

The Importance of Intralipid in Heart Protection: A Brief Review

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Abstract

Intralipid as a first safe fat emulsion for human use has been shown to be cardio protective in some recent studies. This is a brief review with the main focus on recent studies about intralipids and their role in the heart protection. Intralipids as a source of calories have been applied for several years to cure patients. However, there are rare reports in the case of rescuing effect in many toxicities specially cardiotoxicity. Thus, more investigations are still needed to explain the basic mechanism of intralipids concerning to heart protection and resulting new applications.

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Introduction

Intravenous lipid emulsion (ILE) is a new technique to treat local anesthetic systemic toxicity (LAST) as well as an effective antidote for other lipophilic drug poisonings. In recent years numerous applications of intralipids have efficaciously investigated in critical care patients. This emulsion based material has been applied as a main source of essential fatty acids for parenteral nutrition. That is an emulsion of soy bean oil, egg phospholipids and glycerin, and is accessible in three concentrations: 10%, 20% and 30% that the latter concentration has not been accepted for direct intravenous infusion^[1]. Many investigations have been performed in order to understand more the mechanism of this new treatment.

Heart diseases are the main groups for the death of millions of people every year. There are some main risk factors that can be influenced on heart protection. These factors can be changed to lower the risk of cardiovascular disease and therefore death. Three main factors are hypercholesterolemia, hypertension, and cigarette smoking. Controlling of these factors mainly can improve the patient situation. According to reports, even patients with asymptomatic cardiovascular disease have been reported to benefit from aggressive cholesterol-lowering therapy. Furthermore, managing hypertensive disease by new guidelines showed that treatment decisions can be improved^[2,3]. Moreover, former smokers have shown less risk of myocardial

infarction compare to smoker persons^[4,5]. Then, managing of risk factors can convert them into protection factors.

In the most cases, the reperfusion injury is more injuring than the ischemia itself owing to oxidative damage caused by free radicals and calcium overload as an outcome of reintroduction of blood to the tissue. Pharmacological post conditioning has been used to protect the heart against ischemia/reperfusion injury. Though, none of pharmacological agents have been extensively accepted. Li et al have presented a report about post ischemic treatment with intralipid in 2012 as the first safe fat emulsion for human use. The authors stated that such an emulsion can improve the cardiac functional recovery of isolated Langendorff-perfused mouse hearts by ~ 4 fold and outcomes in 70% reduction in the myocardial infarct size^[6].

In this review the importance of intralipid have presented. Indeed, this is a brief review with the main focus on recent studies about intralipids and their role in the heart protection.

Intralipid in Heart Protection

According to reports, sudden cardiac arrest cause up to 400000 deaths yearly in the US. Cardiac arrest could be due to abnormally slow heart rate known as bradycardia. Bradycardia is a catastrophic event which is associated with significant mortality and morbidity^[3,7,8].

Li et al have presented a report about post ischemic



treatment with intralipid in 2012 as the first safe fat emulsion for human use. The authors stated that such an emulsion can improve the cardiac functional recovery of isolated Langendorff-perfused mouse hearts by ~ 4 fold and outcomes in 70% reduction in the myocardial infarct size. Their results showed that intralipid can be as potent as cyclosporine-A in inhibiting mPTP opening. According to authors, intralipid is also more effective than cyclosporine-A in decreasing the infarct size. *In vivo* dose of intralipid (at 5ml/kg) in their work was within recommended range by American Society of Regional Anesthesia and Pain Medicine for rescuing bupivacaine cardiotoxicity in patients. They concluded that according to their results intralipid can introduce as a new beneficial agent for acute myocardial infarction patients^[6].

Rahman et al, showed that intralipid can protect the heart against ischemia/reperfusion injury as well as bupivacaine induced cardiotoxicity^[9] and then their group also examined the effect of intralipid on the heart protection against bradycardia on wild type female mice C57/Bl6 (2 - 4 month old). The recorded results showed that the heart rates at the baseline before inducing bradycardia was 224 ± 7 beats/min and the left ventricular pressures was 64 ± 4 mmHg. Then, administration of Xylazine reduced the heart rate meaningfully to 81 ± 9 beats/min and left ventricular pressure to 5 ± 2 mmHg ($p < 0.001$). Their main result was that the perfusion of the heart with intralipid rapidly restored the heart rate to 209 ± 30 and left ventricular pressure to 59 ± 4 . The amounts those were not meaningfully different than their values before inducing bradycardia at the baseline. They reported that according to in-vivo results, only one bolus of Intralipid (20%) right before reperfusion is enough to protect the heart against ischemia/reperfusion injury. Their results also revealed that application of intralipid at the reperfusion can improve the functional recovery of isolated Langendorff-perfused mouse hearts by ~4 fold and significantly reduces the infarct size. Therefore, intralipid presented the ability to rapidly reverse bradycardia in female mice^[10].

In another study by Motayagheni et al, the results showed that intralipid reduced the infarct size on male Sprague-Dawley young rats of ischemia/reperfusion injury by ~70% and mainly-improved heart functional recovery after an ischemic insult in isolated Langendorff-perfused hearts. As micro RNA (miRNA) has been involved as a regulatory molecule in many cardiovascular diseases (such as myocardial ischemia/reperfusion injury, in that work we evaluated the role of miRNA-1 (miR-1) and MiR-144 in intralipid-induced cardio-protection against ischemia/reperfusion ischemia/reperfusion injury. According to their obtained results, infarct size was significantly smaller in the intralipid group compared to control. The micro-RNA data revealed that the expression of miR-1 was significantly upregulated in the hearts subjected to in-vivo ischemia/reperfusion injury which received one bolus of intralipid compared to control hearts. Expression of miR-144 was also upregulated in intralipid group compared to control in hearts subjected to ischemia/reperfusion injury. The involved cardio protection molecular mechanisms related to intralipid protection were not well understood^[11].

Based on informed reports, over the past decade the prevalence of coronary artery disease through pregnancy has significantly increased in women owing to increased maternal age as well as their lifestyle that become including stress, smoking, diabetes and chronic hypertension. Ischemic heart disease

during pregnancy leads to a noticeably worse prognosis than in non-pregnant women^[12-15]. Lipids, particularly polyunsaturated fatty acids, have gotten superior attention in the field of cardiovascular research and also prevalence of coronary artery disease through pregnancy. Li, et al, recently confirmed that the heart of late pregnant rodents is more prone to ischemia/reperfusion injury compared to non-pregnant rodents. Their results showed that intralipid can protect the heart in late pregnancy against ischemia/reperfusion injury by inhibiting the mPTP opening through Cav2/STAT3/GSK-3 β pathway. Intralipid-induced proposed cardio-protection mechanism against ischemia/reperfusion injury showed that administration of intralipid at the time of reperfusion can protect the heart in late pregnant by recruiting Cav2 causing to phosphorylation increment of STAT3, which converges to phosphorylate GSK-3 β , and, in turn, inhibits the opening of the mPTP and finally induces protection against reperfusion injury^[16].

In another work, Li et al hypothesized that intralipid can protect the heart in late pregnancy by regulating the levels of specific microRNAs. The results based on microRNA-microarray tests recognized MiR122 as a new micro-RNA that its expression was amazingly upregulated more than 10 fold in the heart of late pregnancy rats in intralipid group compared to control group. The authors suggested that miR122 regulates apoptosis in cardio-myocytes related to hypoxia/re-oxygenation since miR122-overexpression caused to diminished apoptosis, whereas knockdown of miR122 increased apoptosis. Pyruvate kinase isoform M2 (PKM2), which is known to regulate cell apoptosis in the liver, is a direct target of miR122. The obtained data showed that Pyruvate kinase isoform M2 (as a cell apoptosis regulator in the liver) and caspase 3 were 2 targets of miR122 since the expression of Pyruvate kinase isoform M2 and caspase-3 in the hearts subjected to ischemia/reperfusion injury was significantly lower in intralipid group compared to control group in late pregnancy^[17].

Other New Applications of Intralipids

In recent studies various applications of intralipid have been reported. Indeed, intravenous lipid emulsion therapy was introduced as a treatment for local anesthetic toxicity. Then, the other applications of intralipid such as ability in heart protection were appeared. It has also been used in other area such as using in pro-inflammatory response treatment, in cancer therapy area or as treating unexplained recurrent spontaneous abortion. Sanches et al, assessed the effects of increasing the energy availability from intralipid on steers alters aspects of the innate immune response to endotoxin challenge. Their results showed increased circulating non-esterified fatty acids with a lipid emulsion modulates the pro-inflammatory response in steers^[18]. In another study, intralipid decreased platinum containing anti-cancer drugs accumulation in the liver, spleen, and kidney. The authors stated that the mechanism was through decreasing reticulo-endothelial system (RES) uptake and then increasing the bioavailability of the anti-cancer drug^[19]. In recent years, the investigators also evaluated the mechanisms of applying intralipid in treating unexplained recurrent spontaneous abortion. The authors suggested that intralipid can use as an alternative to intravenous immunoglobulin^[20].

Conclusion

Although intralipids as a source of calories have been applied for several years, there are rare reports in the case of rescuing effect in many toxicities specially bupivacaine cardiotoxicity. So, more trials are still essential to clarify the basic mechanism of intralipids regarding to heart protection and resulting new applications.

Conflict of interest: The author declares no conflict of interest.

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