Lipid Emulsion, More Than Reversing Bupivacaine Cardiotoxicity: Potential Organ Protection

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ABSTRACT - Efforts to develop a treatment for bupivacaine cardiotoxicity led to the discovery that Intralipid, a popular brand of intravenous lipid emulsion, could be used not only as an effective treatment for anesthetic-induced cardiac arrest, but also as a means of reversing many other toxicities. Contradictory data exist regarding the mechanism of action of lipid emulsion, a combination of fatty acids traditionally used in parenteral nutrition. Some researchers attribute the effects to lipophilicity and the individual characteristics of the lipids, while other data demonstrate a direct empowering mechanism through cellular upstream and downstream pathways. Understanding the underlying mechanism of action of this safe source of calories may assist in the development of novel organ protective agents. In this review, some of the direct cardiac effects of lipid emulsion are briefly discussed.

INTRODUCTION

Intralipid is the brand name of an emulsion of fatty acids that has been used as a source of calories and essential fatty acids in parenteral nutrition for patients unable to consume nutrition orally. It is an emulsion of soy bean oil, egg phospholipids, and glycerin, and it is available in 10%, 20%, and 30% concentrations. **The major fatty acids in Intralipid are linoleic (44–62%), oleic (19–30%), palmitic (7–14%), linolenic (4–11%), and stearic (1.4–5.5%) acids.** Weinberg's group was the first to introduce Intralipid as an effective therapy to rescue bupivacaine toxicity in rat and canine models (1,2). They proposed the theory of the lipid sink and hypothesized that lipid emulsions form a lipid compartment entrapping bupivacaine (2,3). The Eghbali research group demonstrated multiple cardioprotective effects of Intralipid against ischemia-reperfusion injury (5-16). The exact mechanism of action of lipid emulsion has not yet been elucidated, but accumulating evidence suggests multimodal effects exist (4). Several recently discovered applications and effects of lipid emulsions are described below.

Direct Cardiac Effects of Intralipid

Inotropic Effect. Fettiplace *et al.* demonstrated the inotropic effects of lipid emulsion (17,18) by administering 20% soybean oil to male Sprague-Dawley rats and continuously measuring arterial pressure and aortic flow. Lipid infusion increased aortic flow and arterial pressure faster and to a greater extent than saline infusion. The infusion of lipid emulsion in isolated hearts increased the rate, pressure, and myocardial oxygen demand in a dose-dependent manner. Furthermore, the lipid infusion produced higher aortic flow and peak flows than saline infusion. This study showed that lipid emulsion causes rapid, positive inotropic effects resulting in increased tissue blood flow that contributes to the phenomenon of the lipid rescue effect (18).

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Calcium Influx. Gueret et al. evaluated the hemodynamic effect of Intralipid after verapamil intoxication and concluded that fatty acids increase Ca+ influx into cardiac myocytes, which motivates heart isotropy (19).

Fatty Acid Oxidation / Mitochondria / PI3K / Akt / ERK signaling.
Studies done by Eghbali et al. investigate different aspects of Intralipid molecular mechanisms (11-16). They evaluated the hemodynamic function, infarct size, threshold for the opening of mitochondrial permeability transition pores, and phosphorylation levels of protein kinase B (Akt)/extracellular signal regulating kinase (ERK) in in-vivo rat hearts or isolated Langendorff-perfused mouse hearts that were subjected to ischemia followed by reperfusion with Intralipid (1% ex vivo and one bolus of 20% in-vivo) or vehicle. They concluded that Intralipid inhibits the opening of mitochondrial permeability transition pores and protects the heart through glycogen synthase kinase-3β via PI3K/Akt/ERK pathways (13). In 2012, they compared the cardioprotective effects of Intralipid with cyclosporine-A, a potent inhibitor of mitochondrial permeability transition pore opening, both in-vivo in rats and using the Langendorff technique. They concluded that although Intralipid inhibits the opening of the mitochondrial permeability transition pore as efficiently as cyclosporine-A, Intralipid is more effective in reducing the infarct size and improving the cardiac functional recovery (14). In another study, the same group pretreated rats with a single dose of a fatty acid oxidation inhibitor 5 min before inducing arrest with bupivacaine and then administered Intralipid. They observed high Ca+ retention capacity in cardiac mitochondria and improved cardiac function. They concluded that fatty acid oxidation is a requirement for the successful rescue of bupivacaine-induced cardiotoxicity by lipid emulsion, and they demonstrated this rescue effect via inhibition of mitochondrial permeability transition pore opening (15).

Opioid Receptors. In 2015, Partownavid and colleagues showed involvement of peripheral δ- and κ-opioid receptors in the rescue effect of lipid emulsion in bupivacaine-induced cardiotoxicity (16).

Ischemia-Reperfusion. In multiple experiments, the Eghbali group demonstrated that Intralipid mediated cardioprotective effects against ischemia reperfusion injury. In these experiments, Intralipid was able to reverse the heart damage, restore cardiac function, and limit the infarct size when compared with the control group (4-15). According to a recently published research study, lipid emulsion enhanced cardiac performance after ischemia-reperfusion in isolated squirrel hearts (20).

Leptin. In a recent study, Motayagheni *et al.* showed for the first time that crosstalk exists between Intralipid and leptin in cardioprotection. A leptin antagonist abolished Intralipid protection against ischemia-reperfusion injury in an *ex- vivo* heart model (8).

Apoptosis/miRNA. Researchers investigating the effect of miRNA during the administration of Intralipid found that Intralipid was able to affect apoptosis via miRNA (6,11-12).

Receptors. In another study, Nadrowitz *et al.* indicated that lipid emulsion caused a reduction in the availability of $Nav_{1.5}$, but both Intralipid and Lipofundin reversed $Nav_{1.5}$ blocking by bupivacaine. These effects showed a direct interaction of lipids with $Nav_{1.5}$, and also the ability of lipid emulsions to absorb bupivacaine with a consequent reduction of effective concentration (21). Umar *et al.* demonstrated the possible involvement of GPR40 in Intralipid protection (22).

Insulin Signaling. Fettiplace *et al.* demonstrated that glucose handling by AKT and AMPK is critical for rescue from bupivacaine cardiotoxicity. They showed that lipid emulsion enhances insulin signaling in bupivacaine-induced cardiotoxicity (23).

CONCLUSION

Recent Intralipid success stories have led to many trials investigating its mechanism of action in upstream and downstream pathways. Lipid emulsions may form a compartment as an oil droplet or simply remove the drugs in an action similar to that of soap micelles or cause loosening of the drug-receptor bond via a competitive effect. Furthermore, Intralipid may act as a “power source”

for an individual receptor or produce crosstalk with other agents such as leptin, and this may lead to the discovery of a new cascade and novel therapeutic targets. Despite the contradictory debates on mechanism of action, the volume of supporting evidence is enough to consider lipid emulsion as a novel protective target. In addition to understanding the underlying mechanism, further questions including appropriate dose, time of administration, and therapeutic window remain to be answered. Once we have answered these questions, we may be able to utilize lipid emulsion widely as a unique organ-protective agent.

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