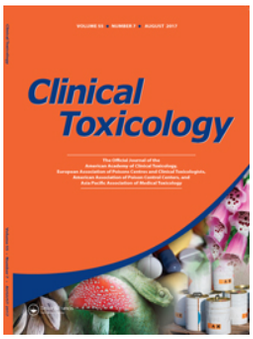

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Lipid emulsion improves survival in animal models of local anesthetic toxicity: a meta-analysis

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REVIEW

Lipid emulsion improves survival in animal models of local anesthetic toxicity: a meta-analysis

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ABSTRACT

Introduction: The Lipid Emulsion Therapy workgroup, organized by the American Academy of Clinical Toxicology, recently conducted a systematic review, which subjectively evaluated lipid emulsion as a treatment for local anesthetic toxicity. We re-extracted data and conducted a meta-analysis of survival in animal models.

Methods: We extracted survival data from 26 publications and conducted a random-effect meta-analysis based on odds ratio weighted by inverse variance. We assessed the benefit of lipid emulsion as an independent variable in resuscitative models (16 studies). We measured Cochran's Q for heterogeneity and I^2 to determine variance contributed by heterogeneity. Finally, we conducted a funnel plot analysis and Egger's test to assess for publication bias in studies.

Results: Lipid emulsion reduced the odds of death in resuscitative models (OR =0.24; 95%CI: 0.1–0.56, $p = .0012$). Heterogeneity analysis indicated a homogenous distribution. Funnel plot analysis did not indicate publication bias in experimental models.

Discussion: Meta-analysis of animal data supports the use of lipid emulsion (in combination with other resuscitative measures) for the treatment of local anesthetic toxicity, specifically from bupivacaine. Our conclusion differed from the original review. Analysis of outliers reinforced the need for good life support measures (securement of airway and chest compressions) along with prompt treatment with lipid.

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Intravenous lipid emulsion; local anesthetics; meta-analysis; systematic review; epinephrine; toxicity

Introduction

The use of intravenous lipid emulsion (ILE) as a treatment for local anesthetic systemic toxicity (LAST) arose in the past 10 years based on animal studies, case reports and mechanistic data [1]. Since LAST is a rare event [2], randomized clinical trials to assess the efficacy of ILE in LAST are impractical. As such, practitioners base the efficacy of ILE, as a treatment for cardiac toxicity, on case studies and animal models. Recently, the American Academy of Clinical Toxicology (AACT) organized a working group (referred to hereafter as "the AACT ILE workgroup" or "workgroup") to conduct a qualitative systematic review of the available literature to assess the efficacy of ILE for LAST and for non-local anesthetic poisonings, along with laboratory interference and complications associated with ILE [3].

In the AACT ILE workgroup paper regarding LAST, they reported a survival percentage of 98% in humans treated with ILE for LAST, but concluded that "… there is currently no consistent evidence that ILE is more effective that vasopressors" [4]. The workgroup asserted that the high survival percentage in human case reports reflected sole-reporting of positive outcomes (i.e., positive-publication bias). As such, they based their conclusion on animal studies. The AACT ILE workgroup used a subjective measure of "supports therapeutic effect of ILE alone" without reporting the quantitative analysis of survival data in the animal studies. As the workgroup stipulated survival as the primary outcome in their methodology paper [3], we re-extracted and quantitatively analyzed survival data from the animal studies included in the original review. We performed a meta-analysis to test whether ILE provides a quantitative survival benefit in animal models of LAST.

Methods

Data extraction

We extracted dichotomous survival outcomes (number surviving, number dying) from the randomized animal studies listed in the AACT lipid emulsion workgroup's paper [5–30]. Criteria for inclusion or exclusion, rationale for inclusion along with other PRISMA reporting checklist items are reported in the original methodology paper [3]. Both authors read the publications (abstracts and articles) and independently extracted survival data and other associated data. Two manuscripts presented multiple interpretations of survival and a third party (see acknowledgements) provided tie-breaking on these manuscripts [22,23]. For datasets

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presented as both a conference abstract and a published article, we only included data from the peer-reviewed journal article [9,22,29]. We tabulated survival based on reported survival along with surrogates for survival defined in the original manuscripts. These surrogates included inference from cardiovascular parameters, return of spontaneous circulation (ROSC) and threshold of cardiac function (e.g., 50% of baseline) based on blood pressure and rate pressure product (RPP). We further identified interventions and differences in methods that may have led to bias in individual studies.

Meta-analysis

We analyzed data in Microsoft Excel (Redmond, WA) and Prism GraphPad 6.0 (San Diego, CA). We conducted a meta-analysis based on the odds ratio of death with weights calculated by the inverse-variance method. Odds-ratio (OR) = (# died ILE/# survived ILE)/(# died control/# survived control). Variance = (1/# died ILE) + (1/# survived ILE) + (1/# died control) + (1/# survived control). Weight =1/variance. Due to a variety of study models (e.g., dog, rat, pig, rabbit) and variety of interventions (e.g., with and without CPR, with and without volume control, with and without epinephrine) we used a random-effects model. For zero-values in odds-ratio calculation, we added 0.5 to all values in the calculation according to convention [31]. We used two-sided *t*-test with $p < .05$ for significance. We examined all experimental studies with survival effects (e.g., we excluded studies in which all animals lived or all animals died), and further included studies with ILE as the independent variable. To quantify effect size, we converted the odds ratio to Cohen's *d* ($d = \text{LogOddsRatio} \times \text{sqrt}(3)/\pi$). To assess heterogeneity, we calculated Cochran's *Q* and further calculated I^2, which is the percentage of variance accounted for by heterogeneity in studies [32]. Next, we generated a funnel plot of odds ratio against the standard error of natural log of odds ratio. This plot is designed to identify additional heterogeneity or skew indicating possible publication bias in studies that is not picked up by the Cochran's *Q*. Finally, we conducted Egger's test regressing standard normal deviate (SND = odds ratio/standard error) against the precision (inverse of standard error) using the equation: $\text{SND} = a + b \times \text{precision}$ and used an *F*-test to determine whether the intercept passed through the origin. This test indicates asymmetry in the funnel plot if $A \neq 0$. We used $p = .1$ as a threshold for significance in Egger's test as recommended since we examined <20 studies [33].

Results

Meta-analysis

We extracted data from 26 original publications [5–30]. Of these manuscripts, 16 used models with an insult in which we could calculate the odds ratio of death/survival, and 13 included ILE as an independent variable (Table 1). We extracted data for the remaining 13 publications and report reason for exclusion and basic conclusion in Table 2. The odds-ratio quantifies the risk of death (including the surrogates: lack of ROSC and failure to recover 20% RPP) when treated with ILE with an odds-ratio <1 supporting ILE. In 16 studies (from 13 publications), investigators used ILE as an independent variable [7,9,14–18,20–23,28,29]. Heterogeneity analysis refuted a heterogeneous population ($Q = 23.67$; $p > .05$; χ^2 for df(15) = 25) with $I^2 = 36\%$ of variance. Random effects model with v0 = 1.1 reduced *Q* to 15.5 and I^2 to 3%. In these studies, treatment with ILE reduced the odds of death (OR =0.24; 95%CI: 0.1–0.56, $Z = -3.26$, $p = .0012$). Taken as the inverse odds-ratio, the odds of survival increased to 4.25 when compared to resuscitative measures not including ILE (Figure 1). The Cohen's *d* (0.786) indicated a large effect size.

Table 1. Publications analyzed for survival benefit.

Publication	Animal model	Baseline treatment	Control treatment	Control survival	ILE treatment	ILE survival	Outcome metric	Confounders
Bushey et al. [7]	Pig	CPR, Epi	+Saline	4/12	+ILE	6/12	ROSC	
De Queiroz et al. [9]	Pig	CPR, Epi	–	6/7	+ILE	10/10	ROSC (>10 min)	No volume control
De Queiroz et al. [9]	Pig	CPR	+Saline	1/7	+ILE	7/9		
Hicks et al. [15]	Pig	CPR, Epi, Vp	+Saline	4/9	+ILE	3/10	ROSC (60 s)	Vasopressin
Mauch et al. [22]	Pig	CPR, Epi	–	5/7	+ILE	6/7	Survival	No volume control
Mauch et al. [23]	Pig	–	+Epi +Rescue Epi	7/7	+ILE +Rescue Epi	8/14	Survival	No CPR Uncontrolled rescue epinephrine No volume control
Gokahmetoglu et al. [14]	Rabbit	CPR, Epi	+Saline	0/12	+ILE	8/12	ROSC	
Karcıoglu et al. [18]	Rabbit	CPR, Epi	+Saline	1/7	+ILE	3/7	ROSC (20 min)	
Li et al. [20]	Rat	CPR, Epi	–	2/8	+ILE	5/8	ROSC (RPP >20%)	No volume control
Li et al. [20]	Rat	CPR	+Saline	0/8	+ILE	3/8		
Litonius et al. [21]	Pig	CPR, Epi for asystole, Defib for VFib	+Ringers	8/10	+ILE	10/10	Survival	
Litonius (mepi) et al. [21]	Pig		+Ringers	10/10	+ILE	9/10		Mepivacaine
Hiller et al. [16]	Rat	CPR	+Saline	1/5	+ILE	5/5	ROSC (15 min)	
Weinberg et al. [29]	Rat	CPR	+Saline	2/5	+ILE	5/5	RPP >20%	
Weinberg et al. [28]	Dog	CPR	+Saline	0/6	+ILE	6/6	RPP >20%	
Karci et al. [17]	Rat	Standard resuscitation	–	0/7	+ILE	5/14	Survival	No volume control

CPR: cardio-pulmonary resuscitation (chest compressions and ventilation); Epi: epinephrine; Vp: vasopressin; ILE: intravenous lipid emulsion; Rescue Epi: doses of Epi delivered if mean arterial pressure <75% of baseline; RPP: rate pressure product.

Table 2. Publications excluded from meta-analysis.

Publication	Animal model	Control treatment	Control survival	ILE treatment	ILE survival	Notes
Bonfim et al. [5]	Pig	Saline	10/10	LCT MCT	10/10 10/10	- Survivable dose of Bupi - Hemodynamic study - Indicates hemodynamic benefit to ILE
Buckenmaier et al. [6]	Pig	–	0/5	ILE	0/6	- Unsurvivable insult - All animals intentionally dosed to death
Candela et al. [8]	Pig	Saline	9/9	LCT MCT	7/7 8/8	- Survivable dose of Bupi - EKG study - Indicates faster reversal of EKG with ILE
De Simone Melo et al. [10]	Pig	Saline	10/10	SMOFlipid	10/10	- Survivable dose - Hemodynamic study - Indicates benefit with SMOFLipid
Di Gregorio et al. [11]	Rat	CPR, Epi, Vp CPR, Vp	3/6 1/6	CPR, ILE	6/6	- No Control, ILE vs Epi - Indicates benefit of ILE over Epi & Vp or Vp
Fettiplace et al. [12]	Rat	Saline Null	7/7 7/7	20% ILE 30% ILE	7/7 7/7	- Survivable dose - Hemodynamic study - Indicates dose-dependent benefit with ILE
	Rat	Saline	6/6	IO Lipid IV Lipid	6/6 6/6	- Survivable dose - Hemodynamic study - Indicates possibility to using IO delivery for benefit of ILE
Li et al. [19]	Rat	None		CPR + LCT CPR + LCT/MCT CPR + LCT CPR + LCT/MCT	22/30 15/30 23/32 17/32	- No non-lipid control - Comparison of LCT and MCT/LCT - Indicates larger benefit with LCT compared to LCT/MCT mixture
Mayr et al. [24]	Pig	CPR, Defib, Epi, Vp	5/5	CPR, Defib, ILE	0/5	- No Control, ILE vs Epi - Asphyxial arrest - Indicates benefit of Epi over ILE
Shi et al. [25]	Rat	Saline Saline	6/6 50/50	ILE ILE	6/6 50/50	- Survivable dose - Pharmacokinetic study - Indicates pharmacokinetic benefit with ILE
Wat et al. [26]	Pig	Cardiac massage, Epi	5/5	Cardiac massage, 10-min delay, ILE	0/5	- No Control, ILE vs Epi - 10 min delay for ILE treatment - Indicates benefit of Epi over delayed ILE
Weinberg et al. [27]	Dog			Bupi + ILE	6/6	- Not a study of local anesthetic toxicity - Study on electrically induced fibrillation
Yoshimoto 2014 et al. [30]	Rat		–		–	- Survival data was not extractable - Study on hyperbaric bupivacaine

CPR: cardio-pulmonary resuscitation (chest compressions and ventilation); ILE: intravenous lipid emulsion; LCT: long-chain triglycerides; MCT: medium chain triglycerides; Bupi: bupivacaine; IO: intraosseous; Epi: epinephrine; Vp: vasopressin; Defib: defibrillation in the case of ventricular fibrillation.

Funnel plot analysis

We used funnel plot analysis to assess for publication bias in studies. For ILE as a treatment, funnel plot analysis demonstrated no publication bias in the data with representation of studies in both sides of the funnel (Figure 2). Two studies fell outside of the 95%CI [21,23]. Egger's test demonstrated no asymmetry with regression through the origin (90%CI: −1.688 to 0.035; $p = .1132$).

Discussion

Meta-analysis of the randomized animal studies from the AACT ILE workgroup demonstrated that ILE provides a survival benefit as a treatment for LAST, specifically in models of cardiac arrest from bupivacaine and when coupled with other resuscitative measures. Funnel plot analysis indicated no evidence of publication bias. The animal data agree with the survival benefit seen in human case reports examined by the AACT ILE workgroup study.

Meta-analysis of adjuvant lipid

Lipid emulsion as a treatment for LAST arose in the anesthesia community because it addressed the medical problem that LAST does not respond well to traditional resuscitation drugs (e.g., vasopressors) in both humans [34,35] and animals [36]. Practitioners rapidly adopted the use of ILE for LAST and professional anesthesia societies recommended the use of ILE [37,38]. However, some authors posit that lipid is ineffective at treating LAST so it is important to know what the body of literature says as a whole. Our meta-analysis confirmed that ILE, when used as a treatment for LAST (in conjunction with other resuscitative measures), reduced the

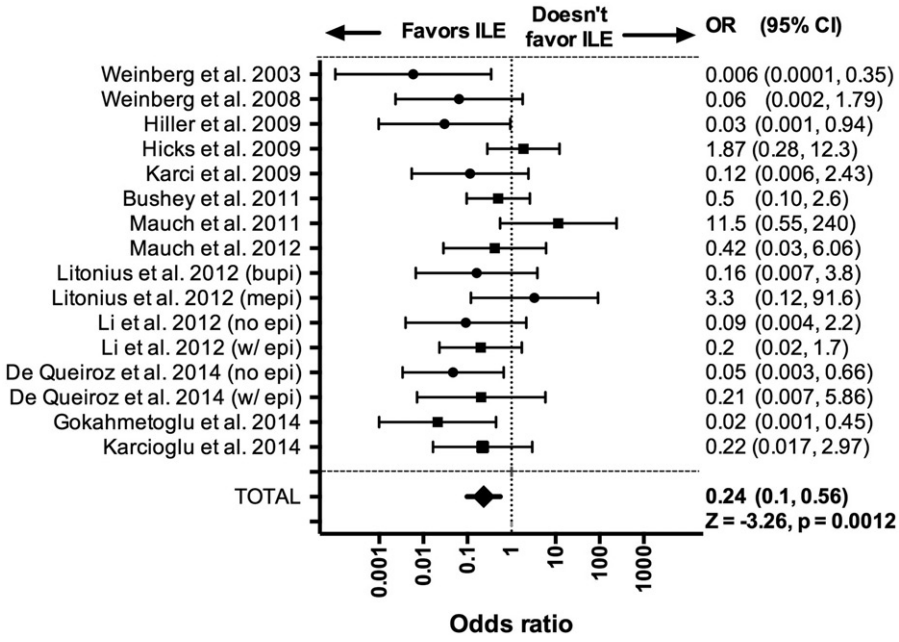

Figure 1. Forest plot of survival with adjuvant intravenous lipid emulsion. Meta-analysis comparing odds ratio (OR) of death based on treatment with adjuvant intravenous lipid emulsion (ILE) compared to standard resuscitation with accompanying 95% confidence interval (95%CI). Odds-ratio less that 1 favors treatment with ILE while odds-ratio above 1 favors treatment without ILE. bupi: treated with bupivacaine; mepi: treated with mepivacaine; w/epi: comparison with epinephrine in both control and ILE group; no epi: comparisson with no epinephrine in both control and ILE group.

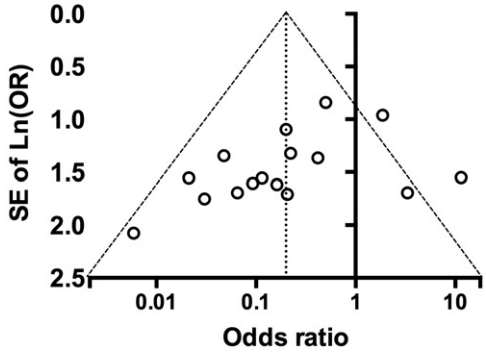

Figure 2. Funnel plot of meta-analysis for intravenous lipid emulsion. Funnel plot accompanying data from Figure 1 to examine for graphical evidence of bias in survival numbers. Odds-ratio of death when treated with intravenous lipid emulsion (ILE) versus control plotted against standard error of natural log of odds-ratio (SE of ln(OR)). Funnel is centered at overall median weighted odds ratio with 95% confidence interval within the funnel

odds of death (OR =0.24; 95%CI: 0.1–0.56) with a large effect size (Cohen's $d = 0.786$). Cochran's Q indicated a homogeneous population and funnel plot analysis did not indicate publication bias in the distribution of studies. Two studies fell outside of the 95% confidence interval in the funnel plot. Each of these studies employed experimental designs that reflect the outlier status and provide insight into future questions about ILE. In one outlier, Litonius et al. investigated ILE for mepivacaine toxicity in contrast to all the other studies which investigated bupivacaine [21]. Based on lipophilic partitioning, it is possible that different local anesthetics (i.e., mepivacaine vs ropivacaine vs bupivacaine) respond differently to lipid resuscitation and the result may reflect the less effective reversal of mepivacaine ($\text{Log}P = 2.04$) toxicity compared to bupivacaine ($\text{Log}P = 3.64$) toxicity. The second outlier, Mauch et al. included a number of confounders (e.g., lack of chest compressions as part of the common treatment, see Table 1). Additionally, the investigators treated animals with additional doses of epinephrine if mean arterial pressure dropped below 75% of baseline and for one animal in the ILE treated group, "the epinephrine rescue dose given at 5 min after cessation of bupivacaine immediately caused short-term ventricular tachycardia followed by ventricular fibrillation and death" [23]. As illustrated by this point, the paper included a mixture of un-timed independent variables, which limited interpretation. Due to the study design of the paper by Mauch et al., we required the input of the third party to define outcome. We agreed to define it as an overall outcome, instead of outcome prior to these additional independent interventions.

Studies without a quantitative difference

Our meta-analysis only included studies with a survival difference and ILE as the independent variable. Of the remaining 13 publications, 10 used study designs not intended to evaluate survival benefit. Of these 10, six indicated that ILE exerted benefits on hemodynamics [5,10,12,13], pharmacokinetics [25] or resolution of electrocardiogram abnormalities [8]. We could not analyze the remaining four for benefit because of lack of a control group [20,27], intentional dosing to death [6], or lack of comparison [30]. None of these studies argued against the use of lipid or supported vasopressors over lipid. Of the remaining three studies, one favored ILE in direct comparison with epinephrine and vasopressin. The other two studies favored epinephrine over ILE [24,26]. However, these two studies employed methods that do not match the other

studies. In order to simulate a tonic–clonic seizure secondary to local anesthetic in Mayr et al., the investigators subjected animals to a simultaneous local anesthetic insult and asphyxial arrest (by mechanically clamping the trachea). Further, the animals received a pancuronium infusion [24]. Lipid is detrimental in asphyxial arrest [39], so it is impossible to know whether the poor outcome with ILE was related to the asphyxia, the pancuronium or failure to reverse bupivacaine toxicity. In the next study, Wat et al. attempted to simulate the delay to administration of ILE. They delivered epinephrine immediately after cardiac arrest, but postponed treatment with ILE by 10 minutes [26]. As such, the study design does not match the other studies. In an attempt to mimic clinical situations, both studies included numerous uncontrolled variables, which makes interpretation difficult. From our perspective, instead of arguing against ILE, they just reinforce core principles in the management of LAST, including securement of the airway, good basic life support, and preventing delay until administration of lipid.

Discrepancies with original review

Our conclusion differed from the original AACT ILE workgroup's conclusion. This difference may arise from our different methodologies and associated methods. The original workgroup used a subjective and qualitative criterion of "favors use of ILE alone". In contrast, we used a quantitative evaluation of survival benefit limited to models of cardiac arrest with ILE as an independent variable (13 out of 29 randomized animal publications). Of the remaining 16 publications, the original workgroup reported three as both abstract and manuscript while we only included the manuscript [6,16,23]. Of the remaining 13 publications, only two argued against ILE but both contained experimental designs that limited comparability with other studies (as discussed in the Studies without a quantitative difference section). During our data extraction, we found a number of discrepancies between survival numbers in the original manuscripts and those reported by AACT ILE workgroup paper. We presume these discrepancies arose as transcription errors in the extraction of data from such a large number of papers. Additionally, we disagreed with the subjective reading of a number of manuscripts. As the authors did not provide a strict definition of how they evaluated "favors use of ILE alone", we could not deduce how our difference in interpretation arose. It is possible that the differences in subjective interpretation and/or transcription errors contributed to our different conclusion.

Considerations of mechanistic benefit

In contrast to other treatments, ILE combats LAST through a known mechanistic benefit that includes a cardiotonic effect and a redistribution benefit, shuttling drug from cardiac tissue to the liver for processing and muscle for storage [40,41]. Two published human trials (unpublished at the time of the original review) support this mechanistic effect. Both investigated whether ILE modified onset of subjective neurological symptoms following a low dose of intravenous local anesthetic (lidocaine, ropivacaine & levobupivacaine). While neither met the primary endpoint, both confirmed a pharmacokinetic benefit to ILE [42,43]. Further, analysis by Dureau et al. indicated that ILE could substantially modify bupivacaine pharmacokinetics when bupivacaine doses were elevated and rising. Both these trials confirm a redistribution benefit provided by ILE in human models, comporting with the animal data. As clinical trials of higher doses are both impractical and unethical, future human questions should focus on retrospective cohort analysis (with propensity score matching) or registry-based studies.

Conclusions

In summary, meta-analysis of the animal data from studies cited by the AACT ILE workgroup found that ILE reduced odds of death from LAST (based on survival data and survival surrogates). Lipid emulsion failed in the context of asphyxial arrest [24], lack of CPR [23] and delay in treatment [26]. As such, the randomized animal data presented in the AACT ILE workgroup paper support the use of ILE in LAST, in combination with good resuscitative measures (i.e., intubation and chest compressions). Further, as neurological symptoms and hypotension often precede cardiovascular arrest in LAST, it follows that practitioners should consider ILE as a preventative agent in these situations to abate progression to cardiac arrest.

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Disclosure statement

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