jurado OM, Spielmann N, et al. Resuscitation strategies from bupivacaine-induced cardiac arrest. Paediatr Anaesth. 2012;22:124–129.
[103] Mauch J, Martin Jurado O, Spielmann N, et al. Comparison of epinephrine vs lipid rescue to treat severe local anesthetic toxicity – an experimental study in piglets. Paediatr Anaesth. 2011;21:1103–1108.
[104] Mauch JY, Martin-Jurado O, Spielmann N, et al. Comparison of four different rescue regimens to treat cardiac arrest due to bupivacaine intoxication – An experimental study in neonatal pig [Abstract]. Eur J Anaesthesiol. 2011;28:118.
[105] Mayr VD, Mitterschiffthaler L, Neurauter A, et al. A comparison of the combination of epinephrine and vasopressin with lipid emulsion in a porcine model of asphyxial cardiac arrest after intravenous injection of bupivacaine. Anesth Analg. 2008;106:1566–1571.
[106] Shi K, Xia Y, Wang Q, et al. The effect of lipid emulsion on pharmacokinetics and tissue distribution of bupivacaine in rats. Anesth Analg. 2013;116:804–809.
[107] Wat CY, Yuen MK, Li RWS, et al. Lipid emulsion infusion vs standard cardiac resuscitation in management of ropivacaine cardiac toxicity in pigs. Anaesth Intensive Care. 2009;37:661–662.
[108] Weinberg G, Paisanthasan C, Feinstein D, et al. The effect of bupivacaine on myocardial tissue hypoxia and acidosis during ventricular fibrillation. Anesth Analg. 2004;98:790–795.
[109] Weinberg G, Ripper R, Feinstein DL, et al. Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. Reg Anesth Pain Med. 2003;28:198–202.
[110] Weinberg GL, Di Gregorio G, Ripper R, et al. Resuscitation with lipid versus epinephrine in a rat model of bupivacaine overdose. Anesthesiology. 2008;108:907–913.
[111] Yan J, Shen Y, Li B, et al. Association of sustained cardiovascular recovery with epinephrine in the delayed lipid-based resuscitation from cardiac arrest induced by bupivacaine overdose in rats. Br J Anaesth. 2012;108:857–863.
[112] Yoshimoto M, Horiguchi T, Nishikawa T. Efficacy of lipid resuscitation in cardiac arrest induced by bupivacaine-glucose mixture in rats. Eur J Anaesthesiol. 2014;31:210.
[113] Callejo D, Sevilla R, Gonzalez J, et al. Analysis of the temporal regression of the QRS widening induced by bupivacaine after intralipid administration: study in an experimental porcine model. Eur J Anaesthesiol. 2014;31:65.

[114] Cave G, Harvey M, Prince G, et al. Effect of hypertonic saline on electrocardiography QRS duration in rabbit model of bupivacaine toxicity resuscitated by intravenous lipid. Anaesthesia. 2010;65:792–798.
[115] Weinberg GL, VadeBoncouer T, Ramaraju GA, et al. Pretreatment or resuscitation with a lipid infusion shifts the dose – response to bupivacaine-induced asystole in rats. Anesthesiology. 1998;88:1071–1075.
[116] Harvey M, Cave G, Prince G, et al. Epinephrine injection in lipid-based resuscitation from bupivacaine-induced cardiac arrest: transient circulatory return in rabbits. Anesth Analg. 2010;111:791–796.
[117] Partownavid P, Umar S, Li J, et al. Fatty-acid oxidation and calcium homeostasis are involved in the rescue of bupivacaine-induced cardiotoxicity by lipid emulsion in rats. Crit Care Med. 2012;40:2431–2437.
[118] Partownavid P, Umar S, Rahman S, et al. Intralipid rescue of bupivacaine-induced cardiotoxicity was abolished by fatty acid oxidation inhibitor CVT-4325 [Abstract]. Circulation. 2010;122.
[119] Partownavid P, Umar S, Rahman S, et al. Intralipid fails to rescue bupivacaine-induced cardiotoxicity in the presence of the opioid antagonist naloxone [Abstract]. Circulation. 2012;126.
[120] Yoshimoto M, Horiguchi T, Nishikawa T, et al. Comparative effects of lipid emulsion on the recovery from levobupivacaine-induced or from ropivacaine-induced cardiac arrest in rats. Br J Anaesth. 2012;108:ii105–ii106.
[121] O'Brien TQ, Clark-Price SC, Evans EE, et al. Infusion of a lipid emulsion to treat lidocaine intoxication in a cat. J Am Vet Med Ass. 2010;237:1455–1458.
[122] Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64:401–406.
[123] Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence – imprecision. J Clin Epidemiol. 2011;64:1283–1293.
[124] Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence–indirectness. J Clin Epidemiol. 2011;64:1303–1310.
[125] Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence – inconsistency. J Clin Epidemiol. 2011;64:1294–1302.
[126] Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence – publication bias. J Clin Epidemiol. 2011;64:1277–1282.
[127] Guyatt GH, Oxman AD, Sultan S, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64:1311–1316.
[128] Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence – study limitations (risk of bias). J Clin Epidemiol. 2011;64:407–415.
[129] Chem Spider Search and Share Chemistry. 2015 [cited 2015 July 23]. Available from: http://www.chemspider.com.

Appendix

Medline (ovid) search strategy for lipid emulsion therapy effect

(1) exp Fat Emulsions, Intravenous/
(2) lipid rescue.ti,ab,kw.
(3) (lipid adj3 emulsi*) .mp.
(4) (fat adj3 emulsi*) .mp.
(5) ((lipid or fat*) adj5 bolus) .mp.
(6) (lipid adj3 (resuscitat* or therap* or infus*)) .mp.
(7) (ILE adj5 (lipid* or emulsi* or fat*)) .mp.
(8) (IFE adj5 (lipid* or emulsi* or fat*)) .mp.
(9) (lipid adj3 sink*) .mp.
(10) (lipid adj3 sequest*) .mp.
(11) intravenous* lipid* .ti,ab,kw.
(12) intralipid*.mp.
(13) or/1-12
(14) exp Cardiovascular Agents/
(15) exp Sodium Channel Blockers/
(16) exp Calcium Channel Blockers/
(17) exp Adrenergic beta-Antagonists/
(18) ((sodium or Na*) adj3 channel block*) .ti,ab,kw.
(19) ((calcium or Ca*) adj3 channel block*) .ti,ab,kw.
(20) (beta adj3 block*) .ti,ab,kw.
(21) B-blocker.ti,ab,kw.
(22) exp Central Nervous System Depressants/
(23) exp Psychotropic Drugs/
(24) exp Anti-Arrhythmia Agents/
(25) local an?esthetic*.mp.
(26) exp Amitriptyline/
(27) amitriptyline.mp.
(28) exp Bupropion/
(29) bupropion.mp.
(30) exp Chloroquine/
(31) chloroquine.mp.
(32) chlorpromazine.mp.
(33) clomipramine.mp.
(34) cocaine.mp.
(35) exp Dothiepin/
(36) (dosulepin or dothiepin) .mp.
(37) glyphosate.mp.
(38) haloperidol.mp.
(39) lamotrigine.mp.
(40) olanzapine.mp.
(41) propofol.mp.
(42) quetiapine.mp.
(43) exp Sertraline/
(44) sertraline.ti,ab,kw.
(45) zopiclone.mp.
(46) ropivacaine.mp.
(47) levobupivacaine.mp.
(48) lignocaine.mp.
(49) diazepam.mp.
(50) exp Carnitine/
(51) carnitine.ti,ab,kw.
(52) exp Poisoning/
(53) poison* .ti,ab,kw.
(54) exp Noxae/ae, po [Adverse Effects, Poisoning]
(55) po.fs.
(56) ae.fs.
(57) to.fs.
(58) exp Street Drugs/
(59) (lipophilic adj3 (drug* or toxin*)) .ti,ab,kw.
(60) overdos* .ti,ab,kw.
(61) exp Antidotes/
(62) antidote* .ti,ab,kw.
(63) (toxic* or intoxic* or pharmacotoxic*) .ti,ab,kw.
(64) Resuscitation/
(65) resuscitat* .ti,ab,kw.
(66) or/14-65
(67) 13 and 66