Lipid Therapy for Cardiac Arrest

*(PICO #ALS-834)*

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**EVREV 1:** Eric Lavonas, COI #240

**EVREV 1:** Mohammed Alhelai, COI #4

**Taskforce:** ALS
COI Disclosure

Eric Lavonas, COI #240
- Commercial/industry
  - None
- Potential intellectual conflicts
  - None

Mohammed Alhelail, COI #4
- Commercial/industry
  - None
- Potential intellectual conflicts
  - None
There is insufficient clinical evidence to suggest any change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest caused by local anesthetics. Animal studies and case reports suggest severe cardiovascular toxicity or cardiac arrest attributable to local anesthetic intoxication may respond to treatment with IV lipid emulsion.
**Population:** Adult patients with cardiac arrest due to suspected drug toxicity
  - e.g. local anesthetics, tricyclic antidepressants, or others

**Intervention:** Administration of intravenous lipid

**Comparison:** No intravenous lipid

**Outcomes:**
- **9 – Critical:** Survival with favorable neurological outcome
  - At discharge, 30 days, 60 days, 180 days, 1 year
- **9 - Critical:** Survival only
  - At discharge, 30 days, 60 days, 180 days, 1 year
- **5 – Important:** ROSC
Inclusion/Exclusion & Articles Found

**Inclusions/Exclusions**

- **Human comparative studies**
  - Clinical trials, case-control studies, case series with comparison groups, etc.
  - Excluded: Not cardiac arrest; case series w/o comparison group; reviews/editorials. Case reports considered for safety data only.

**Number of Articles Identified**

- **RCTs:** Identified 2, included 0
- **non-RCTs:** Identified 1, included 0
- **Excluded:** 789 (+2)
  - Supplemental lit search 2/1/2015: 46 additional excluded articles
Due to a lack of human comparative studies in cardiac arrest and peri-arrest states, we are unable to make any evidence-based treatment recommendation about the use of intravenous lipid emulsion to treat toxin-induced cardiac arrest.
Excluded Clinical Trials

- Minton 1987 467
  - Human volunteer PK study
  - No CA (no toxicity)
  - Little effect on amitriptyline serum levels
Excluded Clinical Trials

Taftachi 2012 38

Small RCT (N = 30) of poisoned adults
  - Excluded local anesthetic toxicity

No CA
  - All patients survived to discharge, including 15/15 controls
  - Mean BP normotensive in both groups

More rapid improvement in GCS in ILE group c/w historic controls
  - Relevant, but not an outcome in this PICO
Excluded Clinical Trials

**Gil 2013 767**

- Small prospective study of adults who ingested glyphosate-surfactant herbicides
  - 22 patients enrolled prospectively and treated with ILE
  - Matched to 22 historical controls (from a population of 42)

- **No CA**
  - Survival: 22/22 cases, 21/22 controls
  - Most patients normotensive

- Possible benefit: less hypotension, arrhythmia
  - Relevant, but not an outcome in this PICO
Excluded Registry Study

- Cave 2014 133
  - 48 subjects reported by 61 sites over 3 years
    - 36 subjects from consecutive-patient registries
    - Outcome assessment: MD assessment (unblinded)
  - **No comparison group**
  - 2 subjects with CA (ropivicaine, propafenone)
    - Both also received ACLS + other interventions
    - Both survived
**Excluded Registry Study**

**Cave 2014 133**

8 subjects with “cardiovascular collapse” from toxicity not due to LA

- No definition of “cardiovascular collapse” provided
- 5 survived, 3 died
- Treating MD’s reported subjective benefit
  - Yes = 3
  - Uncertain = 3
  - No = 2

![Graph](image)  
*Fig. 4 Plot of SBP vs. time: general toxicology patients, cardiovascular collapse indication*
Excluded Case Series

妙 Downes 2014 286

妙 Single-center series, n = 9
  • 5 quetiapine OD, 4 other drugs

妙 No CA: ILE given for CNS depression
  • No temporal improvement in GCS
  • 7/9 patients intubated after ILE

妙 No comparison group
Excluded Studies

- Approximately 103 case reports through 2/14
  - About half involving local anesthetics
  - Only 22 describe “failure” of ILE
  - 1 case of pancreatitis
  - ~ 4 cases of ARDS-like lung effects
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Human Case Reports of ILE Use Through February, 2014

Table from Cao 2014 ePub *J Emerg Med*
Excluded Studies

Approximately 45 intact animal studies

- Most show positive outcomes in bupivacaine toxicity
  - Exception: porcine models

- Mixed results in other toxicants
Animal Studies - Bupivacaine

Positive: 14 studies
- 8 rat, 2 rabbit, 2 dog, 2 pig

Negative: 8 studies
- All pig

References:
- Wang 2009 1787
- Weinberg 2003 198
- Candela 2010 1473
- Melo Mde S 2012 318
- Cave 2009 732
- Gokahmetoglu 2014 275
- Di Gregorio 2009 993
- Fettiplace 2014 915
- Hiller 2009 498
- Li 2012 857
- Oda 2013 500
- Partownavid 2012 2431
- Weinberg 1998 1071
- Weinberg 2008 907
- Mauch 2011 1103
- Mayr 2008 1566
- Bushey 2011 129
- de Querioz Siqueira 2014 729
- Hicks 2009 138
- Litonius 2012 125
- Litonius 2012 901
Animal Studies – Other Local Anesthetics

- **Ropivacaine:**
  - 1 positive (pig); 1 negative (pig)

- **Mepivacaine**
  - 1 negative (pig)

- **Cocaine:**
  - 1 positive (rat)

Carreiro 2014 32
Litonius 2012 901
Bonfim 2012 685
Buckenmaier 2012 894
Animal Studies – Other Toxicants

Positive studies for:
- Clomiprimene (5); Propranolol (3); Verapamil (3); Amiodarone (1); Tramadol (1)

Negative studies for:
- Amitriptyline (3); Metoprolol (1); Flecaainide (1)

Mixed study for parathion (1)
Safety Concerns

- Interference with ACLS (especially epi)
  - Contradictory animal studies
- Increased absorption of toxicant from GI tract
  - 1 animal study
- ARDS-like changes
  - ~4 human reports, ? Causality
- Pancreatitis
  - 1 human report
- Interference with lab assays
  - Multiple reports
Proper Consensus on Science Statement

For the critical outcomes of neurologically intact survival and survival and for the important outcome of ROSC, we have not identified any studies of sufficient quality or relevance to the PICO question to include in this review.
Due to a lack of human comparative studies in cardiac arrest and peri-arrest states, we are unable to make any evidence-based treatment recommendation about the use of intravenous lipid emulsion to treat toxin-induced cardiac arrest.
Knowledge Gaps

*DO NOT USE FOR PLENARY*
- BREAKOUT ONLY

- Other specific systematic review that would be helpful
  - None; there have been several recent excellent reviews

- Specific research required
  - Human RCT
    - Or, well-designed observational study with rigorous matching including propensity adjustment