Comparative Regimens of Lipid Rescue From Bupivacaine-Induced Asystole in a Rat Model

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BACKGROUND: It is currently unknown whether bupivacaine-induced asystole is better resuscitated with lipid emulsion (LE) administered peripherally or centrally, and whether different LE regimens administered peripherally demonstrated similar effects. In this study, we compared the effects of various regimens of lipid administration in a rat model of bupivacaine-induced asystole.

METHODS: Forty-five adult male Sprague-Dawley rats were subjected to bupivacaine-induced asystole and randomly divided into 3 lipid regimens groups: (1) 20% LE was administered continuously via the internal jugular vein (CV-infusion group); (2) 20% LE was administered continuously via the tail vein (PV-infusion group); and (3) 20% LE was administered as divided boluses via the tail vein (PV-bolus group). The maximum dose of LE did not exceed 10 mL·kg⁻¹. External chest compressions were administered until the return of spontaneous circulation (ROSC) or the end of a 40-minute resuscitation period.

RESULTS: The survival rate, rate of ROSC, systolic blood pressure, heart rate, heart rate–blood pressure product, and coronary perfusion pressure during 2–40 minutes in the CV-infusion and PV-bolus groups were significantly higher than those in the PV-infusion group (P < .01), and the plasma total bupivacaine concentration and myocardial bupivacaine content were significantly lower (P < .05). Time to heartbeat return and time to ROSC in the CV-infusion and PV-bolus groups were significantly shorter than those in the PV-infusion group (P < .05).

CONCLUSIONS: In the rat model of bupivacaine-induced asystole, a divided LE bolus regimen administered peripherally provided a better resuscitation outcome than that of a continuous LE infusion regimen peripherally, and performed in a similar fashion as the continuous LE infusion regimen administered centrally. (Anesth Analg 2019;128:256–63)

**KEY POINTS**
- **Question:** Lipid emulsion (LE) administered peripherally or centrally, even different peripheral regimens, can bring a similar effect in resuscitation of bupivacaine-induced asystole?
- **Findings:** A divided LE bolus regimen administered peripherally provided a better resuscitation outcome than that of a continuous LE infusion regimen peripherally, and performed in a similar fashion as the continuous LE infusion regimen administered centrally.
- **Meaning:** A divided LE bolus regimen administered peripherally may be a feasible method when central venous access cannot be established in resuscitation of bupivacaine-induced asystole.

Lipid emulsion (LE) has been demonstrated as an effective treatment for cardiotoxicity induced by local anesthetics,1,2 and has become a treatment recommendation of the Association of Anaesthetists of Great Britain and Ireland and American Society of Regional Anesthesia and Pain Medicine in the management of local anesthetic systemic toxicity.3,4

Usually, only the peripheral vein is prepared in routine surgeries. However, anesthesiologists often urgently establish central venous access for LE administration during resuscitation of local anaesthetic-induced cardiac toxicity,5,6 but not all such attempts at central vein access go smoothly.

Gaddis et al7 reported that the time to peak dye concentration in the proximal aorta was significantly shorter through central vein than peripheral vein in a canine resuscitation model of cardiac arrest. However, it was still not clear whether the effect of peripheral LE administration was the same as central administration in a rat model of bupivacaine-induced asystole. Hiller et al8 reported that in a rat model of 20 mg·kg⁻¹ bupivacaine-induced asystole, two 5 mL·kg⁻¹ boluses of 30% LE were administered via a central vein, and with an infusion at 1 mL·kg⁻¹·minute⁻¹ for 2 minutes achieved a survival rate of 100% at 15 minutes. Li et al9 used the same model, followed by a bolus of 20% LE 5 mL·kg⁻¹ via a central vein, and maintained an infusion at 1 mL·kg⁻¹·minute⁻¹ for 3 minutes, achieving a survival rate of 73.3% at 120 minutes. However, Cave et al10 reported that
in a rabbit model of 10 mg·kg\(^{-1}\) bupivacaine-induced asystole, 20% LE was administered via the ear vein according to the Association of Anaesthetists of Great Britain and Ireland guideline and the survival rate at 20 minutes was only 50%. Nonetheless, none of these studies have compared the effects of LE rescue administered peripherally and centrally in bupivacaine-induced asystole.

In view of these findings, we hypothesized that in the resuscitation of bupivacaine-induced asystole, a divided bolus regimen of LE administered peripherally and a continuous infusion of LE administered centrally provided better resuscitation outcomes than that of a continuous peripheral LE infusion. Therefore, we compared the effects of these regimens of lipid rescue in the resuscitation of bupivacaine-induced asystole in rats. The primary end point was the survival rate at 40 minutes, and the secondary end points were rate of return of spontaneous circulation (ROSC), rate of heartbeat return, time to ROSC, time to heartbeat return, systolic blood pressure (SBP), heart rate (HR), heart rate–blood pressure product (RPP), coronary perfusion pressure (CPP) during resuscitation, plasma total bupivacaine concentration, myocardial bupivacaine content, and arterial blood gas analysis.

**METHODS**

**Animals Preparation**

The studies were conducted with the approval of the Wenzhou Medical University Animal Care and Use Committee (Wenzhou, China). Forty-five male Sprague-Dawley rats, weighing from 300 to 360 g, were provided by the Animal Center of Wenzhou Medical University (Wenzhou, China). The rats were randomly divided into 3 groups (n = 15): (1) LE was administered continuously via the internal jugular vein (CV-infusion group); (2) LE was administered continuously via the tail vein (PV-infusion group); and (3) LE was administered as divided boluses via the tail vein (PV-bolus group).

All rats were fasted for 12 hours and were allowed to drink water freely before the experiment. They were anesthetized with an intraperitoneal injection of 350 mg·kg\(^{-1}\) chloral hydrate (P code: 805C022; Solarbio Co, Ltd, Beijing, China), intubated via tracheotomy, and connected to the ventilator. Ventilator settings were as follows: tidal volume = 6 mL·kg\(^{-1}\), respiratory rate = 60–70 breaths/min, and inspiratory-to-expiratory = 1:1.5. The anesthesia was maintained with 1% sevoflurane (P code: 54221; Maruishi Pharmaceutical Co, Ltd, Osaka, Japan) in 100% oxygen. The left femoral vein was cannulated for bupivacaine infusion, and the left femoral artery was cannulated for arterial blood pressure monitoring using the MedLab data archiving and retrieval system (Medlab-U/4C051; Nanjing Medease Science and Technology Co, Ltd, Nanjing, China). The left internal jugular vein was cannulated for recording internal jugular venous pressure intermittently. CPP was calculated using the arterial diastolic pressure minus the internal jugular venous pressure.\(^{11}\) In the CV-infusion group, the left internal jugular vein was also used for LE administration. The sensor probe and the LE administration catheter were connected to the internal jugular vein catheter via a 3-way stopcock. In the PV-infusion and PV-bolus groups, the tail vein was cannulated for LE administration. Electrocardiography was constantly recorded (standard lead II). On completion of all procedures, the rats were allowed to stabilize physiologically for 15 minutes, and baseline values of HR, SBP, RPP, and CPP were recorded. Then experimental interventions proceeded.

**Asystole Protocol**

At the end of the stabilization period, sevoflurane was discontinued, and 0.2% bupivacaine hydrochloride (P code: 101524503; Sigma-Aldrich Co, St Louis, MO) 20 mg·kg\(^{-1}\) was injected over 10 seconds into the left femoral vein. All rats developed asystole (electrocardiography showed an isopotential line) and this time point was defined as “time 0.”

**Resuscitation Protocol**

On the onset of asystole (time 0), chest compressions were performed immediately at 300 compressions per minute over the lower-middle sternum at the depth of 1 cm, until ROSC or the end of 40 minutes of resuscitation.

At the time of asystole in the CV-infusion and PV-infusion groups, the rats were administered with an LE infusion at 1.5 mL·kg\(^{-1}\)·minute\(^{-1}\) for 1 minute (Intralipid, 20% LE, P code: 801H081; Huarui Pharmaceuticals Co, Ltd, Wuxi, China). Thereafter, an LE infusion was administered at 0.25 mL·kg\(^{-1}\)·minute\(^{-1}\) for 5 minutes. If ROSC did not occur by 6 minutes, the rats were again administered with an LE at 1.5 mL·kg\(^{-1}\)·minute\(^{-1}\) for 1 minute, followed by an LE infusion at 0.5 mL·kg\(^{-1}\)·minute\(^{-1}\) for 5 minutes. If ROSC was still not achieved, the rats were again administered with an LE at 1.5 mL·kg\(^{-1}\)·minute\(^{-1}\) for 1 minute, and thereafter at 0.5 mL·kg\(^{-1}\)·minute\(^{-1}\) to the maximum dose allowed by guideline recommendations (10 mL·kg\(^{-1}\)).\(^{12}\) Any ROSC was considered a successful resuscitation. Whenever the rats achieved ROSC, chest compressions were stopped, and the LE infusion was continued at 0.25 mL·kg\(^{-1}\)·minute\(^{-1}\) for 10 minutes or until the maximum dose 10 mL·kg\(^{-1}\) was reached (Figure 1).

In the PV-bolus group, on the onset of asystole, the rats were administered with 5 mL·kg\(^{-1}\) LE from time 0 to 3 minutes and 20 seconds. If ROSC was not achieved, the rats were further administered with 2.5 mL·kg\(^{-1}\) LE from 6 to 7 minutes and 40 seconds. If ROSC was still not achieved, the rats were again administered with 2.5 mL·kg\(^{-1}\) LE from 12 to 13 minutes and 40 seconds (Figure 1). LE administration rate in the PV-bolus group was 1.5 mL·kg\(^{-1}\)·minute\(^{-1}\). There was no continuous LE infusion between boluses, and the maximum dose of LE did not exceed 10 mL·kg\(^{-1}\).

The criterion for ROSC was defined as a regular autonomic rhythm, and a spontaneous RPP of >20% of baseline values for >1 minute.\(^{9,13,14}\) Heartbeat return is the first heartbeat detected after resuscitation had commenced. The anesthesia was continued with 0.5% sevoflurane in 100% oxygen when the rats achieved ROSC. If asystole recurred after ROSC, chest compressions were performed but without LE. Body temperature was maintained between 38°C and 39°C using an insulated blanket. All intravenous fluids were preheated to 37°C before administration. The experiments were performed by 4 investigators: provider 1 did not participate in resuscitation protocol and did all
procedures before resuscitation; provider 2 managed the LE administration; provider 3 performed chest compressions; and provider 4 managed the airway and assessed RPP values during resuscitation. All wounds and LE administration catheters were covered with surgical pledgets by provider 1, and all providers were blinded regarding the group. All rats were observed for 40 minutes after asystole and were then killed.

**Observation Index**

The following datasets were recorded: (1) Survival parameters: ROSC (yes/no), deaths after ROSC, survival to 40 minutes, the case of heartbeat return, time to heartbeat return, time to ROSC, time required for bupivacaine administration to induced asystole (Ts), and LE cumulative dose. We then calculated the survival rate, the rate of ROSC, and the rate of heartbeat return (the survival rate = cases of surviving at the end of 40 minutes/total rats, rate of ROSC = cases of ROSC/total rats, rate of heartbeat return = cases of heartbeat return/total rats); (2) Hemodynamic parameters: SBP, HR, RPP, and CPP of 3 groups at the end of the stabilization period, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, and 40 minutes. If a rat did not reach ROSC, chest compressions were stopped at the aforementioned time points (no >10 seconds), and the autonomic hemodynamic parameters at that time were recorded; (3) Arterial blood gas parameters: pH, Po2, Pco2, bicarbonate, base excess, and lactate at the end of stabilization period and at the end of 40 minutes of resuscitation; (4) Collections involved acquisition of a 4-mL blood sample for centrifugation and analyses of plasma bupivacaine concentrations, and an incision of the cardiac apex at the end of the observation period with subsequent storage of tissues at −80°C for determination of myocardium bupivacaine content.

**Bupivacaine Measurement**

Frozen heart samples of 0.2 g were homogenized with 2 mL ultrapure water. Plasma 0.2 mL or heart homogenate 2 mL was centrifuged (4000 r·minute−1) for 15 minutes. The supernatant was removed, and 50-ng ropivacaine was added to determine the internal standard. We used a 2 mol·L−1 sodium hydroxide for alkalization, 1 mL n-hexane for degreasing, and 4-mL ethyl acetate. The preparations were mixed with a vortex generator for 1 minute and centrifuged at 2500 rpm for 15 minutes. The upper organic phase was removed and acidified with 0.3-mL 1.5% hydrochloric acid solution, mixed with a vortex generator for 1 minute, and then followed by centrifugation at 2500 rpm for 15 minutes; 200 μL of the aqueous phase was taken for analysis.

The plasma bupivacaine concentration and myocardial bupivacaine content were measured by the liquid chromatography/mass spectrometer method. Mass spectrometry conditions were as follows: electrospray ion source with positive ions detection and an atomizing gas pressure of 30 Psi. The drying gas (N2) flow rate was 7 L·minute−1, and the temperature of the drying gas was 350°C. The multiple reaction monitoring quantitative method involved (1) bupivacaine m/z 289→140, with a cracking amplitude voltage of 0.30 V; and (2) ropivacaine m/z (internal standard) was 275→126 with a cracking amplitude voltage of 0.28 V. Chromatographic conditions were as follows: a column temperature of 30°C with a flow rate of 0.3 mL·minute−1, and the chromatographic column used Zorbax SB-C18 (2.1 × 150 mm, 0.5 μm; Agilent Technologies, Santa Clara, CA) with a mobile phase using acetonitrile-0.1% formic acid 60: 40 (V/V). Sample sizes were 2 μL.

**Statistical Analysis**

All data were analyzed using SPSS 19.0 statistical software (SPSS Inc, Chicago, IL). The Shapiro–Wilks test was
used for normal distribution test. The measured data of normal distribution were expressed as mean (standard deviation), and the data of nonnormal distribution were expressed as medians (Q1–Q3). Frequencies were used in categorical variables. Weight, arterial blood gas values, and hemodynamic parameters at the end of stabilization among 3 groups were compared by 1-way analysis of variance. SBP, HR, RPP, and CPP were analyzed by 2-way repeated-measures analysis of variance and least significant difference posttests when significance was achieved (P < .05). The time to heartbeat return and the time to ROSC used Kaplan–Meier analysis and compared using the log-rank test. Ts, LE dosage, plasma bupivacaine concentration, myocardium bupivacaine content, and arterial blood gas values at the end of 40 minutes were compared by Kruskal–Wallis test and Dunn post hoc multiple comparison tests. Statistical significant was considered as P < .05. The survival rate, rate of ROSC, and heartbeat return among the 3 groups were analyzed with the Fisher exact test. To reduce type I error, statistical significant in post hoc multiple comparisons was corrected as P < .017.

Sample Size Calculation
The power analysis was based on results of our preliminary study using the Power Sample Size (PASS11.0) software program (NCSS Inc, Kaysville, UT). In the preliminary study, 27 rats were subjected to 20 mg·kg⁻¹ bupivacaine-induced asystole and randomly divided into 3 LE regimen groups (n = 9): (1) CV-infusion group; (2) PV-infusion group; and (3) PV-bolus group. We compared the survival rate among 3 groups. Survival was defined as a regular autonomic rhythm, and a spontaneous RPP of >20% of baseline values for >1 minute at the end of 40 minutes of resuscitation. There were 9, 1, and 8 rats in the CV-infusion group, PV-infusion group, and PV-bolus group, respectively, that survived to 40 minutes, with the survival rate of 100%, 11.1%, and 88.9%, respectively. We assumed a type I error of 0.05 and a power of 0.80, and the χ² test was used. There were 14 rats required per group to determine a statistical significance among 3 groups. Considering the loss potential and errors, we decided on 15 rats in each group for the experiment.

RESULTS

Characteristics of Study Subjects
Baseline values of weight, arterial blood gas values, and hemodynamic parameters showed no significant differences among the 3 groups (Table 1).

Resuscitation Outcomes
Asystole occurred in all rats with bupivacaine administration. Ts among the 3 groups showed no significant difference. Survival at the end of 40 minutes was 12, 3, and 11 in the CV-infusion group, PV-infusion group, and PV-bolus group, respectively. ROSC was successful in 12, 3, and 11 rats in the CV-infusion group, PV-infusion group, and PV-bolus group, respectively, with 3, 12, and 4 rats as resuscitation failures, respectively. Survival curves of rats with ROSC are presented in Figure 2; no deaths occurred after resuscitation. The CV-infusion and PV-bolus groups demonstrated significant increases in survival rate and the rate of ROSC as compared to the PV-infusion group. The cases of heartbeat return in the CV-infusion group, PV-infusion group, and PV-bolus group were 15, 10, and 14 rats, respectively. There was no statistical difference in the rate of heartbeat return among the 3 groups. The time to heartbeat return and time to ROSC in the CV-infusion and PV-bolus groups were significantly shorter than those in the PV-infusion group. There was no statistical difference in LE consumption among the 3 groups (Table 2).

Hemodynamics and Coronary Perfusion Pressure
There were significant differences in SBP, HR, RPP, and CPP during times 2–40 minutes among the 3 groups. SBP, HR, RPP, and CPP in the CV-infusion and PV-bolus groups were significantly higher than those in the PV-infusion group (Figure 3).
Lipid Rescue Through Peripheral Vein

Table 2. Resuscitation Outcomes Among the 3 Groups (n = 15)

<table>
<thead>
<tr>
<th></th>
<th>CV-Infusion</th>
<th>PV-Infusion</th>
<th>PV-Bolus</th>
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<tbody>
<tr>
<td>Survival rate, %</td>
<td>80%</td>
<td>20%</td>
<td>73%</td>
</tr>
<tr>
<td>Rate of ROSC, %</td>
<td>80%</td>
<td>20%</td>
<td>73%</td>
</tr>
<tr>
<td>Ts, s</td>
<td>9.0 (8.0–9.0)</td>
<td>9.0 (8.0–9.0)</td>
<td>8.0 (8.0–9.0)</td>
</tr>
<tr>
<td>Rate of heartbeat return, %</td>
<td>100%</td>
<td>67%</td>
<td>93%</td>
</tr>
<tr>
<td>Time to heartbeat return, s</td>
<td>240 (160–300)</td>
<td>480 (300–2400)</td>
<td>300 (270–420)</td>
</tr>
<tr>
<td>Time to ROSC, s</td>
<td>890 (600–1440)</td>
<td>2400 (2400–2400)</td>
<td>1070 (800–2400)</td>
</tr>
<tr>
<td>LE cumulative dose, mL</td>
<td>3.2 (2.8–3.3)</td>
<td>3.2 (3.1–3.4)</td>
<td>3.3 (3.1–3.3)</td>
</tr>
</tbody>
</table>

Non-normal distributed data are expressed as median (Q1–Q3), n = 15 for all groups. The 3 groups displayed differences in survival rate and the rate of ROSC (CV-infusion versus PV-infusion: P = .003; PV-infusion versus PV-bolus: P = .009; CV-infusion versus PV-bolus: P = 1.000). The 3 groups displayed differences in time to heartbeat return (CV-infusion versus PV-infusion: P < .001; PV-infusion versus PV-bolus: P = .015; CV-infusion versus PV-bolus: P = .053) and time to ROSC (CV-infusion versus PV-infusion: P < .001; PV-infusion versus PV-bolus: P = .001; CV-infusion versus PV-bolus: P = .410).

Abbreviations: CV-infusion, 20% lipid emulsion was administered continuously via the internal jugular vein; LE, lipid emulsion; PV-bolus, 20% lipid emulsion was administered as divided boluses via the tail vein; PV-infusion, 20% lipid emulsion was administered continuously via the tail vein; ROSC, return of spontaneous circulation; Ts, time required for bupivacaine administration to induced asystole.

*P < .01 versus PV-infusion.

**P < .05 versus PV-infusion.

Figure 3. SBP (A), HR (B), RPP (C), and CPP (D) versus time during resuscitation. Values are mean (SD), n = 15. CV-infusion, PV-infusion, and PV-bolus groups displayed differences in SBP, HR, RPP and CPP (SBP: CV-infusion versus PV-infusion, P < .001; PV-infusion versus PV-bolus, P = .005; CV-infusion versus PV-bolus, P = .201; HR: CV-infusion versus PV-infusion, P < .001; PV-infusion versus PV-bolus, P = .001; CV-infusion versus PV-bolus, P = .282; RPP: CV-infusion versus PV-infusion, P < .001; PV-infusion versus PV-bolus, P = .007; CV-infusion versus PV-bolus, P = .164; CPP: CV-infusion versus PV-infusion, P < .001; PV-infusion versus PV-bolus, P = .002; CV-infusion versus PV-bolus, P = .211). CPP indicates coronary perfusion pressure; CV-infusion, 20% lipid emulsion was administered continuously via the internal jugular vein; HR, heart rate; PV-bolus, 20% lipid emulsion was administered as divided boluses via the tail vein; PV-infusion, 20% lipid emulsion was administered continuously via the tail vein; RPP, heart rate–blood pressure product; SBP, systolic blood pressure; SD, standard deviation.

Bupivacaine Concentration (Content) and Arterial Blood Gas Values at the End of Resuscitation

Plasma bupivacaine concentration and myocardial bupivacaine content in the CV-infusion and PV-bolus groups were significantly lower than those in the PV-infusion group (Table 3). The values of pH, bicarbonate, and base excess in the CV-infusion and PV-bolus groups were significantly higher than those of the PV-infusion group. The levels of lactate in the CV-infusion and PV-bolus groups were significantly lower than that of the PV-infusion group. There were no significant differences of PaO2 and PaCO2 among the 3 groups (Table 3).

DISCUSSION

In the resuscitation model of bupivacaine-induced asystole in rats, the CV-infusion group and PV-bolus group regimens resulted in higher survival rate, rate of ROSC, higher CPP, SBP, HR, and RPP during resuscitation, and a lower degree of metabolic acidosis, myocardium bupivacaine content, and plasma bupivacaine concentration than PV-infusion group.
Hiller et al.8 and Li et al.9 reported that using LE through central vein in the rat models of 20 mg·kg−1 bupivacaine-induced asystole achieved the survival rates of 100% and 73.3%, respectively. In this study, the survival rates in the CV-infusion group and PV-bolus group were 80% and 73%, respectively, showing that a divided LE bolus regimen administered peripherally provided a similar resuscitation outcome with a continuous LE infusion regimen administrated centrally.

In this study, the higher survival rate, rate of ROSC and shorter time to heartbeat return, and time to ROSC in the PV-bolus group and CV-infusion group were attributed to the lower myocardial bupivacaine content as compared to the PV-infusion group, and that may be the result of the higher peak LE concentration in the heart during the early phase of resuscitation in these 2 groups. When local anesthetics induce a cardiovascular collapse, the primary mechanism of LE detoxification is through a rapid scavenging effect created in the blood by the formation of a lipid compartment by fat droplets. The intravascular lipid compartment provides a medium for bupivacaine to partition in and out of, thus yielding a theoretical “shuttle” or “subway” to transfer bupivacaine from drug-sensitive organs, such as the heart and brain, to organs that can store and detoxify the drug.15 In our previous research of bupivacaine-induced asystole in isolated rat hearts, we found that LE decreased the content of bupivacaine in the myocardium and promoted the recovery of myocardial contractility and electrical conduction.16 Our previous study also showed that in bupivacaine-induced asystole in isolated rat heart, there was a concentration-dependent relationship during the early recovery phase within the LE range of 1%–8%.17 suggesting that early administration of a sufficient volume of LE would result in improved resuscitation outcomes. Peak concentrations in the heart and lungs occurred more rapidly when LE was administered via a central vein; this was followed by rapidly decreasing bupivacaine content in the heart. LE administered as divided boluses, through a peripheral vein, may also be a method that efficaciously leads to a rapid peak concentration effect in the heart and lungs. However, a continuous infusion of LE through a peripheral vein may not be an efficient way to reach a peak and effective concentration in the heart and lungs because the concentration of LE is easily diluted by returned blood volume. In our study, the survival rate and the rate of ROSC in the PV-infusion group were only 20%, which demonstrated that the continuous LE infusion regimen via the peripheral vein during the early recovery phase result in a relatively poor outcome in treating bupivacaine-induced asystole.

LE administered as divided boluses via the peripheral vein significantly decreased the content of myocardial bupivacaine, possibly combining with the volume and cardiotonic effects provided by the long-chain LE, thereby promoting recovery of the cardiac function earlier and increasing CPP and coronary blood flow, which facilitates the delivery of LE to myocardial tissue.18 A recent study by Fettiplace et al.19 also found that there was a multimodal LE detoxification mechanism of scavenging, volume effect, and cardiotonic effect in reversing bupivacaine-induced cardiac toxicity.

In this study, the prompt resuscitation and augmented hemodynamics in the CV-infusion group and PV-bolus group accelerated bupivacaine redistribution to reservoir organs, when compared with the PV-infusion group, thus accelerating the decrease of total bupivacaine concentration in the plasma. Also, the CV-infusion and PV-bolus groups had improved tissue perfusion, a lower degree of metabolic acidosis, and level of lactate that approached normal physiological values. Delayed or failed resuscitation in the PV-infusion group was associated with high level of myocardial bupivacaine content, poor circulatory recovery, significant metabolic acidosis, and higher lactate level. Dureau et al.20 showed that the early use of LE significantly reduced the peak concentration (Cmax) of local anesthetic in blood, supporting the early use of LE.

The potency of “lipid sink” effects is determined by the concentration and volume of the LE used. When LE concentration is fixed, its effectiveness is related to the volume of LE used. In the PV-bolus group, LE was given in divided boluses via the central vein, which is similar to the delivery of LE to myocardial tissue.18 A recent study by Fettiplace et al.19 also found that there was a multimodal LE detoxification mechanism of scavenging, volume effect, and cardiotonic effect in reversing bupivacaine-induced cardiac toxicity.

Table 3. Bupivacaine Concentration (Content) and Arterial Blood Gas Values at the End of Resuscitation Among the 3 Groups (n = 15)

<table>
<thead>
<tr>
<th></th>
<th>CV-Infusion</th>
<th>PV-Infusion</th>
<th>PV-Bolus</th>
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<tbody>
<tr>
<td>Total plasma bupivacaine concentration, ng·mL−1</td>
<td>3448 (2612–8591)a</td>
<td>15,578 (11,245–18,678)</td>
<td>4651 (3653–14,694) b</td>
</tr>
<tr>
<td>Myocardial bupivacaine content, ng·g−1</td>
<td>998 (950–3413)a</td>
<td>4464 (3203–5191)</td>
<td>1184 (891–3602)</td>
</tr>
<tr>
<td>pH</td>
<td>7.26 (7.14–7.36)a</td>
<td>6.93 (6.76–7.03)</td>
<td>7.24 (6.93–7.38)b</td>
</tr>
<tr>
<td>PO2, mm Hg</td>
<td>106 (76–119)</td>
<td>95 (80–105)</td>
<td>98 (77–110)</td>
</tr>
<tr>
<td>PCO2, mm Hg</td>
<td>49 (44–56)</td>
<td>58 (53–62)</td>
<td>55 (44–59)</td>
</tr>
<tr>
<td>HCO3−, mmol·L−1</td>
<td>21.9 (16.6–24.5)a</td>
<td>14.4 (12.4–19.0)</td>
<td>22.4 (14.9–23.6)b</td>
</tr>
<tr>
<td>BE, mmol·L−1</td>
<td>−4.0 (−12.0 to −1.0)a</td>
<td>−19.0 (−22.0 to −12.0)</td>
<td>−5.0 (−18.0 to −2.0)b</td>
</tr>
<tr>
<td>Lactate, mmol·L−1</td>
<td>2.4 (1.3–7.9)a</td>
<td>10.8 (9.0–13.2)</td>
<td>2.6 (2.0–12.1)b</td>
</tr>
</tbody>
</table>

Nonnormal distributed data are expressed as median (Q1–Q3), n = 15 for all groups. The 3 groups displayed differences in plasma bupivacaine concentration and myocardial bupivacaine content (plasma bupivacaine concentration: CV-infusion versus PV-infusion, P < .001; PV-infusion versus PV-bolus, P = .034; CV-infusion versus PV-bolus, P = .188; myocardial bupivacaine content: CV-infusion versus PV-infusion, P = .006; PV-infusion versus PV-bolus, P = .034; CV-infusion versus PV-bolus, P = 1.000). The 3 groups displayed differences in the pH, HCO3−, BE, and lactate (pH: CV-infusion versus PV-infusion, P = .009; PV-infusion versus PV-bolus, P = .011; CV-infusion versus PV-bolus, P = 1.000; HCO3−: CV-infusion versus PV-infusion, P = .008; PV-infusion versus PV-bolus, P = .032; CV-infusion versus PV-bolus, P = 1.000; BE: CV-infusion versus PV-infusion, P = .005; PV-infusion versus PV-bolus, P = .030; CV-infusion versus PV-bolus, P = 1.000; lactate: CV-infusion versus PV-infusion, P = .007; PV-infusion versus PV-bolus, P = .041; CV-infusion versus PV-bolus, P = 1.000).

Abbreviations: BE, base excess; CV-Infusion, 20% lipid emulsion was administered continuously via the internal jugular vein; HCO3−, bicarbonate; PV-bolus, 20% lipid emulsion was administered as divided boluses via the tail vein; PV-infusion, 20% lipid emulsion was administered continuously via the tail vein.

*aP < .01 versus PV-infusion.

*bP < .05 versus PV-infusion.
boluses (5, 2.5, and 2.5 mL·kg⁻¹) every 6 minutes. In this regimen, a relatively larger volume of LE was given in the first 200 seconds (without a continuous LE infusion), which facilitates its use in clinical practice. In urgent clinical situations, local anesthetics toxicity varies in different degrees, and it may be difficult to start an infusion or insert a central line, so knowing that use of boluses peripherally is effective simplifies the intervention.

In this study, we did not use epinephrine in our resuscitation efforts. Although using epinephrine in the treatment of bupivacaine-induced asystole may result in an early resuscitation, its use in rats seems to result in repeated asystole.⁹ Also, epinephrine use in these conditions may impair lung function,²² thereby undermining the effective resuscitation of local anesthetic-induced cardiac toxicity.⁹

There are several limitations to this study: (1) A curve describing the trends for myocardial bupivacaine content and plasma bupivacaine concentration versus time during asystole and resuscitation times of the 3 groups was not plotted, for doing so would have put the animals at risk. Also, the differences of myocardial bupivacaine content and plasma bupivacaine concentration among the 3 groups at the end of resuscitation confirmed our speculation about the reasons for the different outcomes between groups. (2) The inclusion of a divided bolus regimen of LE administered by a central vein would have resulted in a full factorial design for LE regimens and venous access and allowed an analysis of LE regimen, venous access, and their interaction. This combination was not conducted because the purpose of this study was to search for a better regimen of lipid rescue via a peripheral route in the event that central venous access could not be established in a timely manner to treat local anesthetic-induced cardiac toxicity.

In summary, in the rat model of bupivacaine-induced asystole, a divided LE bolus regimen administered peripherally provided a better resuscitation outcome than that of a continuous LE infusion regimen peripherally, and performed in a similar fashion as the continuous LE infusion regimen administered centrally. Therefore, the results imply that the future studies regarding local anesthetic systemic toxicity resuscitation should address the route of administration of LE, that is, through a peripheral vein or central vein, and should emphasize the optimal way to administer LE peripherally because central venous access is not always available.

**DISCLOSURES**

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