WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

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<th>Worksheet author(s)</th>
<th>Date Submitted for review:</th>
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<td>John James Picard</td>
<td>2/3/2010</td>
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<td>Richard Shih</td>
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<td>Eric Lavonas</td>
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Clinical question.

ALS-SC-073-01A  "In adult cardiac arrest (prehospital or in-hospital) due to local anaesthetic toxicity (P), does use of any specific interventions (I) as opposed to standard care (according to treatment algorithm) (C), improve outcome (O) (eg. ROSC, survival)?".

Is this question addressing an intervention/therapy, prognosis or diagnosis? Yes - an intervention

State if this is a proposed new topic or revision of existing worksheet: New

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).

Author #1: Pub Med, searching on “local anesthetic lipid toxicity”, last searched September, 2009.

Author #2: PubMed “anesthetic toxicity” or anesthetic poisoning” as MESH (headings) AND “lipids” or “lipid emulsion.”

EMBASE search using text words (all fields) lipid emulsion AND (anesthetic toxicity OR anesthetic poisoning)

AHA EndNote Master library, Cochrane database for systematic reviews, Central Register of Controlled Trials, Review of references from articles.

Last searched February, 2009.

Author #3 conducted two supplemental searches to ensure that additional relevant literature was not missed:

(1) PubMed database, 1950 – 2010 Week 3, conducted on 1-31-2010, using the OVID search engine. Terms were Anesthetics, Local [MeSH] / ae, po, to [Adverse effects, poisoning, toxicity] AND Heart Arrest [MeSH]/th [Therapy], no additional limits. The search produced 46 citations.


The results of these searches were examined for publications that might change the Consensus on Science or Treatment Recommendations. These searches produced two human case reports (Pham Dang, 2000, 356; Braque, 2008, 91) and one animal study (De La Coussaye, 1994, 624) concerning the use of clonidine in treatment of local anesthetic toxicity. These were graded and inserted into the worksheet. Several additional case reports describe patients who recovered from cardiac arrest or near-arrest following lipid emulsion therapy, and one publication (Calenda, 2009, 472) reports a treatment failure despite lipids. Because these reports did not appear to provide new information beyond the studies already included in previous searches conducted by the primary authors, they were not graded. Overall, no studies were identified that were considered likely to alter the Consensus on Science and Treatment Recommendations approved by the ALS Task Force on September 21, 2009.

State inclusion and exclusion criteria

Included: (1) Human clinical studies, case series, and case reports involving the treatment of cardiac arrest or life-threatening acute cardiovascular toxicity due to local anesthetic intoxication, and (2) reports of whole animal experiments of cardiac arrest or life-threatening acute cardiovascular toxicity due to local anesthetic intoxication.

Excluded: (1) Reports of experiments on single organs, (2) publications in abstract form only, and (3) Reviews, editorial, commentary and similar publications.

Number of articles/sources meeting criteria for further review:

The search found 23 articles meeting inclusion criteria, including 12 human case reports and 11 animal studies.
Summary of evidence

Evidence Supporting Clinical Question

All reports pertain to lipid emulsion therapy except those marked with †, which describe the use of clonidine.

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<td>Cave 2009, 732 E</td>
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<td>Weinberg 1998, 1071 E</td>
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<td>Cho 2000, 1096 A^‡</td>
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<td>Kim 2004, 728 A^‡</td>
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<td>Warren 2008, 1578 ABC</td>
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Level of evidence

A = Return of spontaneous circulation  C = Survival to hospital discharge  E = Other endpoint
B = Survival of event  D = Intact neurological survival  Italics = Animal studies
Evidence Neutral to Clinical question

All reports pertain to lipid emulsion therapy, except those marked with (†), which describe the use of clonidine, and (‡), which describe use of high dose insulin/glucose therapy.

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<th>Litz, 2008, 1575 ABC</th>
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<td>Braque 2008, 91 ABCD</td>
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<td>Hicks 2009, 138 A</td>
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Level of evidence

A = Return of spontaneous circulation       C = Survival to hospital discharge       E = Other endpoint
B = Survival of event                      D = Intact neurological survival          Italics = Animal studies

Evidence Opposing Clinical Question

All reports pertain to lipid emulsion therapy, except those marked with (†), which describe the use of clonidine.

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Level of evidence

A = Return of spontaneous circulation       C = Survival to hospital discharge       E = Other endpoint
B = Survival of event                      D = Intact neurological survival          Italics = Animal studies
Local anesthetic intoxication is a rare but immediately life-threatening event. Local anesthetic toxicity typically occurs in the setting of regional anesthesia, when a bolus of bupivicaine, mepivicaine, ropivicaine, or lidocaine inadvertently enters the arterial or venous system, leading to refractory seizures and/or rapid cardiovascular collapse.

Because this condition is very uncommon and occurs in a setting in which informed consent is virtually impossible to obtain, it is unlikely that a human controlled trial could ever be conducted. Indeed neither a clinical trial nor a case series was identified in this review; for this reason, we considered controlled animal experiments (intact animals only) and human case reports in this review.

Animal research:
Three studies (LOE 5, good quality: Weinberg, 1998, 1071; Weinberg, 2003, 198; Cave, 2009, 732) compared the outcomes obtained with lipid emulsion therapy with BLS resuscitation (CPR, ventilation, and saline). All three studies showed lipid emulsion to be superior to BLS resuscitation.

Three studies compared the outcomes obtained with lipid emulsion therapy to ALS resuscitation (vasopressin + epinephrine). Two studies (LOE 5, good quality: Weinberg, 2008, 907; DiGregorio, 2009, 993) found lipid emulsion therapy to be superior to vasopressors. These results are contradicted by the report of Mayr, 2008, 1566 (LOE 5, fair quality), which found vasopressors to be superior to lipid emulsion in a model that used a lower dose of bupivicaine and a prolonged period of hypoxia to induce cardiac arrest.

Two studies examined whether lipid emulsion therapy, given in addition to vasopressors (vasopressin + epinephrine), improved outcome compared with vasopressors alone. The results of these experiments are mixed. One study (LOE 5, good quality: Hicks, 2009, 138), conducted in pigs, showed that lipids conferred no additional benefit in animals who had already received a high dose of epinephrine (0.1 mg/kg). A second study (LOE 5, good quality: Hiller, 2009, 498), conducted in rats, showed an incremental improvement when lipid infusions were added to standard dose epinephrine (0.001 and 0.025 mg/kg), but not when lipid emulsion was added to higher doses of epinephrine (0.01 and 0.025 mg/kg).

In addition to the above, two studies (LOE 5, good quality: Cho, 2000, 1098; Kim, 2004, 728) conducted in dogs demonstrated improved survival in animals treated with high dose insulin (1-2 units/kg IV bolus), accompanied by glucose and, in some treatment arms, potassium. Although all animals received BLS resuscitation, vasopressors were not used in these experiments. One dog study (LOE 5, fair quality: De La Coussaye, 1994, 624) demonstrated partial improvement in bupivicaine-induced cardiac conduction delays with administration of high dose clonidine (0.01 mg/kg IV).

Human case reports:
Two human case reports (LOE 4, good quality: Litz, 2006, 800; Rosenblatt, 2006, 217) describe patients in prolonged cardiac arrest, unresponsive to standard ALS measures, who developed ROSC almost immediately after receiving a lipid emulsion bolus. There are three further peer reviewed case reports of cardiac arrest in which the picture was less clear, but recovery of effective cardiac output was apparently associated with lipid infusion. Although these studies remain LOE 4 because they directly address the question of cardiac arrest, they are downgraded to “fair quality” because the relative contributions of lipid emulsion and concurrent therapies are less clear. (Warren, 2008, 1578; Marwick, 2009, 1344; Smith, 2008, 1581)

In addition, five peer reviewed case reports describe the administration of lipid emulsion to patients who were had acute/life-threatening cardiovascular toxicity, but who were not pulseless at the time of lipid administration. These are classified as LOE 5 with regard to the question of cardiac arrest, because they pertain to a slightly different patient population. The patients in two reports (Foxall, 2007, 516; Shah, 2009, 439; Zimmer, 2007, 449) evidenced rapid improvement, and were counted as favorable to the clinical question. The patients in two other reports (Litz, 2008, 1575; Ludot, 2008, 1572) had transient worsening of their condition followed by ROSC and survival; these were counted as neutral to the clinical question. If a slightly different clinical question was considered (patients with severe/life-threatening acute cardiovascular toxicity), the reports of Foxall, 2007, 516, Litz, 2008, 1575, and Zimmer, 2007, 449 would be LOE 4; the reports of Ludot, 2008, 1572 and Shah, 2009, 439 would remain LOE 5 because they do not involve adult patients.
Three human case reports (LOE 4, fair quality: Braque, 2009, 91; Pham Dang, 2000, 256; Zimmer, 2007, 449) describe the use of clonidine, in addition to standard resuscitation. The patients in the first two of these reports received large total doses of epinephrine (6 mg and 40 mg, respectively), and all three had prolonged resuscitation times (90 and 55 minutes to ROSC in the former 2 reports and 150 minutes to resolution of the event in the latter). All patients eventually achieved neurologically intact survival. None of the three patients responded favorably to an initial dose of 150 mcg clonidine; one patient responded favorably to a second dose (Pham Dang, 2000, 256), while the other two required multiple additional measures to achieve ROSC (Braque, 2009, 91) or resolution of severe tachycardia and ventricular ectopy (Zimmer, 2007, 449). No case provides clear support for the use of clonidine in this setting. A dog study (LOE 5, fair quality: De La Coussaye, 1994, 624) demonstrated partial improvement in bupivicaine-induced intracardiac conduction delays following clonidine administration (0.01 mg/kg IV), but non-perfusing rhythms were not studied.

**Future research questions:**

1. What is the ideal dose and formulation of lipid emulsion? Although the vast majority of studies have involved a 20% solution of an emulsion comprised of long-chain fatty acids (Intralipid), neither this concentration nor the exclusion of medium- or short-chain fatty acids have been formally studied. On in vitro study (Mazoit, 2009, 380) suggests that the combination of long- and medium-chain fatty acids bind local anesthetics better than long chain fatty acids alone, but this has yet to be translated to living animals (human or otherwise).

2. What is the ideal dose of lipid emulsion? The vast majority of studies have involved a bolus of 1.5 ml/kg over 1 minute. The ideal frequency of repeat boluses and maximum safe dose have not been determined. At least one report (Marwick, 2009, 1344) describes recurrent cardiotoxicity that developed 40 minutes after ROSC. Whether a lipid infusion should be initiated following ROSC, and the dose and duration of such maintenance therapy, is not currently known.

3. How should intravenous lipid be combined with other cardioactive drugs? At this time, it is unclear whether lipid emulsion should be administered before, following, or instead of standard ACLS medications, nor whether the doses of epinephrine and vasopression should be modified in patients who receive lipid emulsion therapy.

**Conflicts of Interests:**

Dr. Picard contributed to the construction of the lipidrescue.org and lipidregistry.org sites and to the Association of Anaesthetists of Great Britain and Ireland treatment guidelines. Neither has revenue, and he reports no financial interest in their past, present or future. Having drawn his colleagues’ attention to the potential benefits of lipid emulsion in poisoning by LA, he therefore would be vindicated by its adoption by ILCOR.

Dr. Shih declares no conflict of interest.

**Acknowledgements:**

Dr. Picard would like to thank his colleagues, including Guy Weinberg and Tim Meek.

Dr. Lavonas would like to thank Dr. Bernd Boettiger for translating the Zimmer manuscript.

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**Citation List**

**Not graded (no primary data):** Recommends that lipid therapy be considered in refractory cardiac arrest attributable to LA intoxication, and provides specific dosing recommendations.

**Not grade (no primary data):** Recommends that lipid be given if patients suffer cardiac arrest which is likely to be attributable to LA intoxication.

**LOE 4, fair quality, neutral (clonidine):** In this case report, a patient developed cardiac arrest (alternating between episodes of ventricular fibrillation and asystole). His resuscitation included administration of two 150 mcg IV bolus doses of clonidine.
Following the first dose of clonidine, his rhythm improved from ventricular fibrillation to SVT, but only for a few minutes. Following the second clonidine dose, the patient’s rhythm briefly improved from ventricular tachycardia to SVT, but he then developed persistent asystole that resolved only after an additional dose of 3 mg IV epinephrine bolus plus an epinephrine infusion. This report cannot be used to support a treatment benefit from clonidine in lidocaine/bupivacaine-associated cardiac arrest.


LOE 5, good quality, supporting (lipids) (animal study): From a laboratory unrelated to Weinberg et al. A rabbit model of LA intoxication, with a 40% initial survival amongst the control group (and so no significant initial survival advantage compared with lipid.) A significant difference then arose in the following 20 minutes.


LOE 5, good quality, supporting (insulin) (animal study): A canine model of cardiovascular collapse short of full blown arrest. Suggests insulin/glucose may be an alternative antidote for LA intoxication. Such high doses of insulin are unfamiliar to clinicians in, for example, the UK, though less so in the US.


LOE 5, fair quality, supporting (clonine) (animal study): Although this study was primarily designed to explore the physiologic mechanisms of bupivacaine-induced acute cardiovascular insufficiency (short of cardiac arrest), it contains useful data about the effect of clonidine (group 2) vs. placebo (group 1). In this model of moderately severe cardiovascular toxicity, administration of a high dose of clonidine (0.01 mg/kg) partially reversed cardiac conduction delays. Although methodologically good, this report was downgraded to "fair" quality because it did not induce or reverse non-perfusing rhythms.


LOE 5, good quality, supporting (lipids) (animal study): The first research addressing the question: "Should lipid emulsion be preferred to conventional vasoactive drugs during resuscitation after cardiac arrest attributable to LA?" Suggests lipid may be preferable. Does not answer the more pertinent question: "Should conventional vasoactive drugs be given as well as lipid or not?"


LOE 5, good quality, supporting (lipids): A case report in which lipid seemingly restored haemodynamic stablility in a patient.


LOE 5, good quality, neutral (lipids) (animal study): After cardiac arrest attributable to bupivacaine overdose, and followed by a large dose of epinephrine, lipid neither helped- nor particularly hindered the animals' recovery. This study therefore addressed the salient question of how lipid and vasopressors should be used together. At first glance, it suggests that given vasopressors, lipid may be redundant. But the epinephrine dose (100μg/kg) may undermine this finding's clinical relevance.


LOE 5, good quality, neutral (lipids) (animal study): In a rodent model, cardiac arrest attributable to local anaesthetic intoxication was better reversed with lipid and low doses of epinephrine than by lipid and higher doses of epinephrine, suggesting that when combined with lipid, high doses of epinephrine may actually be harmful.


LOE 5, good quality, supporting (insulin) (animal study): A canine model of cardiovascular collapse short of cardiac arrest. Suggests insulin beneficial at doses of 2 international units/kg/kilogram.

LOE 4, good quality, supporting (lipids): The second peer reviewed case report of apparently intractable cardiac arrest attributable to LA overdose apparently quickly reversed by lipid emulsion therapy.


LOE 5, good quality, neutral (lipids): A peer reviewed case report of lipid's swift reversal of neurologic and cardiovascular derangements attributable to LA intoxication. The lipid was given before the patient's collapse proceeded to cardiac arrest.


LOE 5, good quality, neutral (lipids): The first peer reviewed report of lipid emulsion's use to a child (albeit a teenager). Also the first reported use of a lipid other than Intralipid. Once again, the lipid was given before full blown cardiac arrest. LOE 5 because the patient was not in cardiac arrest at the time of lipid administration, and also because this was not an adult patient.


LOE 4, fair quality, supporting (lipids): After cardiac arrest attributable to LA intoxication, lipid emulsion's administration was followed swiftly by ROSC. But the patient once again became cardiovasculry unstable once the lipid emulsion's infusion ended, suggesting that some patients may benefit from an infusion as well as an initial bolus.


LOE 5, fair quality, opposing (lipids) (animal study): A porcine model of asphyxia combined with LA intoxication, suggesting that lipid was inferior to the combination of vasopressin with epinephrine.


Not graded (does not meet inclusion criteria) (see future research discussion): An in vitro study of the physical interaction between long acting LAs and two different lipid emulsions, suggesting that Intralipid binds LAs with greater affinity than the other.


LOE 4, fair quality, supporting (clonidine): In this interesting case report, a patient who had not responded to 55 minutes of ACLS, including a total of 40 mg epinephrine and a bolus of 150 mcg IV clonidine had ROSC, survival to hospital discharge, and neurologically intact recovery following a second 150 mcg IV clonidine bolus. Although the report itself is well-written, it is considered fair quality because it is difficult to separate the relative contributions of multiple therapies to the outcome.

Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB. Successful use of a 20% lipid emulsion to resuscitate a patient.

LOE 4, good quality, supporting (lipids): The first peer reviewed case report of lipid's successful reversal of protracted cardiac arrest attributable to LA intoxication in a human patient.


LOE 5, good quality, supporting (lipids): The first peer reviewed report of lipid's successful reversal of cardiovascular collapse in an infant. The clinical circumstances suggest intravascular injection of bupivacaine was responsible for the collapse. LOE 5 because the patient was not pulseless at the time of lipid administration, and because the patient was not an adult.


LOE 4, fair quality, supporting (lipids): ROSC quickly followed administration of lipid after cardiac arrest attributed to LA intoxication.


LOE 4, fair quality, supporting (lipids): ROSC rapidly followed lipid emulsion's administration during otherwise refractory cardiac arrest attributable to intoxication by LA.

LOE 5, good quality, supporting (lipids) (animal study): Index study showing that the lethal dose of bupivacaine is much increased in rats if in the induced cardiac arrest the animals receive BLS and lipid rather than saline.


LOE 5, good quality, supporting (lipids) (animal study): Suggests that when combined with BLS and compared with saline lipid emulsion substantially improves survival in a canine model of cardiac arrest attributable to LA intoxication. No dogs received other cardioactive drugs.


LOE 5, good quality, supporting (lipids) (animal study): Using a rat model, this study addresses the question "In cardiac arrest attributable to LA intoxication, is lipid better than epinephrine when combined with BLS?" It suggests that lipid is superior. It does not address the question: "If such patients receive epinephrine, would they benefit further from lipid?"


LOE 5, fair quality, supporting (lipids) and opposing (clonidine): A case report of a patient overwhelmed by LA overdose, short of cardiac arrest. The patient's heart rate increased and ventricular ectopy developed after administration of 150 mcg IV clonidine. Ventricular ectopy resolved, heart rate improved after lipid administration. The patient survived to hospital discharge, but neurologic outcome is not reported. This patient received multiple concurrent therapies over a prolonged (2.5 hour) course, making clear conclusions about cause/effect troublesome.