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

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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 lipid emulsion workgroup was therefore established by the American Academy of Clinical Toxicology to review the evidence on the efficacy of ILE for LA toxicity.

Methods: We performed a systematic review of the literature published through December 15th 2014. Relevant articles were determined based on predefined 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, 75 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 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, 3 observational studies, 5 case series and one case report; bupivacaine was used in 29 of these reports (76%). Of 14 controlled experiments in animals, 8 showed improved survival or time to return of spontaneous circulation and 5 no benefit of ILE versus saline or non-ILE treatments. Combining ILE with epinephrine improved survival in 5 of the 6 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.

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 has been reported by previous reviews to consist primarily of human case reports and controlled animal experiments that cannot necessarily be extrapolated to human clinical settings.(5-8)

The American Academy of Clinical Toxicology (AACT) therefore created a Lipid Emulsion 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 American Academy of Clinical Toxicology 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 at Appendix 1. 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 December 15th 2014.

In addition, conference abstracts from the European Association for Poison Centres 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 has been 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, 75 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 120mL of 20% ILE or of 0.9% saline, administered two minutes 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 (Cmax) 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 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 Cmax and a 20% increase in volume of distribution of the LA at a comparable mean dose, were not statistically significant and disappeared after 45 minutes.(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 msec 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.

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 8 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/hr (range 0.015-6.0 g/kg/hr). Overall, the total volume of lipid emulsion administered ranged from 9 mL to 2,480 mL (Table 1). The bolus dose in infants up to the age of one year was 1-2 mg/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 (24%) cases 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%)(40) (Table 1).

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 4 (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 6 (7%) cases before other treatment, and in 16 (19%) cases lipid emulsion was used concomitantly. The sequence of treatment was not reported in 3 (4%) cases (Table 1).

Other treatments used included benzodiazepines or other sedatives (n=41; 49%), vasopressors (n=29; 35%), sodium bicarbonate (n=7; 8%), antiarrhythmic 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 3 (4%) cases the patient was already intubated when features of LA toxicity appeared. Oxygen supply by mask was initiated in 9 cases (11%). Cardiac defibrillation was reported in 4 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), 3 (8%) were observational studies (1 study on pigs, 1 on rats, 1 on rabbits)(113-115), 5 (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 studied the 38 studies 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 (58%) studies. In three (8%) studies an infusion was used without an initial bolus. The median bolus dose was 0.80 g/kg or 4mL/kg of 20% ILE (range 0.20-3.0 g/kg) and median infusion dose was 6.0 g/kg/hr (range 0.60-54 g/kg/hr). In 22 (58%) studies, 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 vs. 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 effects 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 effect 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 vs. LA induced venticular fibrillation); this study was therefore considered not useful for evaluating the effect 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 given over 10 seconds or 4-30 mg/kg (Table 3). Levobupivacaine was used in four studies (14%),(88,89, 98,99) with a dose of 500 mg/hr (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).

Resuscitation treatments were generally initiated immediately or within three minutes 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 three minutes (2 studies),(97, 105) four minutes (1 study),(86) 10 minutes (2 studies), (109, 111) or 20 minutes (1 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 vs. 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 two minutes 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.(113) (Table 3)

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 minutes 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 4 of these 5 studies,(116-119) and levobupivacaine and ropivacaine were used in the other study each at a dose of 2 mg/kg/hr.(120) Intravenous lipid emulsion was initiated immediately or up to one minute 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 2 human controlled studies reporting the effect 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, 6 studies favoring vasopressors and 7 studies favoring the combination of vasopressors and ILE. These studies are too heterogenous 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 8 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 heterogenous and the formulation of ILE was not reported in one publication. Finally, two studies demonstrated 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 efficacy of the intervention. As stated in the

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 because of likely reporting and publication bias . In most 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.

Our inability to deliver some of the results as intended in the 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 ~~reported~~ 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 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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Conflict of interest

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).

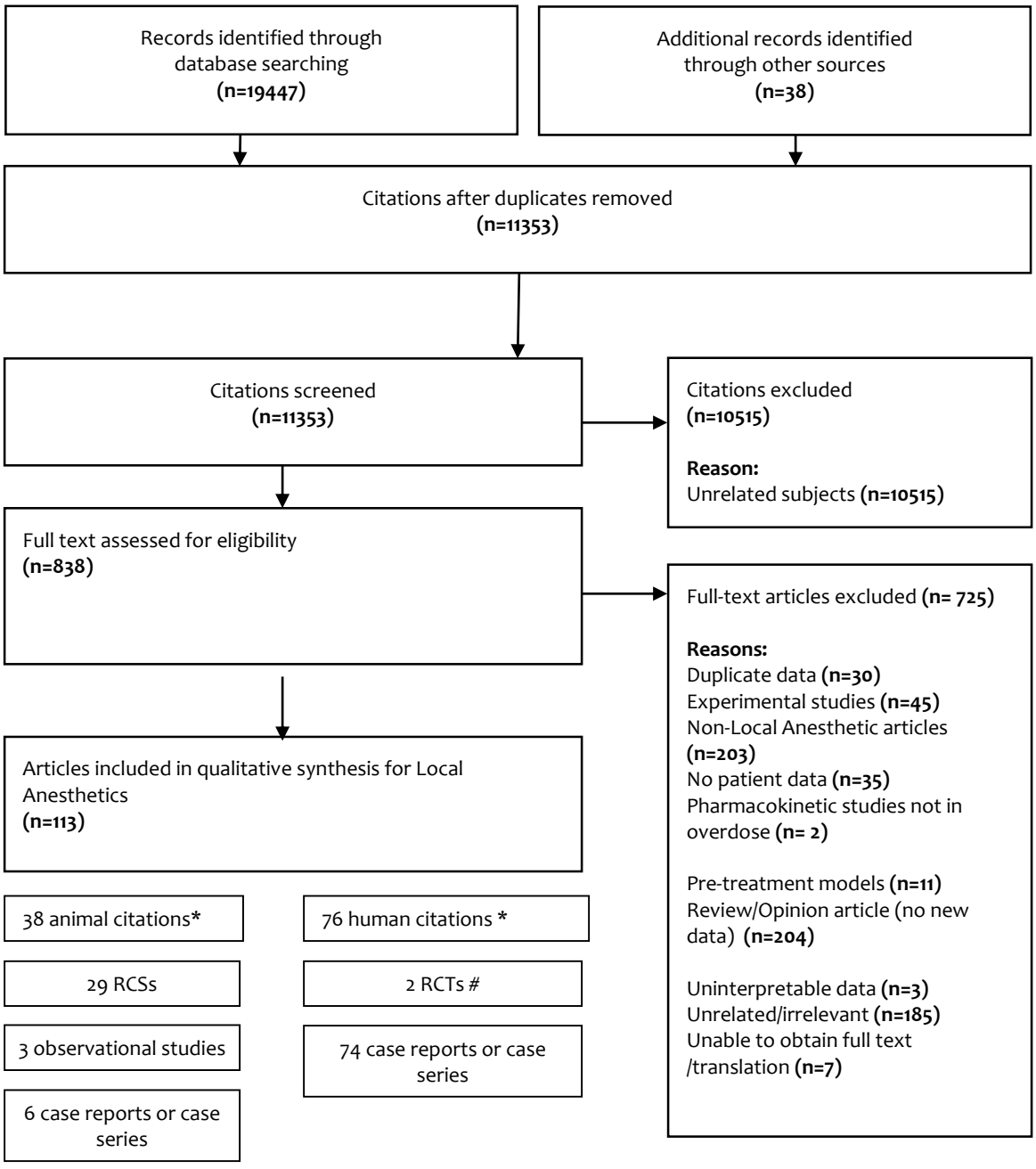
Appendix 1: Medline (ovid) search strategy for lipid emulsion therapy effect

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

Figure 1: Selection of articles flow diagram

Search date December 15th 2014.



*one citation included both one animal study and one human case report. # The two citations covers one single study.

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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.

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.
#: The total dose in g/kg was infrequently available, and could only be calculated if bodyweight was reported.
¤: Available as abstracts only at the time of writing.

Reference	Study type	Age/sex, weight	Local anesthetic and dose	Log D (129)	Route of administration	Symptoms	ILE used	ILE dose#	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
RCT												
Dureau 2014/R010+R011 (10, 11) ¤	RCT, cross-over	Age 18-40 y/8F+8M	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 (parasthesia, 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 vs control groups ., (75.7 =/- 29.1 mg vs 81.7 =/-22.3 mg for ropivacaine and 69.4 =/- 26.2 mg vs 80.8 =/- 31.7 mg for levobupivacaine
Case reports/series												
AdMani, 2010 (12)	Case report	3 mth/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/hr)	No	Dexamethasone 2mg, hydrocortisone 20mg, thiopental 5mg Mechanical ventilation	Probably no effect required benzodiapine after seizures restarted in ICU	Survival, no sequelae
Al-Alami, 2011 (13)	Case report	16 y/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/hr in 3 hrs	No	Midazolam 0.5 mg	ILE was safe and successful in reversing LA-induced early CNS and cardiac abnormalities	Survival, no sequelae
Aveline, 2010 (14)	Case report	52 y/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) x2 bolus	No	Midazolam 3mg, thiopental 300mg and suxamethonium 80mg Intubation	ILE not effective	Survival, no sequelae

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Reference	Study type	Age/sex, weight	Local anesthetic and dose	Log D (129)	Route of administration	Symptoms	ILE used	ILE dose#	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Bazerbachi, 2013 (15)	Case report	57 y/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, 2012 (16)	Case report	53 y/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, 2012 (17)	Case report	29 y/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 x3 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, 2009 (18)	Case report	72 y/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 (1st seizure); Thiopental 125 mg (2nd seizure) Mechanical ventilation	ILE not effective in stopping 2nd seizure	Survival, no sequelae
Cave, 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
Cave, 2014 (Lipid Registry) (19)	Case series, No 2	67 y/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/hr) in 20 min. Total dose 500 mL (2.04 g/kg)	No	Midazolam	ILE was thought to have prevented death	Survival, sequelae NR
Cave, 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, 2014 (Lipid Registry)(19)	Case series, No 4	68 y/M, 75 kg	Ropivacaine 200 mg	4.21	Nerve block	Seizure Cardiac arrest	20%, Intralipid	100 mL (0.27 g/kg) x3 bolus. Total dose 300 mL (0.80 g/kg)	No	Midazolam, epinephrine, sodium bicarbonate, magnesium, and hydrocortisone	NR	Survival, sequelae NR
Cave, 2014 (Lipid Registry) (19)	Case series, No 5	69 y/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/hr (1.0 g/kg/hr). Total dose 500 mL (1.25 g/kg)	NR	NR	ILE was thought to have prevented death	Survival, sequelae NR

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Reference	Study type	Age/sex, weight	Local anesthetic and dose	Log D (129)	Route of administration	Symptoms	ILE used	ILE dose#	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Cave, 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, 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, 2014 (Lipid Registry) (19)	Case series, No 8	30 y/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/hr) Total dose 640 mL 1.58 g/kg)	NR	NR	ILE was thought to have prevented death	Survival, sequelae NR
Cave, 2014 (Lipid Registry) (19)	Case series, No 9	47 y/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/hr) Total dose 900 mL (3.0 g/kg)	NR	NR	NR	Survival, sequelae NR
Cave, 2014 (Lipid Registry) (19)	Case series, No 10	75 y/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/hr (3.05 g/kg/hr) Total dose 587 mL 1.95 g/kg)	NR	NR	NR	Survival, sequelae NR
Charbonneau, 2009 (20)	Case report	19 y/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, 2012 (21)	Case report	26 y/F, 34w 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, 2010 (22)	Case report	17 y/F, weight NR	Bupivacaine 75 mg	2.68	Nerve block	Seizure Tachycardia (180/min)	20%, brand NR	100 mL x3 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) ¤	Case report	44 y/F, 104 kg	Lidocaine 150 mg Bupivacaine 200 mg	1.26 2.68	Nerve block	Metalic taste Sinus bradycardia (34/min), hypotension (80/45 mmHg)	NR	100 ml in 10 min.	No	Atropine 2mg, ephedrine 5 mg, saline 500 ml	Resolution of cardiac symptoms in 15 min.	Survival, no sequelae
Diaz, 2012 (24)	Case report	Adult/F, 75 kg	Levobupivicaine 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/hr) in 2 hrs	No	Phenylephrine, ondansetron 4 mg, sufentanil 20.5 mcg, clonidine 138 mcg	Resolution of cardiac and neurologic symptoms	Survival, no sequelae

Reference	Study type	Age/sex, weight	Local anesthetic and dose	Log D (129)	Route of administration	Symptoms	ILE used	ILE dose#	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Dix, 2011 (25)	Case report	57 y/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) ¤	Case report	38 y/F, 62 kg	Ropivacaine 100 mg, Lidocaine 200 mg	4.21 2.26	Nerve block	Grand mal seizures 1 minutes post injection Coma	20% Intralipid	100 mL (0.32 g/kg) bolus then 0.25 mg/kg/hr infusion, duration NR	No	Midazolam >2 mg Intubation	Resolution of seizure unclear timing Resolution of coma 30 minutes later	Survival, no sequelae
Espinet, 2009 (27)	Case report	36 y/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 180/110mmHg, ST depression	20 %, Intralipid	100 mL (0.25 g/kg) x2 bolus then 100 mL (0.25 g/kg/hr) in 1 hour	No	Crystalloid (Hartmann's solution) 1 L Oxygen	Resolution of cardiac and neurologic symptoms	Survival, no sequelae
Etesse, 2011 (28)	Case report	23 y/F, 38w 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 2mg, magnesium sulfate 1 g in 20 min and then 1 g/hr Oxygen	Resolution of neurologic symptoms	Survival, no sequelae
Fenten 2014 (29)	Case report	67 y/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 hr after	Survival, no sequelae
Foxall, 2007 (30)	Case report	75 y/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, 2012 (31) ¤	Case report	11 mth/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, 2010 (32)	Case report	13 y/F, 50 kg	Bupivacaine 25 mg	2.68	Intravenous	Decreased BP (from 90 to 60mmHg) and broad complex ventricular tachycardia	20%, Intralipid	100 mL (0.4 g/kg) bolus	No	Saline 500 mL. Epinephrine 10 mcg x2 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

Reference	Study type	Age/sex, weight	Local anesthetic and dose	Log D (129)	Route of administration	Symptoms	ILE used	ILE dose#	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Gallagher, 2010 (33)	Case report	28 y/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 reportd)	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, 2009 (34)	Case report	82 y/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, 2011 (35)	Case report	26 y/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, 2011 (36) ¤	Case report	84 y/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 x2 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, 2012 (37)	Case report	46 y/F, 46 kg	Bupivacaine 37.5 mg + 18.75 mg/hr, 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, 2011 (38)	Case report	69 y/F, 80 kg	Lidocaine 50 mg, Bupivacaine 150 mg	1.26	Nerve block	Unresponsiveness, GCS 3 Seizure HR 50/min, AV block, BP 51/29mmHg	20%, Intralipid	100 mL (0.25 g/kg) bolus then 400 mL 1.33 g/kg/hr) 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, 2012 (39) ¤	Case report	60 y/F, weight NR	Lidocaine 1500 mg	1.26	Intrapleural	Seizure Cardiac arrest	20%, brand NR	500 mL bolus then 50 mL/hr	No	Unspecified conventional therapy	Resolution of cardiac symptoms	Survival, no sequelae
Hurley 2009 (40) ¤	Case report	54 y/M, weight NR	Bupivacaine, dose NR	2.68	NR	Cardiac arrest Asystoly	NR	NR	NR	NR	Resolution of toxicity within a few minutes	Survival , no sequelae
Jensen, 2011 (41) ¤	Case report	41 y/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, 2012 (p.463) (42)	Case report	59 y/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, 2012 (p.701)(43)	Case report	74 y/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
Lange, 2012 (44)	Case report	31 y/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

Reference	Study type	Age/sex, weight	Local anesthetic and dose	Log D (129)	Route of administration	Symptoms	ILE used	ILE dose#	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Larson, 2013 (45)	Case report	4 month/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, 2014(46)	Case report	20 y/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 hours	Yes	NR	NR	Survival, increased lipase 185 IU/L suggesting pancreatitis, resolved after 14 days
Li 2013 (47) ¤	Case report	57 y/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, 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, 2006 (49)	Case report	84 y/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/hr) Total dose 200 mL (0.8 g/kg)	No	Thiopental 150 mg, epinephrine 3x 1 mg Intubation, CPR	Resolution of cardiac symptoms	Survival, no sequelae
Litz, 2008 (50)	Case report	91 y/M, 57 kg	Mepivacaine 300 mg, Prilocaine 100 mg	1.40 1.33	Nerve block	Dizziness, agitation and developed unresponsiveness Bigemeny and PVCs	20%, Intralipid	100 mL (0.35 g/kg) bolus then 0.25 mL/kg/min (3 g/kg/hr) Total dose 200 mL (0.70 g/kg)	No	Dolastrone 12.5 mg	Resolution of cardiac and neurologic symptoms	Survival, no sequelae
Liu, 2012 (51) ¤	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 hrs	Yes	NR	Unclear if any symptoms developed or were reversed	Survival, sequelae NR
Ludot, 2008 (52)	Case report	13 y/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, 2009 (53)	Case report	17 y/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

Reference	Study type	Age/sex, weight	Local anesthetic and dose	Log D (129)	Route of administration	Symptoms	ILE used	ILE dose#	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Marraffa, 2013 (54) ¤	Case report	66 y/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 x2 bolus	No	Hydromorphone 60 mg with the LA. Bicarbonate empirically given, dopamine. Naloxone 0.4mg x2, icepacks were applied every 2 hr at the injection site, lorazepam 0.2 mg Intubation	Resolution of cardiac symptoms	Survival, no sequelae
Marwick, 2009 (55)	Case report	33 y/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/hr) 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 y/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, 2008 (57)	Case report	82 y/F, weight NR	Bupivacaine 150 mg	2.68	Nerve block	Seizures x2 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, 2011 (58)	Case report	24 y/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, 2012 (59)	Case report	19 y/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 x2 Oxygen	Resolution of neurologic symptoms	Survival, no sequelae
Ogugua, 2009(60) ¤	Case report	47 y/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, 2010 (61) ¤	Case report	59 y/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

Reference	Study type	Age/sex, weight	Local anesthetic and dose	Log D (129)	Route of administration	Symptoms	ILE used	ILE dose#	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Rosenblatt, 2006 (1)	Case report	58 y/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/hr) 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, 2010 (62)	Case report	40 y/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	5x 10 ml (0.25 g/kg) bolus, then 100 ml (0.5 g/kg) in 50 min., then 20 ml/hr (0.1 g/kg/hr). Total dose 230 ml	No	Etilefrine (dose NR), diazepam 5 mg	Resolution of symptoms	Survival, no sequelae
Schaeffer, 2010 (63)	Case report	74 y/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 2011 (64)	Case report	54 y/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 2013 (65) ¤	Case report	25 y/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, 2011 (66) ¤	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, 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 x2, albumin 5% 20 mL. Mechanical ventilation during general anesthesia	Resolution of cardiac symptoms	Survival, no sequelae
Shenoy, 2014 (68)	Case report	3 y/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/hr (2.73 g/kg/hr) 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

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Reference	Study type	Age/sex, weight	Local anesthetic and dose	Log D (129)	Route of administration	Symptoms	ILE used	ILE dose#	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Shih, 2011 (69)	Case report	69 y/F, 48.5 kg	Lidocaine 225 mg, Bupivacaine 37.5 mg	1.26 2.68	Nerve block	Bradycardia, reduced blood pressure Obtuned, unable to fully arouse	20%, Lipovenoes	50 mL (0.21 g/kg) bolus	No	Atropine 0.5 mg x3, ephedrine 10 mg	Resolution of cardiac and neurologic symptoms	Survival, no sequelae
Smith, 2008 (70)	Case report	83 y/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/hr)	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 of effect is related to ILE	Survival, no sequelae
Sonsino, 2009 (71)	Case report	92 y/F, weight NR	Ropivacaine 150 mg	4.21	Nerve block	Generalized tonic-clonic seizure x1 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 2014 (72) ¤	Case report	46 y/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 y/F, 38w 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) x2 bolus	No	General anesthesia for delivery Neonatal intubation	Resolution of neurologic symptoms	Survival, no sequelae
Sturini, 2010 (74) ¤	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 2011 (75)	Case report	71 y/M, 78 kg	Bupivacaine 50 mg, Lidocaine 200 mg	2.68 1.26	Nerve block	Loss of consciousness, dyspnea, hypotension 65/40 mmHg, ventricular extrasystoles, tachycardia 140 bpm, seizures	20% Intralipid	0.5 mL/kg/min (6.0 g/kg/hr) 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, 2010 (76)	Case report	27 y/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 hrs	No	Midazolam 5 mg x2. Mechanical ventilation until resolution of respiratory symptoms	Rapid beneficial effect on neurologic symptoms	Survival, no sequelae
Varela, 2010 (77)	Case report	83 y/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/hr) x2 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, 2008 (78)	Case report	60 y/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/hr) infusion in 30 min	No	Sodium bicarbonate 8.4% 100 mL, atropine 1 mg, epinephrine 1 mg x3, vasopressin 40U, magnesium sulfate 6 g CPR, defibrillation x11	Longer intervals of sustained cardiac rythm during defibrillation	Survival, no sequelae

Reference	Study type	Age/sex, weight	Local anesthetic and dose	Log D (129)	Route of administration	Symptoms	ILE used	ILE dose#	ILE only used	Other treatments received, dose included if reported	ILE effect	Outcome
Whiteman 2014 (79)	Case report	32 y/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/hr) for 60 min	No	Unspecified medical therapy, cardiac defibrillation x2, surgery with evacuation of 60 mL fluid from the right rectus sheath CPR	ROSC and normocardia after 45 min. Resolution of cardiac arrythmia 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 2014 (81)	Case report	62 y/F, weight NR	Ropivacaine 150 mg	4.21	Nerve block	Unconsciousness, nystagmus, muscle twitching	20%, Intralipid	100 mL (1.5 mL/kg) x2 bolus – 10 min interval, then 50 mL/hr for 10 hrs	No	Diazepam, few doses (specific dose NR)	Resolution of neurologic symptoms	Survival , no sequelae
Wong, 2010 (82)	Case report	6 y/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
Zhurda, 2010 (83)	Case report	78 y/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 75/35mmHg	20%, Intralipid	60 mL (0.19 g/kg) bolus	No	Midazolam 3 mg, atropine Oxygen	Resolution of cardiac symptoms	Survival, no sequelae
Zimmer, 2007 (84)	Case report	84 y/F, 53 kg	Bupivacaine 43 mg	2.68	Nerve block	Agitation, confusion, restless. Seizure. Supraventicular 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/hr (0.1 g/kg/hr)	No	Clonidin 150 mcg, midazolam 5 mg, lidocain 100 mg, propofol 1% 50 mg x2	Resolution of cardiac and neurologic symptoms	Survival, no sequelae

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**	8	Mepivacaine/Prilocaine	1
Bupivacaine	26	Mepivacaine/Ropivacaine	3
Mepivacaine	4	Lidocaine**/Ropivacaine	5
Ropivacaine	33*	Lidocaine**/Levobupivacaine	1
Levobupivacaine	18*	Lidocaine**/Prilocaine	1
		Bupivacaine/Lidocaine**	9
		Bupivacaine/Mepivacaine	3
		Bupivacaine/Ropivacaine	2
		Bupivacaine/Prilocaine	1

*The 16 volunteers received ropivacaine and levobupivacaine on each occasion, both are included in the table.

**Note: Lidocaine and lignocaine are synonyms : lidocaine is used in the table.

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

* Drugs used for general anesthesia or euthanasia are not included.
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, PmO2: 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.
#: The bolus dose in g/kg and infusion dose in g/kg/hronly be calculated if lipid concentration was reported.
¤: Available as abstracts at the time of writing.

Reference (Species)	Model	Local anesthetic (dose)	Log D (129)	Symptoms	ILE used	ILE bolus #	ILE infusion #	Study arms	Timing of rescue, time from LA termination	Other treatments received *	Parameter measured	Outcome	Support therapeutic effect of ILE alone
RCS													
Bonfim, 2012 (85) (Pig)	RCS; compared LCT and MCT/LCT	Ropivacaine (7 mg/kg in 30 sec)	4.21	Decrease in mean arterial pressure	20%, Lipovenos MCT and Lipovenos	4 mL/kg (0.8 g/kg)	No	MCT/LCT ILE vs LCT ILE vs 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, 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 vs No ILE	LA and study treatment were dosed simultaneously	Saline 1-2 mL/kg/hr	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, 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/hr) for 10 min	ILE vs 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, 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. Haemodynamics: 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/hr)	(MCT/LCT and LCT) ILE+Saline vs Saline	Study treatment at 30 sec.	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

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Reference (Species)	Model	Local anesthetic (dose)	Log D (129)	Symptoms	ILE used	ILE bolus #	ILE infusion #	Study arms	Timing of rescue, time from LA termination	Other treatments received *	Parameter measured	Outcome	Support therapeutic effect of ILE alone
De Queiroz, 2012 (88) ¤ (Pig)	RCS; resuscitation model	Levobupivacaine (500 mg/hr until symptoms)	2.68	MAP decrease by 50% for 15 sec	20%, brand NR	4 mL/kg (0.8 g/kg)	0.25 mL/kg/min (3 g/kg/hr)	ILE vs ILE+EPI vs EPI vs Control (no additional drugs)	NR	EPI 10mg/kg every 3min	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, 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/hr)	ILE vs EPI vs ILE+EPI vs Saline	Std CPR immediately, then study treatment	Std CPR (chest compressions and manual ventilation)	Time to ROSC in survivors: ILE 460 sec, EPI 296 sec, ILE+EPI 304 sec, Saline 720 sec 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, 2012 (90) ¤ (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 vs 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
Di Gregorio, 2008 (91) ¤ (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/hr)	ILE vs EPI vs 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, 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/hr)	ILE vs VASO vs 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 vs 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

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Reference (Species)	Model	Local anesthetic (dose)	Log D (129)	Symptoms	ILE used	ILE bolus #	ILE infusion #	Study arms	Timing of rescue, time from LA termination	Other treatments received *	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Fettiplace, 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 vs 20% ILE vs 0.9% Saline vs Control (no treatment)	Study treatment after 10 sec	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, 2014 (94) (Rats)	RCS; resuscitation model	Bupivacaine (10 mg/kg in 10 sec)	2.68	Asystole	30%, Intralipid	IO 10 mL/kg (3.0 g/kg) in 180 sec; IV 10 mL/kg (3.0 g/kg) in 90 sec.	0.5 mL/kg/min (9 g/kg/hr)	ILE (IO) vs ILE(IV) vs Saline (IO)	Study treatment at 10 sec.	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, 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 x3, 5 min interval if absense of ROSC	0.25 mL/kg/min (3 g/kg/hr), increased if absense of ROSC after additional boluses	ILE vs Levosimendan 3 mcg/kg/min vs ILE+Levosimendan 3 mcg/kg/min vs 0.9% Saline	30 sec 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 prefered coadministration of EPI+ILE+Levosimendan compared to EPI+ILE or Levosimendan+EPI
Hicks, 2009 (96) (Pig)	RCS; resuscitation model	Bupivacaine (10 mg/kg in 10 sec)	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/hr)	ILE vs 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

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Reference (Species)	Model	Local anesthetic (dose)	Log D (129)	Symptoms	ILE used	ILE bolus #	ILE infusion #	Study arms	Timing of rescue, time from LA termination	Other treatments received *	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Hiller, 2009 (97) (Rats)	RCS; resuscitation model	Bupivacaine (20 mg/kg)	2.68	Asystole	30%, Intralipid	5 mL/kg (1.5 g/kg) x2	1 mL/kg (9 g/kg/hr) for 2 min	ILE vs ILE+EPI vs 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, 2009 (98) ¤ (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/hr) for 30 min (one group) time NR for other groups	Post-treatment ILE or Simultaneous-treatment ILE vs no ILE vs 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
Karcioglu, 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 absebse of ROSC	No	ILE vs Saline	30 sec 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, 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/hr) for 3 min	MCT/LCT ILE vs 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) vs MCT/LCT (8/30)	Not studied; Supports LCT over a MCT/LCT. Did not have a control without ILE resuscitation

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Reference (Species)	Model	Local anesthetic (dose)	Log D (129)	Symptoms	ILE used	ILE bolus #	ILE infusion #	Study arms	Timing of rescue, time from LA termination	Other treatments received *	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Litonius, 2012 (101) (Pig)	RCS; resuscitation model	Bupivacaine (2 mg/kg/min) or Mepivacaine (6 mg/kg/min)	2.68	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/hr) for 29 min	ILE vs 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, 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 vs ILE+EPI vs ILE+VASO vs EPI	Other treatment immediately after LA, study treatment at 1 min.	Vasopressors 2IU, EPI 10 ug/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
Mauch, 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 vs ILE 4 ml/kg vs 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 t1-5 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

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Reference (Species)	Model	Local anesthetic (dose)	Log D (129)	Symptoms	ILE used	ILE bolus #	ILE infusion #	Study arms	Timing of rescue, time from LA termination	Other treatments received *	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Mauch, 2011 (104) ¤ (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 vs EPI vs ILE+EPI vs 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 haemodynamic support was given in 3 of 5 surviving pigs; ILE - Secondary high dose EPI was needed in all surviving pigs; low dose EPI for haemodynamic 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
Mayr, 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/hr) for 10 min	ILE vs VASO+EPI	Other treatment at 1 min., study treatment at 2 min.	Ringer's solution, gelatin 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

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Reference (Species)	Model	Local anesthetic (dose)	Log D (129)	Symptoms	ILE used	ILE bolus #	ILE infusion #	Study arms	Timing of rescue, time from LA termination	Other treatments received *	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Shi, 2003 (106) (Rats)	RCS; Evaluation of the effect on hemodynamics and LA pharmacokinetics	Bupivacaine (2 mg/kg/min for 4 min)	2.68	Hypotension, bradycardia	30%, Intralipid	No	3 ml/kg/min (54 g/kg/hr for 5 min)	ILE Vs Saline	Study treatment or other treatment immediately after LA	No	HR, MAP: Comparable Plasma-bupivacaine: distribution constant, elimination half-life(t½β) decreased in ILE groups, elimination half-life(t½α), 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, 2009 (107) ¤ (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/hr)	ILE vs EPI vs 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, 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/hr) for 10 min	LA+ILE vs Saline+Fibrillation (no LA, fibrillation until same symptoms as LA group)	Defibrillation at 20 min or at myocardial pH≤7.0	Fibrillation in non-ILE group	PmO2 was comparable in saline vs 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 vs LA+ILE group	Survival: LA+ILE 8/8, Saline 8/8	Not studied
Weinberg, 2003 (109) (Dogs)	RCS; resuscitation model	Bupivacaine (10 mg/kg in 10 sec)	2.68	Cardiac arrest	20%, Intralipid	4 mL/kg (0.8 g/kg)	0.5 mL/kg/min (6 g/kg/hr) for 10 min	ILE vs Saline	Other treatment immediately, study treatment at 10 min.	Mechanical ventilation, internal cardiac massage	Hemodynamics: PmO2, 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

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Reference (Species)	Model	Local anesthetic (dose)	Log D (129)	Symptoms	ILE used	ILE bolus #	ILE infusion #	Study arms	Timing of rescue, time from LA termination	Other treatments received *	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Weinberg, 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/hr)	ILE vs EPI vs 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, 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/hr)	ILE vs ILE+EPI vs EPI vs Saline	Other treatment immediately, study treatment at 10 min.	No	Hemodynamic parameters at 25min., 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 2014 (112) ¤ (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/hr)	ILE vs 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, 2014 (113) ¤ (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 vs Saline	NR	NR	QRS widening was reversed after ILE	Survival NR. ILE: ?/6, Saline ?/3	No; Suggests concomitant resuscitation measures

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Reference (Species)	Model	Local anesthetic (dose)	Log D (129)	Symptoms	ILE used	ILE bolus #	ILE infusion #	Study arms	Timing of rescue, time from LA termination	Other treatments received *	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Cave, 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/hr)	ILE vs ILE+Hypertonic saline (21%)	Other treatment at 30 sec., 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
Weinberg, 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/hr) for 2 min Total dose 4 g/kg	ILE vs 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													

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Reference (Species)	Model	Local anesthetic (dose)	Log D (129)	Symptoms	ILE used	ILE bolus #	ILE infusion #	Study arms	Timing of rescue, time from LA termination	Other treatments received *	Parameter measured	Outcome	Support therapeutic effect of ILE alone
Harvey, 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 vs ILE+EPI	Other treatment at 30 sec., 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 2012 (p.2431) (117) (Rats)	Case series; resuscitation model	Bupivacaine (10 mg/kg)	2.68	Asystole	NR	5 mL/kg	0.5 mL/kg/min	ILE vs 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, 10 min.	Survival rate unclear	Not studied; Naloxone abolishes ILE rescue of bupivacaine-induced cardiotoxicity in a dose dependent manner
Partownavid 2010 (118)¤ (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/hr)	ILE vs 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 Ca2+ overload)	Survival rate unclear	Not studied; Fatty-acid oxidation is required for successful rescue of bupivacaine-induced cardiotoxicity by ILE
Partownavid 2012 (119) ¤ (Rats)	Case series; resuscitation model	Bupivacaine (10 mg/kg)	2.68	Asystole	NR	5 mL/kg	0.5 mL/kg/min	ILE vs 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, 10 min.	Survival rate unclear	Not studied; ILE rescue of bupivacaine-induced cardiotoxicity is abolished by fatty acid oxidation Inhibitor CVT-4325
Yoshimoto, 2012 (120) ¤(Rats)	Case series; compared ILE effect between 2 LA, no control	Levobupivacaine (2 mg/kg/hr) or Ropivacaine (2 mg/kg/hr)	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/hr)	Levobupivacaine+ ILE vs 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
Case report													

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Reference (Species)	Model	Local anesthetic (dose)	Log D (129)	Symptoms	ILE used	ILE bolus #	ILE infusion #	Study arms	Timing of rescue, time from LA termination	Other treatments received *	Parameter measured	Outcome	Support therapeutic effect of ILE alone
O'Brien, 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/hr) for 30 min	NA	Other treatment immediately, ILE treatment at 15 min.	lactate ringer oxygen	Hemodynamics: improvement in cardiovascular variables; CNS: Improvement in behavioral variables (more responsive to stimuli, could hold its head up without assistance).	Survived	Yes; 15 minutes after initiation of the ILE emulsion, the cat was more responsive to stimuli

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****	**Interpretation**	**Quality Assessment***	**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

*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.
**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.

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