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REVIEW ARTICLE

# The role of lipid emulsion during advanced cardiac life support for local anesthetic toxicity

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**ABSTRACT**
Lipid emulsion has recently emerged as a potential antidote for local anesthetic systemic toxicity. This review examines the literature and guidelines for administration of lipid emulsion in the setting of advanced cardiac life support.


## Introduction

Local anesthetic toxicity following epidural anesthesia is a rare event with an incidence of approximately 4 per 10,000.[1] Clinical symptoms can range from prodromal symptoms, such as lightheadedness and perioral numbness, to central nervous symptom depression or excitation, and ultimately cardiovascular depression.[2] Over the past 30 years, the incidence of local anesthetic systemic toxicity has been decreasing, largely due to heightened awareness of local anesthetic toxicity and implementation of safety measures such as frequent aspiration and the use of incremental injection.[1] However, toxicity continues to be reported, even in the labor and delivery setting.[3] In a recent review of published case reports, epidural block was the most common anesthetic technique associated with local anesthetic systemic toxicity.[4] While treatment has traditionally been largely supportive, lipid emulsion has emerged as a potential antidote for local anesthetic toxicity. The objective of this article is to review the literature and guidelines surrounding the role of lipid emulsion in the setting of advanced cardiac life support (ACLS) in the setting of local anesthetic toxicity.

## Mechanism of action

While the exact mechanism of action is not known, several hypotheses exist as to how lipid emulsion works in the setting of local anesthetic toxicity. The first is the 'lipid sink' hypothesis that suggests that lipid-soluble local anesthetic molecules in the aqueous phase are extracted by the injected lipid.[5] The lipid sequesters the local anesthetic and reduces the concentration of tissue-bound local anesthetic. Alternatively, the metabolic hypothesis postulates that lipid impedes local anesthetic's inhibition of acyl carnitine, thereby improving mitochondrial metabolism.[6,7] Finally, it has been proposed that lipid emulsion increases calcium concentrations in myocytes thereby improving contractility.[8]

## Literature review

The seminal work on lipid emulsion as a treatment for local anesthetic toxicity was performed by Weinberg's group.[5] Sprague-Dawley rats were anesthetized with isoflurane and the animals were given a bolus dose of intravenous bupivacaine, ranging from 10 to 20 mg/kg. Following the bolus, isoflurane was discontinued, and the rats were ventilated with 100% oxygen. Immediately after the bupivacaine bolus, the animals were randomized to receive a bolus of saline or 30% lipid emulsion, followed by an infusion of the same solution for 2 min. Chest compressions were performed for asystole lasting more than 15 s. The primary outcome was survival at 5 min. Remarkably, at a bupivacaine dose of 15 mg/kg, all rats in the saline group died, whereas all rats in the lipid group survived. Lipid emulsion increased the $LD_{50}$ dose of bupivacaine by 48%. Weinberg et al. subsequently repeated these studies with similar findings using a dog model.[9]

Almost ten years elapsed before lipid emulsion was first used in the clinical setting. In 2006, Rosenblatt reported the case of a 58-year-old patient undergoing a rotator cuff repair under interscalene block.[10] After identification of the brachial plexus using nerve stimulation, 0.5% bupivacaine 20 mL and 1.5% mepivacaine 20 mL were injected incrementally. Thirty seconds after the

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final injection, the patient became unconscious and developed tonic-clonic seizures. Oxygen was administered, propofol 50 mg was injected, and the seizures stopped. A second dose of propofol was administered after the patient seized again. Pulseless electrical activity subsequently developed and ACLS was initiated. Over the 20-min resuscitation, 3 mg epinephrine, 2 mg atropine, 300 mg amiodarone, and 40 units vasopressin, as well as 4 defibrillations, were administered. As plans were being made to institute cardiopulmonary bypass, 100 mL of lipid emulsion were administered. After one additional defibrillation, a discernable rhythm appeared. An additional milligram of atropine and epinephrine were given, and within 15 s, sinus rhythm returned. An infusion of lipid emulsion was started, and the patient was extubated 2 h later and made a full neurological recovery. Following Rosenblatt's report, several other case reports were published describing lipid emulsion's use in the setting of local-anesthetic toxicity, as well as its use for the treatment of overdoses of other lipid-soluble drugs, all with positive outcomes.[3,11–23] The possible role of lipid emulsion during ACLS in the setting of local-anesthetic toxicity was broached; specifically, whether it should be used after traditional resuscitation had failed, or if it should be administered early in the resuscitation, or whether it should replace traditional resuscitation. Several investigators have addressed this question.

Mayr et al. using their established model of porcine arrest and resuscitation, sought to compare survival using a combination of vasopressin and epinephrine to lipid emulsion alone.[24] The swine were anesthetized with isoflurane, a bolus dose of 5 mg/kg bupivacaine was administered, and isoflurane and mechanical ventilation were discontinued. Chest compressions and ventilation with 100% oxygen were initiated 1 min after onset of asystole. This sequence mimicked the delay in recognition and initiation of treatment that occurs in actual clinical scenarios. Two minutes after the start of the resuscitation, the animals were randomized to receive a bolus and infusion of lipid emulsion or an escalating dose mixture of vasopressin/epinephrine administered every 5 min. Defibrillations were administered if ventricular fibrillation occurred. Hemodynamic variables were evaluated at 5, 15, 30, and 60 min; the primary outcome was survival. All the animals in the lipid group died, whereas all of the vasopressor group animals survived. Additionally, all of the animals in the vasopressor group had higher coronary perfusion pressures during the resuscitation. Possible explanations for the disparate findings between this and the Weinberg study include differences in species, lipid dose (smaller in Mayr's study), and the incorporation of hypoxemia in the model, therefore making it unclear if the cardiac arrest was bupivacaine- or hypoxemia-induced in the setting of local anesthetic toxicity.

Also in 2008, Weinberg's group published two studies addressing the questions raised by the Mayr study. In the first, they compared resuscitation among three groups who received lipid, epinephrine, and saline in their established murine model of bupivacaine-induced cardiac toxicity.[25] Their primary outcome was a rate-pressure product 20% above baseline values at 10 min. The rate-pressure product is an estimation of myocardial work and is derived by multiplying systolic blood pressure by heart rate. Rats assigned to the epinephrine group initially had a higher rate-pressure product than the other two groups, but by 5 min, the lipid rats had a higher rate-pressure product that was sustained until the end of the experiment. In addition, the rats in the lipid group had a better metabolic profile than the other two groups, and four of the five epinephrine animals developed pulmonary edema. In a second experiment, the investigators compared the efficacy of lipid infusion to vasopressin, and a vasopressin/epinephrine mixture.[26] The lipid group received a bolus followed by infusion, the vasopressin group was administered a 0.4 U/kg bolus, and the vasopressin/epinephrine group was given 0.4 U/kg vasopressin with 30 μg/kg epinephrine. Boluses were repeated at 2.5 and 5 min. Again, the lipid rats had a better hemodynamic profile, as well as better tissue perfusion at 10 min. Of concern, all of the rats in the vasopressin group developed pulmonary edema, mimicking the findings of their previous study with epinephrine.

Hicks et al. tried to address the limitations of the Mayr study by comparing lipid emulsion to saline in a resuscitation protocol that included epinephrine and vasopressin in a swine model.[27] A larger dose of bupivacaine was used to induce cardiac arrest and the animals were ventilated with 100% oxygen throughout the resuscitation. One minute after cardiac arrest, chest compressions were started. Epinephrine and vasopressin were given to all animals at 3 min. In order to simulate the delay in obtaining lipid emulsion, they administered the study drug 5 min after arrest. Animals received either a bolus and infusion of 4 mL/kg lipid or an equal volume of saline. Resuscitation consisted of epinephrine every 3 min and defibrillations if indicated. Return of spontaneous circulation was defined as an organized rhythm with a mean arterial blood pressure of at least 60 mm Hg for at least 60. If return of spontaneous circulation had not occurred by 20 min, another 4 mg/kg lipid bolus was given, and the resuscitation continued. The investigators found no differences in the return of spontaneous circulation or coronary perfusion pressures between the two groups at any time point. The authors concluded that there was no advantage to lipid therapy over vasopressor therapy alone.

The unexpected results of the two swine studies raised the questions of whether high doses of epinephrine were