

Efficacy of resuscitation with Intralipid in a levobupivacaine-induced cardiac arrest model

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Aim: Cardiac toxicity due to the administration of local anesthetics may be fatal. In this study, we evaluated the efficacy of a 20% lipid solution combined with epinephrine in a levobupivacaine-induced cardiac arrest model.

Materials and methods: A total of 14 New Zealand rabbits were sedated and mechanically ventilated. Asystole was induced with intravenous levobupivacaine injection. The rabbits were randomized into groups receiving the same volume of either 0.9% saline (CR group) or a 20% lipid solution (LE group) along with a 100 µg/kg epinephrine bolus, which were administered immediately upon asystole. Standard advanced cardiac life support protocols were performed.

Results: Four subjects in the LE group as well as 3 subjects in the CR group had a spontaneous recovery ($P = 0.592$). In the 20th minute after arrest, 3 subjects in the LE group had maintained spontaneous circulation, while there was only 1 subject from the CR group with the same outcome.

Conclusion: We found that adding a lipid solution to epinephrine for the resuscitation of rabbits that underwent levobupivacaine-induced cardiac arrest increased recovery rates of circulation and therefore the likelihood of survival. Further studies are needed to develop clinical therapies for the systemic toxicity of local anesthetics.

Key words: Levobupivacaine, lipid emulsion, epinephrine, toxicity, resuscitation

1. Introduction

In cases where toxicity was caused by long-acting local anesthetic agents, the infusion of a lipid emulsion was shown to facilitate spontaneous circulation recovery and to increase the rate of revival in both animals and humans (1). Studies have shown that lipid dosing for resuscitation varies in experimental models having toxicity due to local anesthetics and lipophilic cardiotoxins (1). Similarly, clinical reports in which the subjects were successfully resuscitated from local anesthetic-induced cardiac arrest have been reported using different doses (2–7). However, studies testing lipid dosing have never been conducted in animals or humans. An intravenous lipid emulsion has been shown to be effective in the treatment of bupivacaine-induced cardiac arrest (1,8–10). Clinical trials in which a lipid emulsion was used in resuscitating subjects with local anesthetic-induced cardiotoxicity have had successful results (3,4,6,7,11). In light of the efficacy in experimental

and clinical trials, lipid emulsion is now considered a critical component of resuscitation in systemic toxicity caused by local anesthetics (12).

Epinephrine is administered during cardiopulmonary resuscitation because it regulates coronary and cerebral perfusion pressures and blood flow. Although epinephrine is used globally in resuscitation, there is insufficient evidence of its survival benefit in humans. There are reports of both favorable and toxic effects of epinephrine administration in the cardiopulmonary resuscitation of animals and humans (13).

The inappropriate use of local anesthetics in routine procedures may have devastating effects (14). Several case reports indicated successful resuscitation with lipids on human subjects in cases where cardiopulmonary resuscitation (CPR) with epinephrine and atropine failed to treat cardiovascular collapse (2,3,6). Trials with human volunteers and local anesthetics with potential fatal effects

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have not been approved, but lipid emulsion administration has promise in relieving local anesthetic toxicity (14).

There are several studies investigating the effect of Intralipid against bupivacaine-induced cardiac arrest model, but there is a little information about levobupivacaine-induced cardiac arrest. In the literature, levobupivacaine is usually preferred instead of bupivacaine due to its lower cardiac toxic effects. According to the English-language literature, this is the first study exploring the effect of Intralipid against levobupivacaine-induced cardiac arrest models in rabbits.

This study aims to evaluate the effects of adding a lipid emulsion to epinephrine-based resuscitation. We tested the hypothesis that epinephrine-based resuscitation in combination with a lipid emulsion may have a better outcome in subjects with levobupivacaine-induced asystole.

2. Materials and methods

After obtaining the consent of the Mustafa Kemal University Ethics Committee for Animal Trials, the study was conducted at the Experimental Animal Application and Research Center. A total of 14 adult white New Zealand rabbits at 110–140 days of age, including both sexes, were included in the study. Subjects were divided into 2 groups of 7 as follows:

Group 1: Conventional resuscitation group (CR group),

Group 2: Lipid emulsion Group (LE group).

The rabbits were sedated with 50 mg/kg ketamine and 4 mg/kg xylazine intramuscularly on the day of the trial. After sedation, the animals were put on the operating table and venous access was opened at the marginal ear vein. Ketamine infusion was initiated at an hourly rate of 10 mg/kg and was maintained throughout the experiment. Subjects were monitored by ECG at all times. Tracheostomy was performed following a 2-mL subcutaneous lidocaine injection. Pressure-controlled mechanical ventilation (at 15 cm of H₂O inspiratory pressure) was then initiated at a rate of 17 respirations/min using 100% oxygen (inspiratory-to-expiratory ratio = 0.5:3). End-tidal CO₂ was maintained in a range between 2% and 5%. Vecuronium, a muscle relaxant, was administered at a dose of 0.1 mg/kg after mechanical ventilation.

The left carotid artery, the internal jugular vein, and the right subclavian vein were dissected and visualized. The internal carotid artery was catheterized using a 20-gauge cannula through the proximal aorta and continuous blood pressure monitoring was provided. Monitoring was also initiated with a 20-gauge catheterization from the superior vena cava through the right atrium. Both transducers were calibrated regarding the middle thorax and were reset at room air. After the invasive period, the operation was paused for stabilization (around 10 min).

2.1. Levobupivacaine arrest protocol

To achieve arrest, 10 mg/kg levobupivacaine was administered through the ear marginal vein for 5 s.

2.2. Resuscitation protocol

Clinical response was evaluated in a 30-s period without intervention after asystole. Basic life support, including manual chest compression and mechanical ventilation, was performed according to arterial blood pressure (160 compression rate and 17 respirations/min).

During the first minute, subjects were randomly enrolled in either the LE or CE group. In the LE group, 1.5 mL/kg 20% intravenous Intralipid was administered within 1 min via the ear vein. For subjects that failed to have spontaneous circulation, or those that had another cardiac arrest after spontaneous circulation, 1.5 mL/kg intravenous Intralipid was administered in 5-min intervals

In the CR group, 1.5 mL/kg 0.9% intravenous saline was administered within 1 min via the ear vein. In subjects that failed to have spontaneous circulation, or those that had another cardiac arrest after spontaneous circulation, 1.5 mL/kg 0.9% intravenous saline was administered in 5-min intervals

If the mean arterial pressure was over 50 mmHg and the heart rate exceeded 120 bpm, this was considered as recovery of spontaneous circulation.

After initial boluses, 100 µg/kg intravenous epinephrine was given to both groups in 5-min intervals until spontaneous circulation was maintained.

Chest compression was continued until spontaneous circulation was maintained. In cases of asystole, or in those where the mean arterial pressure decreased, chest compression was initiated.

We continued resuscitation for 20 min, after which all subjects were euthanized using 300 mg of intravenous pentobarbital.

2.3. Statistical analysis

Assuming that the difference in coronary perfusion pressure (CPP) measurements between the CR and LE groups was 10 mmHg, the standard derivation was 11, and if $\alpha = 0.05$ and $\beta = 0.5$, the sample size was estimated to be 7 for each group. A Mann–Whitney U test was used to compare the estimated values, and a chi-square test was used to compare the categorical variables.

3. Results

Table 1 summarizes the features of the subjects and their basal hemodynamic parameters. The 2 groups were statistically comparable with respect to heart rate (HR), mean arterial pressure (MAP), CPP, and right atrium pressure (RAP) prior to the procedure.

Arterial blood gas (ABG) variables recorded 20 min before and after cardiac arrest are presented in Table 2. ABG variables were not statistically different between the 2 groups before and after cardiac arrest.

Table 1. Baseline animal characteristics and haemodynamic metrics. Data are mean (SEM).

	CR (n = 7)	LE (n = 7)	P-value
Sex (male:female)	4:3	4:3	1.0
Age (days)	124 (10)	121 (9)	0.522
Weight (kg)	3.45 (0.29)	3.32 (0.25)	0.274
HR (beats/min)	181 (13)	187 (14)	0.482
MAP (mmHg)	67 (8)	63 (5)	0.124
CPP (mmHg)	57 (10)	52 (4)	0.276
RAP (mmHg)	2.7 (0.9)	2.4 (0.7)	0.476

Table 2. Arterial blood gas variables at baseline. Data are mean (SEM).

	CR (n = 7)	LE (n = 7)	P-value
pH	7.41 (0.06)	7.37 (0.05)	0.178
PaO ₂ (mmHg)	235 (51)	246 (33)	0.848
PaCO ₂ (mmHg)	33 (6)	33 (5)	0.652
HCO ₃ (mmol/L)	24 (4.1)	24 (2.8)	0.270
Base excess (mmol/L)	1.5 (4.1)	2.5 (3.4)	0.516
Lactate (mmol/L)	2.0 (1.05)	2.1 (0.55)	0.563

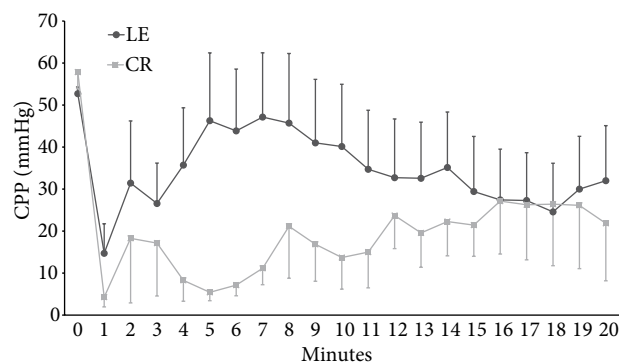
Within 12 s after levobupivacaine injection, asystole was observed in all subjects. Recovery of spontaneous circulation (ROSC) was 6.5 ± 4.1 min in the LE group and 9.0 ± 1.5 min in the CE group ($P = 0.285$).

CPP values before and after cardiac arrest are shown in Figure 1. There were significant differences in CPP between the 2 groups at the 4th, 5th, 6th, and 7th minutes of CPR ($P = 0.045$, $P = 0.010$, $P = 0.022$, and $P = 0.029$, respectively).

Four subjects in the LE group and 3 subjects in the CR group had ROSC ($P = 0.592$). Two of the 3 subjects in the CR group collapsed twice and persistent cardiac arrest occurred. One of 4 subjects in the LE group collapsed in the 15th minute and did not respond to resuscitation. Finally, 3 subjects in the LE group and 1 subject in the CR group maintained ROSC for 20 min ($P = 0.237$).

Figure 2 shows the MAP values. There were significant differences in MAP between the 2 groups at the 1st, 2nd, 5th, 7th, and 11th minutes of CPR ($P = 0.017$, $P = 0.05$, $P = 0.007$, $P = 0.05$, $P = 0.05$; respectively).

Heart rate values can be seen in Figure 3. There was no difference between groups.

**Figure 1.** Coronary perfusion pressure (CPP) vs. time during the 20 min of resuscitation. Data represent mean \pm SEM. LE = Lipid emulsion group; CR = conventional resuscitation group. *: $P < 0.05$.

Analysis at the 20th minute after cardiac arrest revealed no difference between groups (Table 3).

Necropsy confirmed the appropriate positioning of the tracheal tube and vascular catheters in all animals.

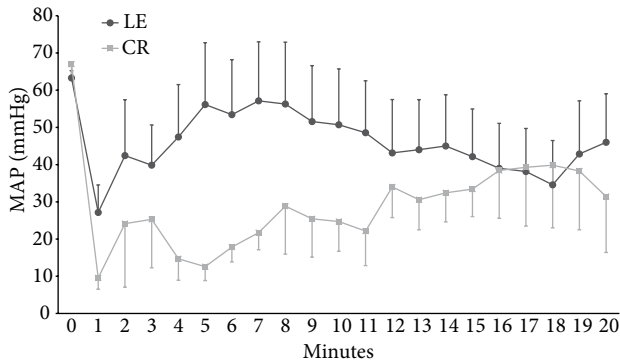


Figure 2. Mean arterial pressure (MAP) vs. time during the 20 min of resuscitation. Data represent mean \pm SEM. LE = Lipid emulsion group; CR = conventional resuscitation group. *: $P \leq 0.05$; **: $P < 0.01$.

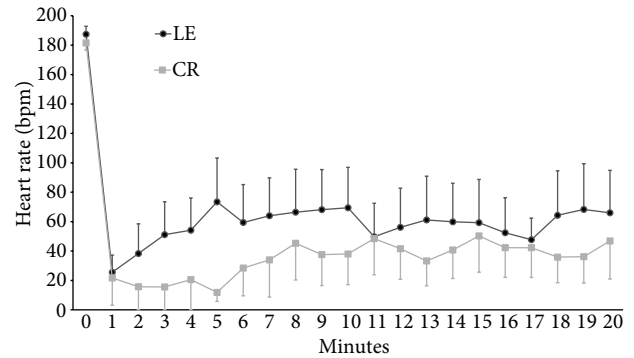


Figure 3. Heart rate (HR) vs. time during the 20 min of resuscitation. Data represent mean \pm SEM. LE = Lipid emulsion group; CR = conventional resuscitation group.

Table 3. Arterial blood gas variables at 20th minute. Data are mean (SEM).

	CR (n = 7)	LE (n = 7)	P-value
pH	6.99 (0.07)	6.99 (0.06)	0.563
PaO ₂ (mmHg)	37 (16.3)	40 (8.6)	0.520
PaCO ₂ (mmHg)	77 (18)	87 (9.2)	0.222
HCO ₃ (mmol/L)	30 (8)	28 (6.23)	0.897
Base excess (mmol/L)	-10 (1.8)	-13 (7.48)	0.333
Lactate (mmol/L)	11 (2.4)	10.5 (3.1)	0.654

4. Discussion

Our data show that adding a lipid emulsion to resuscitation had better hemodynamic outcomes than using epinephrine alone in a levobupivacaine overdose in rabbits. To the best of our knowledge, this is the first study evaluating efficacy of Intralipid against a levobupivacaine-induced cardiac arrest model in rabbits.

Although there was no difference in metabolic measures, several aspects of cardiac functions were better in animals that also had lipid administration than in those who received epinephrine alone.

The results show that epinephrine + lipid administration is superior to epinephrine alone in the setting of levobupivacaine-induced cardiac toxicity management.

Many clinical reports state that lipid administration after the failure of adrenergic therapy can recover spontaneous circulation in a short period of time (2,3).

When epinephrine was used alone to recover circulation in local anesthesia-induced cardiac arrest, those subjects still had life-threatening, unfavorable hemodynamic outcomes. In contrast, subjects who underwent lipid therapy had initially worse hemodynamic outcomes, but gradual improvement was subsequently achieved (15).

This condition is consistent with the results of the study conducted by Weinberg et al. In that study, the group receiving epinephrine experienced increased blood pressure (168/120) followed by severe hypotension (70/40) and prolonged mechanical ventilation (16).

Previous cardiac arrest models have used blood pressure as their primary recovery criterion (17–20). However, Weinberg et al. observed that increased systolic pressures during the first minutes of epinephrine administration were not maintained, nor were they correlated with cardiac and metabolic measures at the end of the trial (16). In this study, some of the results from the rats in the epinephrine group were less favorable than those in the saline group [i.e. rate pressure product, lactate, partial pressure of oxygen in arterial blood (PaO₂)], and some of the results were much worse [i.e. central venous oxygen saturation, pH, partial pressure of carbon dioxide in arterial blood (PaCO₂)]. In contrast, the systolic pressures of the group that was administered a lipid emulsion were significantly lower than those of the epinephrine group at 2.5 and 5 min, but were significantly higher by the end of the trial (16). This model suggests that during bupivacaine overdose, early systolic hypertension is not a reliable indicator for recovery.

Harvey et al. used increments of coronary perfusion pressure as a recovery criterion (21). Similarly, Weinberg et al. performed a study on dogs, which have larger CPP values, and found that open chest compression increased general survival (9). These results are consistent with the findings of a previous rabbit study (findings of the group without epinephrine injection) (1).

Mayr et al. created a bupivacaine-induced asphyxia model for pigs. In that study, they reported that the epinephrine group had higher CPP levels than the group receiving lipids only. In addition, survival rates were higher in the group receiving only lipids (20).

We considered systolic pressure as a recovery criterion in our study, but we also observed that increased CPP and its maintenance improved survival rates. Both groups were shown to have higher CPP after epinephrine administration. This increase was maintained in the LE group for 10 min but, in the CR group, CPP decreased. This also affected the number of animals that survived, as in the LE group there were more subjects that survived.

Inadequate circulation to recover spontaneous circulation causes not only insufficient perfusion but also an insufficient flow effect for the clearance of toxins. In this situation, the sink effect is not strong enough. The sink hypothesis suggests that to decrease toxicity, lipophilic drugs should be dissolved in an expanded plasma lipid phase (21). In humans, CPR can be achieved if CPP is as high as 10–20 mmHg (22), and therefore the highest priority should be to optimize myocardial perfusion in subjects with local anesthesia-induced cardiac arrest (9).

Harvey et al. conducted a bupivacaine-induced cardiac arrest study on rabbits. In that study, all treatment groups exhibited profound respiratory acidosis and hypoxia at 15 min regardless of epinephrine administration, although they all had same prearrest adjustment (21).

In this study, both groups had profound respiratory acidosis and hypoxia at the 20th minute. The potential causes of death for subjects may be decreased pH, recovered spontaneous circulation (23), ongoing hypoxia, or cardiac depression (24). Epinephrine administration supports spontaneous circulation under these circumstances. Although the final outcome might have been unfavorable in these subjects, these results still support the benefits of epinephrine administration (21).

Intravenous lipid emulsion has been shown to cause a profound increase in pulmonary vascular resistance in animal models (25,26) and neonates (27,28). These effects become worse in settings of hypoxia.

Lipid particles of larger than 5 μm may cause lipid embolism (29), which can cause an increase in pulmonary vascular resistance and impair pulmonary flow during slow-paced CPR.

All of these factors may have impaired gas exchange in our study. We did not evaluate pulmonary vascular pressures in this model, and so the level of impact on gas exchange cannot be evaluated.

Numerous studies have reported that arrhythmia caused by epinephrine in the treatment of bupivacaine-induced toxicity is quite problematic (16). Heavner et al. found that if epinephrine was given to rats under bupivacaine-induced asystole, ventricular extrasystoles occurred at higher frequencies (17). Similarly, Groban et al. observed that epinephrine caused persistent ventricular fibrillation in more than half of the dogs that had bupivacaine overdose (19). Similarly, Weinberg et al. found that all of the subjects in the epinephrine group had persistent ventricular ectopy during the experiment, while none of the subjects in this study had ventricular ectopy. In comparison with the lipid group, epinephrine worsened tissue perfusion, cardiac output, and oxygen delivery (16). Moreover, epinephrine may have a direct metabolic effect by increasing serum lactate levels without tissue perfusion (30).

We observed ectopic beats in both groups, but we noticed them especially in CR subjects that had recovered spontaneous circulation, recurrent collapse, persistent ventricular arrhythmia, and fibrillations after epinephrine administration. These subjects could not survive, and in the LE group, severe arrhythmias, with the exception of ventricular ectopic beat, were not observed.

Reinikainen et al. reported that prolonged pulmonary edema occurred after epinephrine administration in patients with local anesthetic-induced cardiac arrest (31). Pulmonary edema causes hypoventilation and subsequent hypercapnia, both of which facilitate acidosis. We observed hypercapnia and prolonged acidosis in both groups, but we think that the pulmonary edema findings were subtle.

Different criteria for ROSC may cause variable outcomes. Mayr et al. (20) uses the criterion of systolic pressure over 80 mmHg for at least 5 min. Weinberg et al. used their own criteria, and 4 out of 5 subjects in the epinephrine group and all 5 subjects in the lipid group reached their recovery criteria. If the criterion from Mayr et al. had been used, only 3 of the 5 subjects in the epinephrine group and only 2 of the 5 subjects in the lipid group would have achieved recovery (16). However, the study by Weinberg et al. shows that systolic pressure is not a significant and sufficient criterion for recovery in the setting of resuscitation for local anesthesia toxicity.

Timing of experiments, route of anesthesia, measurements on long-term survival, neurologic improvement, and other organ injury may change the results of this study.

In conclusion, we observed that adding a lipid emulsion to epinephrine improved hemodynamic outcomes and increased survival rates, but resulted in

similar metabolic parameters. These results are not strong enough to translate into a clinical setting, but our findings

will support the management of experimental studies and human trials using lipid infusion.

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