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Can intralipid infusion open a coronary occlusion causing acute myocardial infarction?

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Abstract

Coronary heart disease remains the leading cause of morbidity and mortality in Western countries. The best hope of salvaging viable myocardium after a coronary occlusion is by rapid reperfusion of the ischemic myocardium, either by thrombolysis or primary percutaneous coronary intervention. The use of intravenous intralipid infusion instead of thrombolysis or primary percutaneous coronary intervention is first suggested in the medical literature.

Thrombolysis or primary percutaneous coronary intervention or Intralipid Infusion?

Coronary heart disease remains the leading cause of morbidity and mortality in Western countries. The best hope of salvaging viable myocardium after a coronary occlusion is by rapid reperfusion of the ischemic myocardium, either by thrombolysis or primary percutaneous coronary intervention. Although reperfusion restores blood flow, oxygen, and nutrients to the cardiac muscle, it also has the potential to induce reperfusion injury.

Postconditioning of the heart with brief episodes of reperfusion/occlusion at the onset of reflow has been shown to limit infarct size. However, this approach is not practical for patients treated with thrombolytic agents and therefore a more generic pharmacologic postconditioning is still needed. The ideal pharmacologic candidates need to be safe and effective when administered during the first few minutes of reperfusion by inducing cellular protection or enhancing myocardial tolerance to ischemia/reperfusion injury. Several drugs have yielded encouraging results in animals and a few have been tested in humans; however, none of these modalities has been widely accepted.

Lipids and in particular polyunsaturated fatty acids have received special cardiovascular research attention because polyunsaturated fatty acid-rich diets are associated with a decreased risk of coronary artery disease. Acute application of polyunsaturated fatty acids to cardiomyocytes has also been shown to shorten action potential duration and this could account for the antiarrhythmic mechanism of the polyunsaturated fatty acids. Intralipid (Sigma, St. Louis, MO) is a brand name for the first safe fat emulsion for human use; Intralipid 20% is an emulsion of soybean oil (20%), egg yolk phospholipids (1.2%), and glycerol (2.2%). Intralipid has been widely used in patients who need total parenteral nutrition and as a vehicle for different drugs such as propofol. It has been shown recently that postischemic administration of Intralipid protects the isolated rat heart against ischemia/reperfusion injury. However, the molecular mechanism in which Intralipid mediates cardioprotection is completely unknown [1].

Intralipid, a brand name for the first safe fat emulsion for human use, has been shown to be cardioprotective. However, the mechanism of this protection is not known. The authors investigated the molecular mechanism(s) of Intralipid-induced cardioprotection against ischemia/reperfusion injury, particularly the role of glycogen synthase kinase-3β (GSK-3β) and mitochondrial permeability transition pore in this protective action.

In vivo rat hearts or isolated Langendorff-perfused mouse hearts were subjected to ischemia followed by reperfusion with Intralipid (1% in ex vivo and one bolus of 20% in in vivo) or vehicle. The hemodynamic function, infarct size, threshold for the opening of mitochondrial permeability transition pore, and phosphorylation levels of protein kinase B (Akt)/extracellular signal regulating kinase (ERK)/GSK-3β were measured.

Administration of Intralipid at the onset of reperfusion resulted in approximately 70% reduction in infarct size in the in vivo rat model. Intralipid also significantly improved functional recovery of isolated Langendorff-perfused mouse hearts as the rate pressure product was increased from 2,999 ± 863 mmHg*beats/min in the control group to 13,676 ± 611 mmHg*beats/min (mean±SEM) and the infarct size was markedly smaller (18.3 ± 2.4% vs. 54.8 ± 2.9% in the control group, $P < 0.01$). The Intralipid-induced cardioprotection was fully abolished by LY294002, a specific inhibitor of PI3K, but only partially by PD98059, a specific ERK inhibitor. Intralipid also increased the phosphorylation levels of Akt/ERK1/glycogen synthase kinase-3β by eightfold, threefold, and ninefold, respectively. The opening of mitochondrial permeability transition pore was inhibited by Intralipid because calcium retention capacity was higher in the Intralipid group (274.3 ± 8.4 nM/mg vs. 168.6 ± 9.6 nM/mg in the control group).

Postischemic treatment with Intralipid inhibits the opening of mitochondrial permeability transition pore and protects the heart through glycogen synthase kinase-3β via PI3K/Akt/ERK pathways (1).

It was recently shown that postischemic administration of intralipid protects the heart against ischemia-reperfusion injury.

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Here we compared the cardioprotective effects of intralipid with cyclosporine-A, a potent inhibitor of the mitochondrial permeability transition pore opening.

In vivo rat hearts or isolated Langendorff-perfused mouse hearts were subjected to ischemia followed by reperfusion with intralipid (0.5%, 1% and 2% ex-vivo, and 20% in vivo), cyclosporine-A (0.2 μM, 0.8 μM, and 1.5 μM ex- vivo and 10 mg/kg in vivo), or vehicle. The hemodynamic function, infarct size, calcium retention capacity, mitochondrial superoxide production, and phosphorylation levels of protein kinase B (Akt)/glycogen synthase kinase- 3β (GSK-3β) were measured. The values are mean ± SEM.

Administration of intralipid at reperfusion significantly reduced myocardial infarct size compared with cyclosporine-A in vivo (infarct size/area at risk) %: 22.9 ± 2.5% vs. 35.2 ± 3.5%; P = 0.030, n = 7/group). Postischemic administration of intralipid at its optimal dose (1%) was more effective than cyclosporine-A (0.8 μM) in protecting the ex vivo heart against ischemia-reperfusion injury, as the rate pressure product at the end of reperfusion was significantly higher (mmHg · beats/min: 12,740 ± 675 [n = 7] vs. 9,203 ± 10,781 [n = 5], P = 0.024), and the infarct size was markedly smaller (17.3 ± 2.9 [n = 7] vs. 29.2 ± 2.7 [n = 5], P = 0.014). Intralipid was as efficient as cyclosporine-A in inhibiting the mitochondrial permeability transition pore opening (calcium retention capacity = 280 ± 8.2 vs. 260.3 ± 2.9 nmol/mg mitochondria protein in cyclosporine-A, P = 0.454, n = 6) and in reducing cardiac mitochondrial superoxide production. Unlike intralipid, which increased phosphorylation of Akt (6-fold) and GSK-3β (5-fold), cyclosporine-A had no effect on the activation of these prosurvival kinases.

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 [2].

It was recently demonstrated that the heart of late pregnant (LP) rodents is more prone to ischemia/reperfusion (I/R) injury compared to non-pregnant rodents. Lipids, particularly polyunsaturated fatty acids, have received special attention in the field of cardiovascular research. Here, we explored whether Intralipid (ITLD) protects the heart against I/R injury in LP rodents and investigated the mechanisms underlying this protection.

In-vivo female LP rat hearts or ex-vivo isolated Langendorff-perfused LP mouse hearts were subjected to ischemia followed by reperfusion with PBS or ITLD (one bolus of 5mg/kg of 20% in in-vivo and 1% in ex-vivo). Myocardial infarct size, mitochondrial calcium retention capacity, genome-wide expression profiling, pharmacological inhibition and co- immunoprecipitation were performed. One bolus of ITLD at reperfusion significantly reduced the in-vivo myocardial infarct size in LP rats (23.3±2% vs. 55.5±3.4% in CTRL, p<0.01). Postischemic administration of ITLD also protected the LP hearts against I/R injury ex-vivo. ITLD significantly increased the threshold for the opening of the mitochondrial permeability transition pore in response to calcium overload (nmol-calcium/mg- mitochondrial protein: 290±17 vs. 167±10 in CTRL, p<0.01) and significantly increased phosphorylation of STAT3 (1.8±0.08 vs. 1±0.16 in CTRL, p<0.05) and GSK-3β (2.63±0.55 vs.1±0.0.34 in CTRL, p<0.05). The ITLD-induced cardioprotection was fully abolished by Stattic, a specific inhibitor of STAT3. Transcriptome analysis revealed caveolin 2 (Cav2) was significantly upregulated by ITLD in hearts of LP rats under I/R injury. Co- immunoprecipitation experiments showed that Cav2 interacts with STAT3. ITLD protects the heart in late pregnancy against I/R injury by inhibiting the mPTP opening through Cav2/STAT3/GSK-3β pathway [3].

Recent studies have demonstrated that intralipid (ILP) conferred myocardial protection against ischemia-reperfusion (IR) injury through activation of reperfusion injury salvage kinase (RISK) pathway. As RISK signal has been shown to be impaired in hypertrophied myocardium, we investigated whether ILP-induced cardiac protection was maintained in hypertrophied rat hearts. Transverse aortic constriction was performed on male Sprague- Dawley rats to induce left ventricular hypertrophy, then sham-operated or hypertrophied rat hearts were isolated and perfused retrogradely by the Langendorff for 30 min (equilibration) followed by 40 min of ischemia and then 120 min of reperfusion. The isolated hearts received 15-min episode of 1% ILP separated by 15 min of washout or three episodes of 5-min ischemia followed by 5-min reperfusion before ischemia. The hemodynamics, infarct size, apoptosis, phosphorylated protein kinase B (p-Akt), phosphorylated extracellular regulated protein kinase 1/2 (ERK1/2), phosphorylated glycogen synthase kinase 3β (GSK3β), Bcl-2, phosphorylated Bad, and Bax were determined. We found that ILP significantly improved left ventricular hemodynamics and reduced infarct size and the number of TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling)-positive cells in the sham- operated rat hearts exposed to IR. However, such myocardial infarct-sparing effect of ILP was completely blocked by phosphatidylinositol-3-kinase inhibitor wortmannin, but only partially by mitogen-activated protein kinase kinase inhibitor PD98059 in sham-operated hearts. Intralipd upregulated the phosphorylation of Akt, extracellular regulated protein kinase 1/2 (ERK1/2), and their downstream target of GSK3β and antiapoptotic Bcl-2 expression in healthy rat hearts. Nonetheless, ILP failed to improve left ventricular hemodynamics and reduced infarct size and apoptosis and increase the phosphorylated Akt, ERK1/2, GSK3β, and antiapoptotic Bcl-2 in hypertrophied myocardium. In contrast, ischemic preconditioning increased the phosphorylation of Akt, ERK1/2 and GSK3β, improved heart pump function, and reduced myocardial necrosis in sham-operated hearts, a phenomenon partially attenuated by ventricular hypertrophy. Interestingly, GSK inhibitor SB216763 conferred cardioprotection against IR injury in sham-operated hearts, but failed to exert cardioprotection in hypertrophied myocardium. Our results indicated that ventricular hypertrophy abrogated ILP-induced cardioprotection against IR injury by alteration of RISK/GSK3β signal [4].

Elevated low-density lipoprotein cholesterol and triglycerides are major risk factors for coronary artery disease. However, fatty acids from triglycerides are a major energy source, low-density lipoprotein cholesterol is critical for cell membrane synthesis, and both are critical for cell survival. This study was designed to clarify the relationship between lipid profile, morbidity as assessed by Killip classification, and 30-day mortality in patients with acute myocardial infarction.

Seven hundred twenty-four patients with acute myocardial infarction in the coronary care program of the Bureau of Health Promotion were analyzed. Low-density lipoprotein cholesterol and triglyceride levels were significantly lower in high- Killip (III+IV) patients compared with low-Killip (I+II) patients and in those who died compared with those who survived beyond 30 days (both p<0.001). After adjustment for risk factors, low-density lipoprotein cholesterol less than 62.5 mg/dL and triglycerides less than 110 mg/dL were identified as optimal threshold values for predicting 30-day mortality and were associated with hazard ratios of 1.65 (95% CI, 1.18-2.30) and 5.05 (95% CI, 1.75-14.54), and the actual mortality rates were 23% in

low low-density lipoprotein, 6% in high low- density lipoprotein, 14% in low triglycerides, and 3% in high triglycerides groups, respectively. To test the synergistic effect, high-Killip patients with triglycerides less than 62.5 mg/dL and low-density lipoprotein cholesterol less than 110 mg/dL had a 10.9-fold higher adjusted risk of mortality than low-Killip patients with triglycerides greater than or equal to 62.5 mg/dL and low-density lipoprotein cholesterol greater than or equal to 110 mg/dL ($p<0.001$). The lipid paradox also improved acute myocardial infarction short-term outcomes prediction on original Killip and thrombolytic in myocardial infarction scores.

Low low-density lipoprotein cholesterol, low triglycerides, and high Killip severity were associated with significantly higher 30-day in-hospital mortality in patients presenting with acute myocardial infarction. The initial lipid profile of patients with acute myocardial infarction may therefore hold prognostic value [5].

Emulsified isoflurane (EIso)

Volatile anesthetic postconditioning reduces myocardial infarct size against ischemia/reperfusion (I/R) injury. We tested the hypothesis that emulsified isoflurane (EIso) administrated after ischemia exerts cardioprotection in a rat model of myocardial I/R. Male SD rats underwent 30-min coronary occlusion followed by 3-h reperfusion except for sham rats. All vehicles were administrated intravenously at reperfusion onset for 30 min. In the first study, 56 rats were given saline (CON), 30% intralipid (IL) and 1, 2, 4, 8 or 16 mL/kg EIso for infarct size measurement. In a second study, 32 rats were randomized to four groups and administrated saline in sham (sham) and control (CON) groups, 30% intralipid in IL group and 2 mL/kg emulsified isoflurane in EIso group. Cardiomyocytic enzyme activity was determined. Myocardial mitochondria and cytosol were isolated to determine mitochondrial energy metabolism, cytochrome c release, mitochondrial membrane potential ($\Delta\Psi m$) and opening of the mitochondrial permeability transition pore (mPTP). Morphologic changes in mitochondria were observed by transmission electron microscopy. Compared with CON and IL, 2, 4 and 8 mL/kg EIso limited infarct size ($P < 0.01$). Serum levels of cardiac enzyme leakage were reduced in EIso-treated hearts compared with CON ($P < 0.01$ or $P < 0.05$). EIso preserved the ultrastructure of mitochondria, protected against mPTP opening, decreased cytochrome c release and preserved ATP production and $\Delta\Psi m$. In conclusion, EIso is effective in reducing infarct size and in preserving mitochondrial function after ischemia and reperfusion injury [6].

The purpose of this study was to investigate whether adding emulsified isoflurane to St Thomas cardioplegia solution could enhance the cardiac protection after cardioplegic arrest in rats. Thirty isolated heart preparations (male Sprague-Dawley rats) were randomly divided into 3 groups (n = 10/group) according to the different cardioplegia solutions being given: St Thomas solution mixed with emulsified isoflurane (containing 2.8% of isoflurane, group EI), St Thomas solution mixed with emulsified Intralipid (Huarui Pharmacy, Wuxi, Jiangsu, China) (group EL), and St Thomas solution alone (group St). In the 35-minute normothermic ischemia period, infusion of cardioplegia solution was repeated every 15 minutes. After the 35-minute ischemia period, the heart was perfused with Krebs-Henseleit buffer for another 2 hours.

The functional parameters of the heart were monitored throughout the experiments. The coronary effluent was collected for measuring the activity of CK-MB 30 minutes after reperfusion, and the infarct size was assessed at the end of reperfusion. The infarct size in group EI (24% +/- 4%) was reduced when compared with that in group EL (31% +/- 8%, $p < 0.05$) and group St (43% +/- 9%, $p < 0.001$). The CK-MB activity in group EI was decreased significantly when compared with that in group EL and group St ($p < 0.05$). The functional recovery in group EI also was improved. Compared with standard St Thomas solution alone, adding 30% Intralipid alone also significantly reduced the infarct size and the CK-MB leakage and improved the recovery of the mechanical function.

St Thomas cardioplegia solution supplemented with emulsified isoflurane enhanced its cardioprotection in an isolated heart ischemia reperfusion injury model in rats [7].

Pretreatment with volatile anesthetics has been demonstrated to exert cardioprotective effects. The purpose of this study was to examine the effect of emulsified isoflurane, a new formulation of isoflurane in lipid emulsion, administered intravenously in an ischemia and reperfusion model of myocardial injury. Thirty-two Sprague Dawley rats of both sexes were subjected to 30 min of myocardial ischemia followed by 180 min of reperfusion. Each was assigned to one of four pretreatment groups to receive an isovolumetric intravenous infusion of saline: control group, 30% intralipid group, 8% emulsified isoflurane 2 ml kg^{-1}group, and sham group (each group, n = 8). The vehicles were administered at a constant rate for 30 min and then discontinued 30 min before left anterior descending coronary artery occlusion. The cardioprotective effects were examined by determining hemodynamics, infarct size, enzyme activity, and cardiomyocytic apoptosis.

Pretreatment with emulsified isoflurane 2 ml kg^{-1}($P = 0.000$) significantly reduced infarct size (22.6 +/- 2.2%) compared with control (34.8 +/- 2.3%) and 30% intralipid (31.1 +/- 2.9%). When compared with the control and intralipid groups, emulsified isoflurane increased Bcl-2 expression while decreasing Bax and Caspase-3 expression and enhancing Bcl-2/Bax ratios. The apoptotic index in the emulsified isoflurane treatment group showed a significant reduction compared with that in the control group ($P = 0.000$) and the intralipid group ($P = 0.001$). In addition, the serum levels of lactate dehydrogenase and creatine kinase were markedly reduced in the emulsified isoflurane treatment group compared with the control and intralipid groups (lactate dehydrogenase, $P = 0.015$ vs. control; creatine kinase, $P = 0.000$ vs. control and intralipid).

These data support a cardioprotective effect of intravenous emulsified isoflurane against myocardial ischemia and reperfusion injury, which are mediated, at least in part, by the inhibition of apoptosis and cell damage [8]. It has been shown that inhaled isoflurane limits the size of myocardial infarcts. The aim of the present study was to examine the effects of emulsified isoflurane on cardiac function and myocardial apoptosis in an ischaemia model of myocardial injury. In the first study, 48 rats were randomly allocated to six groups (n = 8 in each): control (saline); emulsified isoflurane (EIso) at 1, 2 or 4 mL/kg; 30% intralipid (vehicle for EIso); and sham operated. Rats received isovolumetric intravenous infusions for 30 min and then, 30 min after cessation of the infusion, 90 min coronary occlusion. Haemodynamics and myocardial infarct size were measured. In the second study, another 48 rats were randomized into six groups (n = 8 in each). After 90 min ischaemia, rats were killed for histopathological study, immunohistochemical evaluation and apoptosis measurement. Pretreatment with 2 and 4 mL/kg EIso significantly attenuated decreases in left ventricular systolic pressure and dP/dt(max), and increases in left ventricular end-diastolic pressure and -dP/dp(max), and alleviated myocardial injury compared with the control, intralipid and 1 mL/kg EIso groups ($P < 0.05$). Infusion of 1 mL/kg EIso and

intralipid had no effect on haemodynamics, infarct size or histological variables. Expression of Bcl-2 was increased, whereas expression of Bax and caspase 3 was decreased, after preconditioning with 2 and 4 mL/kg EIso ($P < 0.05$). The apoptotic index in the 2 and 4 mL/kg Eiso-treated groups was reduced compared with that in the control and intralipid groups ($P < 0.01$). In conclusion, EIso ameliorates cardiac dysfunction, attenuates myocardial damage and inhibits apoptosis after ischaemia, which may be attributed, in part, to diminished expression of apoptosis-related protein [9].

To evaluate the protective effects of 8% emulsified isoflurane after myocardial ischemia- reperfusion injury and its mechanism in rabbits. Twenty-four male adult New Zealand white rabbits were anesthetized with intravenous injection of 30 mg/kg pentobarbital followed by 5 mg x kg^{-1} x h^{-1} infusion. All rabbits were subjected to 30 minutes of left anterior descending coronary artery (LAD) occlusion and 3 hours of subsequent reperfusion. Before LAD occlusion, the rabbits were randomly allocated into three groups for preconditioning treatment (eight for each group). The control group (C group) received intravenously 0.9% NaCl for 30 minutes. The emulsified isoflurane group (EI group) received 8% emulsified isoflurane intravenously till 0.64% end-tidal concentration for 30 minutes that was followed by a 15-minute washout period.

The Intralipid group (IN group) received 30% Intralipid for 30 minutes. The infarcted area, plasma malondialdehyde (MDA) content, superoxide dismutase activity (SOD) and nitrite concentration after 3-hour myocardial perfusion were recorded simultaneously.

For the myocardial ischemia-reperfusion injury animals, the infarcted size in the EI group was significantly reduced (91.9% +/- 8%) as compared with control group (39% +/- 6%, $t=5.19$, $P<0.01$). The plasma SOD activity and nitrite concentration in EI group were significantly higher than those in control group ($t=2.82$, $t=8.46$, $P<0.05$), but MDA content was lower in EI group than that in control group ($t=2.56$, $P<0.05$).

The results indicate that emulsified isoflurane has a cardioprotection effect against ischemia- reperfusion injury. This beneficial effect of emulsified isoflurane is probably through NO release and consequently by increase in antioxidation of myocardium [10]. In this study, we examined the cardioprotective effects of parental emulsified isoflurane compared with inhaled isoflurane.

Thirty-two rabbits were subjected to 30 min of myocardial ischemia induced by temporary ligation of the left anterior descending coronary artery followed by 3 h of reperfusion. Before left anterior descending coronary artery occlusion, the rabbits were randomly allocated into one of four groups (eight for each group): group C, no ischemia preconditioning treatment; group IS, inhaled isoflurane 1.1% end-tidal; group EI, a continuous infusion of 8% emulsified isoflurane to an end-tidal concentration of 0.64%; and group IN, a continuous infusion of 30% Intralipid started 30 min. Treatments were started 30 min before ischemia followed by a 15 min washout period for isoflurane groups. Myocardial infarct volume, lactate dehydrogenase, and creatine kinase levels were measured and changes in mitochondrial ultrastructure assessed after 3 h myocardial reperfusion.

Myocardial infarct size 3 h after reperfusion was lower in groups IS and EI compared with groups C and IN (20% +/- 8%, 18% +/- 8%, 39% +/- 6%, and 34% +/- 9%, respectively, $P < 0.01$). There were no differences in myocardial infarct size between groups IS and EI or between groups C and IN. Plasma lactate dehydrogenase and creatine kinase levels were lower in group IS (456 +/- 58 U/L and 1725 +/- 230 U/L) and group EI (451 +/- 54 U/L and 1686 +/- 444 U/L) 3 h after myocardial reperfusion compared with groups C (676 +/- 82 U/L and 2373 +/- 529 U/L; $P < 0.01$). Mitochondrial ultrastructure changes were less pronounced in groups IS and EI compared with group C.

Our results indicate that, in rabbits, i.v. emulsified isoflurane provides similar myocardial protection against ischemia-reperfusion injury as inhaled isoflurane [11].

The Intralipid Sink Effect

Papadopoulou A et al. [12] hypothesized that by substituting a dye surrogate in place of local anesthetic, they could visually demonstrate dye sequestration by lipid emulsion that would be dependent on both dye lipophilicity and the amount of lipid emulsion used.

They selected 2 lipophilic dyes, acid blue 25 and Victoria blue, with log P values comparable to lidocaine and bupivacaine, respectively. Each dye solution was mixed with combinations of lipid emulsion and water to emulate "lipid rescue" treatment at dye concentrations equivalent to fatal, cardiotoxic, and neurotoxic local anesthetic plasma concentrations. The lipid emulsion volumes added to each dye solution emulated equivalent intravenous doses of 100, 500, and 900 mL of 20% Intralipid in a 75-kg adult. After mixing, the samples were separated into a lipid-rich supernatant and a lipid-poor subnatant by heparin flocculation. The subnatants were isolated, and their colors compared against a graduated dye concentration scale.

Lipid emulsion addition resulted in significant dye acquisition by the lipid compartment accompanied by a reduction in the color intensity of the aqueous phase that could be readily observed. The greatest amount of sequestration occurred with the dye possessing the higher log P value and the greatest amount of lipid emulsion. This study provides a visual demonstration of the lipid sink effect. It supports the theory that lipid emulsion may reduce the amount of free drug present in plasma from concentrations associated with an invariably fatal outcome to those that are potentially survivable.

Local anesthetic (LA) intoxication with cardiovascular arrest is a potential fatal complication of regional anesthesia. Lipid resuscitation has been recommended for the treatment of LA- induced cardiac arrest. Aim of the study [13] was to compare four different rescue regimens using epinephrine and/or lipid emulsion and vasopressin to treat cardiac arrest caused by bupivacaine intoxication.

Twenty-eight piglets were randomized into four groups (4 × 7), anesthetized with sevoflurane, intubated, and ventilated. Bupivacaine was infused with a syringe driver via central venous catheter at a rate of 1 mg·kg^{-1}·min^{-1} circulatory arrest. Bupivacaine infusion and sevoflurane were then stopped, chest compression was started, and the pigs were ventilated with 100% oxygen. After 1 min, epinephrine 10 μg·kg^{-1} (group 1) Intralipid(®) 20% 4 ml·kg^{-1} (group 2), epinephrine 10 μg·kg^{-1} + Intralipid(®) 4 ml·kg^{-1} (group 3) or 2 IU vasopressin + Intralipid(®) 4 ml·kg^{-1} (group 4) were administered. Secondary epinephrine doses were given after 5 min if required.

Survival was 71%, 29%, 86%, and 57% in groups 1, 2, 3, and 4. Return of spontaneous circulation was regained only by initial administration of epinephrine alone or in combination with Intralipid(®). Piglets receiving the combination therapy survived without further epinephrine support. In contrast, in groups 2 and 4, return of spontaneous circulation was only achieved after secondary epinephrine rescue.

In cardiac arrest caused by bupivacaine intoxication, first-line rescue with epinephrine and epinephrine + Intralipid(®) was more effective with regard to survival than Intralipid(®) alone and vasopressin + Intralipid(®) in this pig model [14]. Local anesthetic (LA) intoxication with severe hemodynamic compromise is a potential catastrophic event. Lipid resuscitation has been recommended for the treatment of LA- induced cardiac arrest. However, there are no data about effectiveness of Intralipid for the treatment of severe cardiovascular compromise prior to cardiac arrest. Aim of this study was to compare effectiveness of epinephrine and Intralipid for the treatment of severe Hemodynamic compromise owing to bupivacaine intoxication, anesthetized Piglets were with sevoflurane, intubated, and ventilated. Bupivacaine was infused with a syringe driver via a central venous catheter at a rate of 1 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$ until invasively measured mean arterial pressure (MAP) dropped to 50% of the initial value. Bupivacaine infusion was then stopped, and epinephrine 3 $\mu g{\cdot}kg^{-1}$ (group 1), Intralipid(®) 20% 2 $ml{\cdot}\ kg^{-1}$ (group 2), or

Intralipid 20% 4 $ml{\cdot}\ kg^{-1}$ (group 3) was immediately administered. Twenty-one piglets (3 × 7), were recorded. All animals in group 1 (100%) but only four of seven (57%) piglets in group 2 and group 3, respectively, survived. Normalization of hemodynamic parameters (HR, MAP) and ET(CO_2) was fastest in group 1 with all piglets achieving HR and MAP values. hemodynamic compromise owing to bupivacaine intoxication in piglets, first-line rescue with epinephrine was more effective than Intralipid with regard to survival as well as normalization of hemodynamic parameters and ET(CO_2) [15]. Intravenous lipid emulsion (ILE) has been proposed as a rescue therapy for severe local anesthetic drugs toxicity, but experience is limited with other lipophilic drugs. An 18-year- old healthy woman was admitted 8 h after the voluntary ingestion of sustained-release diltiazem (3600 mg), with severe hypotension refractory to fluid therapy, calcium salts, and high-dose norepinephrine (6.66 µg/kg/ min). Hyperinsulinemic euglycemia therapy was initiated and shortly after was followed by a protocol of ILE (intralipid 20%, 1.5 ml/kg as bolus, followed by 0.25 ml/kg over 1h). The main finding attributed to ILE was an apparent rapid decrease in insulin resistance, despite a prolonged serum diltiazem elimination half- life. Diltiazem is a lipophilic cardiotoxic drug, which could be sequestered in an expanded plasma lipid phase. The mechanism of action of ILE is not known, including its role in insulin resistance and myocardial metabolism in calcium-channel blocker poisoning [16].

Conclusion

The use of intravenous intralipid infusion instead of thrombolysis or primary percutaneous coronary intervention is first suggested in the medical literature.

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