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Hemodynamic changes with two lipid emulsions for treatment of bupivacaine toxicity in swines[1]

Artur Udelsmann[I], Marcos De Simone Melo[II]

[I]Associate Professor, Department of Anesthesiology and Laboratory of Experimental Anesthesia, State University of Campinas (UNICAMP), Brazil. Conception, intellectual and scientific content of the study; manuscript writing, critical revision.
[II]PhD, Anesthesiologist, Hospital UNICAMP, Campinas-SP, Brazil. Acquisition and interpretation of data.

ABSTRACT

PURPOSE: To compare the hemodynamic changes following two different lipid emulsion therapies after bupivacaine intoxication in swines.

METHODS: Large White pigs were anesthetized with thiopental, tracheal intubation performed and mechanical ventilation instituted. Hemodynamic variables were recorded with invasive pressure monitoring and pulmonary artery catheterization (Swan-Ganz catheter). After a 30-minute resting period, 5 mg.kg^{-1} of bupivacaine by intravenous injection was administered and new hemodynamic measures were performed 1 minute later; the animals were than randomly divided into three groups and received 4 ml.kg^{-1} of one of the two different lipid emulsion with standard long-chaim triglyceride, or mixture of long and medium-chain triglyceride, or saline solution. Hemodynamic changes were then re-evaluated at 5, 10, 15, 20 and 30 minutes.

RESULTS: Bupivacaine intoxication caused fall in arterial blood pressure, cardiac index, ventricular systolic work index mainly and no important changes in vascular resistances. Both emulsion improved arterial blood pressure mainly increasing vascular resistance since the cardiac index had no significant improvement. On the systemic circulation the hemodynamic results were similar with both lipid emulsions.

CONCLUSION: Both lipid emulsions were efficient and similar options to reverse hypotension in cases of bupivacaine toxicity.

Key words: Anesthesia, Local. Bupivacaine. Fat Emulsions, Intravenous. Hemodynamics. Swine.

Introduction

Local anesthetics (LA) are drugs commonly used in medical practice. Despite major advances in pharmaceutical products and regional anesthesia techniques, adverse effects such as overdose from intravascular injection still occur. Although local anesthetic overdose is uncommon, severe toxicity is estimated at 0.075 to 0.2% in peripheral nerve blocks and approximately 0.04% in epidural anesthesia[1]. Specific patient risk factors, concurrent medication use, block site and technique, type and dose of local anesthetics, along with time for detection and appropriateness of treatment, all influence the likelihood and severity of systemic toxicity. Bupivacaine is currently the most widely used local anesthetic due to its quality of anesthesia and prolonged action[2,3]. However, a 1979 issue of the journal Anesthesiology[4] cited the severe cardiovascular effects of accidental intravascular injection of bupivacaine, leading to the search for newer less toxic agents with antidotes to counter their effects. Bupivacaine intravascular injection may result in severe cardiovascular and neurologic toxicity. Central nervous system toxicity precedes cardiovascular symptoms. Manifestations of neurologic toxicity include tinnitus, metallic taste, visual disturbances, perioral numbness, unconsciousness, seizures and coma. Cardiac toxicity is characterized by decreased ventricular contractility, loss of vasomotor tonus, cardiovascular collapse, dysrhythmia and asystole[5]. In an attempt to decrease these complications, safety measures such as aspiration before local anesthetic injection, use of a test dose and epinephrine have been adopted[6]. In a review article from 1995, Brown *et al.*[7] reported that the incidence of complications was 1.2 per 10,000 epidural anesthesias, obtaining a result similar to that found by Auroy *et al.*[8] in France. Other long-acting local anesthetics expected to be safer alternatives, e.g. ropivacaine and levobupivacaine were synthesized and launched on the market[9]. Weinberg *et al.*[10] demonstrated that lipid emulsions (LE) used in parenteral nutrition were efficient to decrease local anesthetic cardiotoxicity, increasing the mean lethal bupivacaine dose by 50% in rats. Rosenblatt *et al.*[11] and subsequently Litz *et al.*[12] were the first authors to publish the successful use of LE for treatment of cardiac arrest due to local anesthetic toxicity in human. Since that time, the successful use of LE in the management of local anesthetic toxicity has been reported[13,14]. Several lipid preparations are available in the market and have been used *in-vivo* and *in-vitro* experiments. The source of lipids is the most significant difference between these preparations. Solutions derived from soybean oil, containing

long-chain triglycerides (LCT), emulsions based on coconut oil and soybean oil (MCT) containing 50% medium-chain and 50% long-chain triglycerides, and more recently solutions that also incorporate olive oil and fish oil[15] are currently the most widely used preparations. Each solution is of particular interest to parenteral nutrition, although results are controversial in the management of local anesthetic toxicity. According to some authors, LCT lipid emulsions is more effective[16,17]. Others believe that LCT is as efficient as MCT[18]. Still other authors have found better results with MCT emulsions[19]. Lipid emulsions have also been recently used in the treatment of toxicity due to several other lipophilic drugs such as cyclic antidepressants, verapamil, β-blockers and barbiturates among others[20]. The aim of this study was to evaluate the hemodynamic results produced by management of bupivacaine toxicity in swines, using two different lipid emulsions in our setting that contain different types of triglycerides, in comparison to saline use.

Methods

The protocol was approved by the Institutional Animal Research Ethics Committee, State University of Campinas under number 2157-1.

Thirty pigs, weighing from 19.5 to 25 kg were fasted on the night before the experiment, with free access to water. On the morning of the study, animal weight was recorded, with estimation of body surface area[21]. Data was entered into the hemodynamic EngstronAS/3 monitor for calculation of hemodynamic indexes. A catheter was placed in the ear vein of the animal and anesthesia was induced with 25 mg.kg^{-1} of sodium thiopental. The animals were intubated, maintained under mechanical ventilation, using a mixture of air and O_2 on a CO_2 absorption circuit with tidal volume of 15 ml.kg^{-1} and respiratory rate adequate to achieve $P_{ET}CO_2$ between 32 and 34 mmHg. Hemoglobin saturation was maintained >97% and measured by a probe placed on the animal tongue. A cardioscope was also used in a lead similar to DII. Maintenance of anesthesia was performed with isoflurane in O_2 at an expired fraction of 1%. Local anesthesia was applied to the inner thigh of the animal unilaterally, using 5 ml of 1% lidocaine without vasopressor for dissection of the femoral artery and vein. Dissection was required for continuous monitoring of arterial blood pressure and insertion of a Swan-Ganz 7F catheter, which was located in a pulmonary artery branch identified by the morphology of the pressure curve obtained. Thirty minutes after a stabilization and resting period, the first baseline

hemodynamic measurements (T_0) were recorded: mean arterial pressure, heart rate, central venous pressure, mean pulmonary arterial pressure, pulmonary capillary pressure, cardiac index, systemic and pulmonary vascular resistance indexes, left and right ventricular systolic work indexes. Then intravenous bupivacaine was administered at a dose of 5 mg.kg^{-1}. At one minute (T_1) new hemodynamic parameters were recorded and the animals were randomly divided into three groups. In the first group, 4 ml.kg^{-1} of LCT were injected immediately after toxicity. In the second group, the same volume of MCT was injected. The third group, which was considered the control group (CTRL), received the same volume of saline infusion. New hemodynamic measurements were taken at five, 10, 15, 20 and 30 minutes (T_5 to T_{30}). To compare numerical variables between groups, the Kruskal-Wallis test was used. For comparison of longitudinal measurements between groups and time points, repeated measures ANOVA was used, followed by Tukey's multiple comparison test to compare groups at each time point and the contrast profile test to analyze the progress between evaluations in each group. The significance level adopted was 5%, or $p<0.05$.

Results

There were no significant differences between groups regarding weight, body surface area, or baseline hemodynamic parameters, as shown in Table 1.

TABLE 1 – Weight and body surface area.

Group	Weight ± SD (Kg)	BSA ± SD (m^2)
LCT	22.65 ± 1.14	0.67 ± 0.02
MCT	22 ± 1.5	0.66 ± 0.03
CTRL	21.15 ± 1.29	0.64 ± 0.03

$p>0.05$

Mean arterial blood pressure (MAP)

As shown in Figure 1, after bupivacaine injection a significant and similar MAP decrease occurred in all groups. $T_0 = T_{20} = T_{30}$ and $T_1<T_5<T_{10}<T_{15}$ in CTRL; $T_0 = T_5 = T_{30}$ and $T_0<T_{10}$ a T_{20} in LCT; $T_0 = T_5$ and $T_0 < T_{10}$ to T_{30} in MCT ($p<0.001$). Among groups, there were no differences between MCT and LCT, but MCT > CTRL from T_5 to T_{30} and LCT > CTRL from T_5 to T_{20} ($p<0.001$).
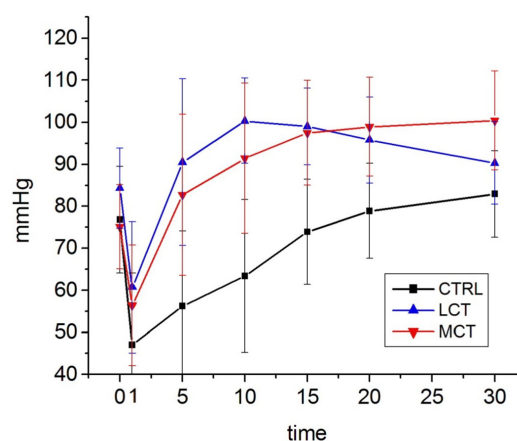

FIGURE 1 - Mean arterial blood pressure.

Heart rate (HR)

Figure 2 shows that after bupivacaine injection in T_1 there was a significant decrease in HR in all groups. In the CTRL group, all values remained lower than T_0 values; $T_0=T_5=T_{10}$ in the LCT and MCT groups, but all other values were lower than baseline values ($p<0.001$). There were no differences between LCT and MCT ($p=0.814$). However, CTRL<MCT in T_1 and CTRL>LCT in T_{30} with no other differences between groups ($p<0.001$).
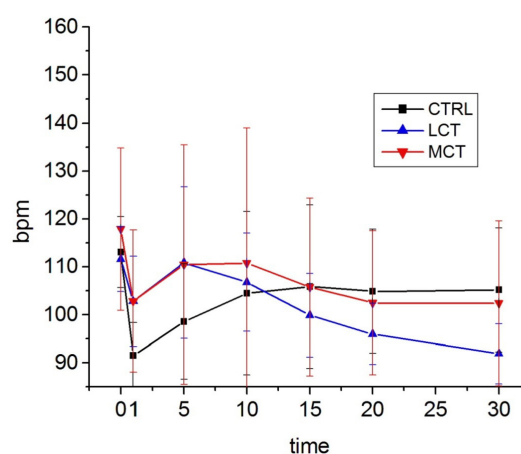

FIGURE 2 - Heart rate,

Central venous pressure (CVP)

Figure 3 shows that following toxicity, there was a significant and similar increase in CVP the three groups in T_1. In CTRL and MCT, all other values remained higher than T_0 values. In the LCT group, values were higher than T_0 until T_{20} ($p<0.001$). There were no differences between LCT and MCT. However, CTRL<LCT in T_5 and CTRL<MCT from T_5 to T_{15} ($p=0.023$).
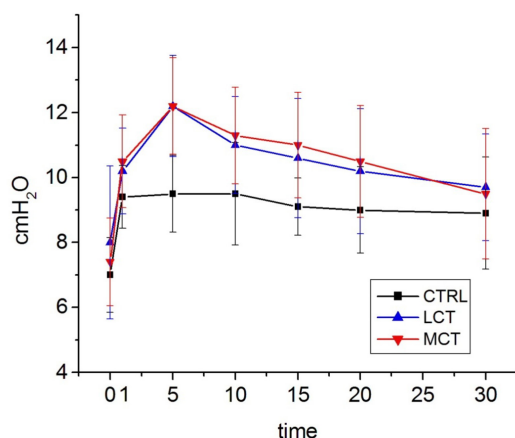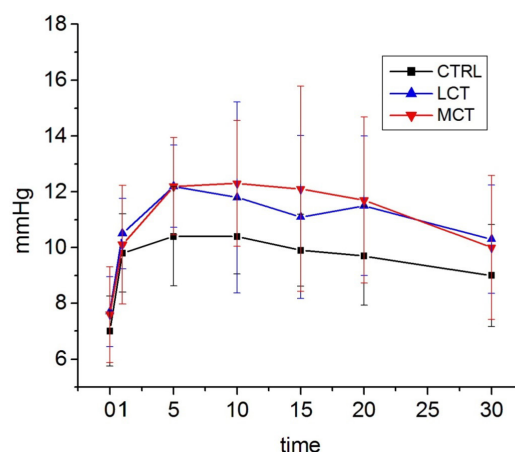
FIGURE 3 - Central venous pressure.

FIGURE 5 - Pulmonary capillary wedge pressure.

Mean pulmonary artery blood pressure (MPAP)

As shown in Figure 4, after bupivacaine injection there was no change in T_1 in any group. In CTRL, all values remained similar to T_0 value; in LCT and MCT, all values were higher than baseline values after T_5. However, values decreased significantly after T_{10} in LCT. This was not observed in MCT, where values remained elevated, although there were no differences between LCT and MCT (p<0.001). After T_5 in the CTRL group, values were all lower than in LCT and MCT. There were no significant differences between both groups (p<0.001).
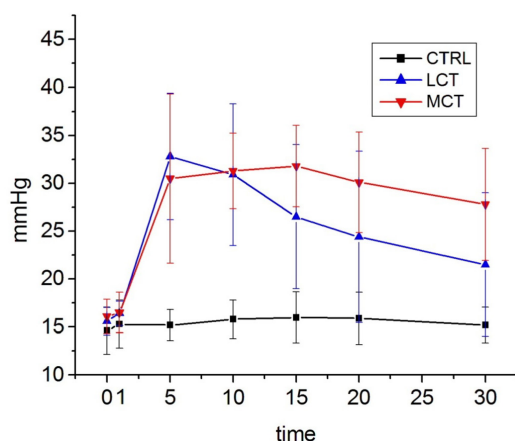
Cardiac index (CI)

Figure 6 shows that after bupivacaine injection, PCWP decreased similarly in T_1 in all groups persisting until the end of the experiment. There were no differences in time points between CTRL and LCT, while $T_{20}<T_{30}$ (p<0.001) in MCT. There were no differences among groups (p=0.454).
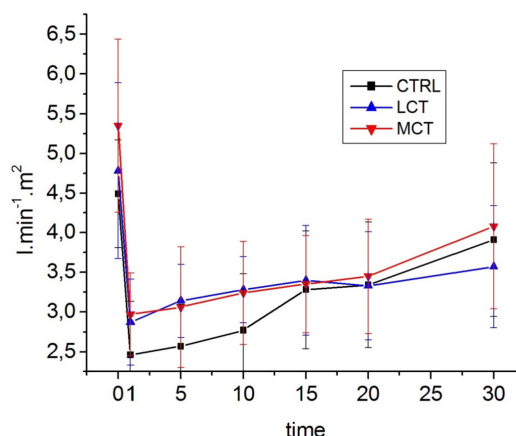

FIGURE 4 - Mean pulmonary artery blood pressure.

Pulmonary capillary wedge pressure (PCWP)

Figure 5 shows that after intoxication, values increased significantly and similarly in the three groups. Values remained significantly elevated in the three groups until the end of the experiment, but $T_5>T_1$ (p<0.001) in both LCT and MCT. No differences between groups were observed (p=0.105).

FIGURE 6 - Cardiac index.

Systemic vascular resistance index (SVRI)

Figure 7 shows that after bupivacaine toxicity, SVRI did not change in T_1 in any group. After T_{10} in CTRL, and T_5 in LCT and MCT, the remaining values were all higher than T_o. $T_{20}>T_{30}$ (p<0.001) in LCT and MCT. There were no differences between LCT and MCT, but CTRL was <LCT from T_5 to T15 and CTRL<MCT in T_{15} (p=0.032).
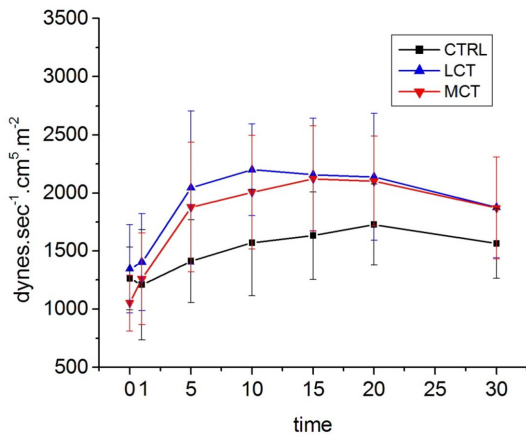
FIGURE 7 - Systemic vascular resistance index.

Pulmonary vascular resistance index (PVRI)

As shown in Figure 8, toxicity in T_1 initially produced no change in any of the three groups. In CTRL, values remained unchanged until T_{30} with no significant differences. In contrast, lipid therapy with both agents provoked a significant increase in PVRI after T_5. All values were higher than T_0. In LCT, $T_{10}>T_{15}$ and $T_{20}>T_{30}$, while $T_{20}>T_{30}$ ($p<0.001$) in MCT. After T_5, all LCT and MCT values were higher that CTRL values ($p<0.001$). However, there were no differences between LCT and MCT values.
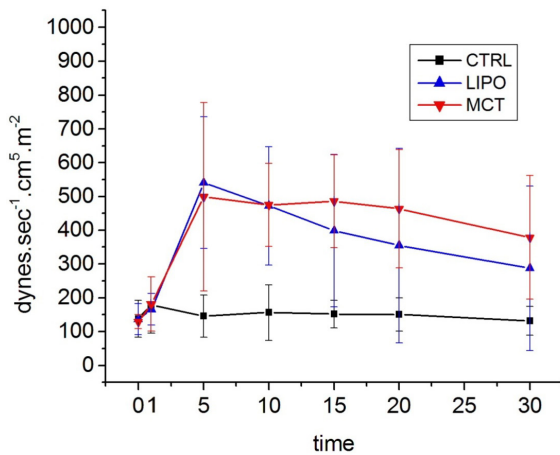

FIGURE 8 - Pulmonary vascular resistance index.

Left ventricular stroke work index (LVSWI)

Figure 9 shows that bupivacaine toxicity produced a significant and similar decrease in LVSWI in T_1 in the three groups. Subsequently, the CTRL group only recovered values similar to baseline values in T_{20}, in addition to $T_1<T_5=T_{10}<T_{15}=T_{20}<T_{30}$; $T_0=T_{15}$ in LCT and $T_1<T_5<T_{10}$; $T_0=T_{15}$ and $T_1<T_5<T_{10}<T_{15}=T_{20}<T_{30}$ in MCT ($p<0.001$). Among groups, there was no difference

between LCT and MCT. However, CTRL<LCT from T_5 to T_{15} and CTRL<MCT in T_5 and T_{10} ($p=0.017$).
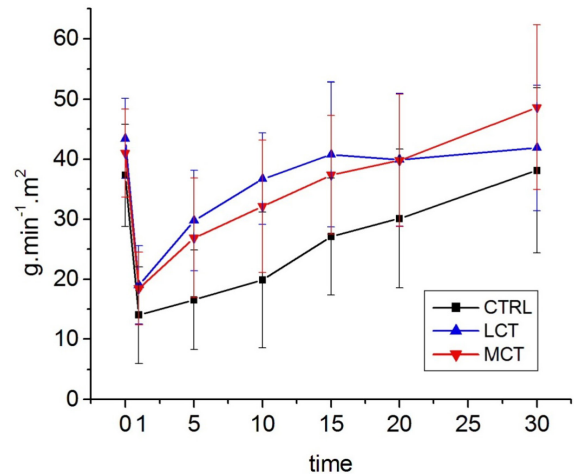

FIGURE 9 - Left ventricular stroke work index.

Right ventricular stroke work index (RVSWI)

Figure 10 shows that toxicity caused a similar fall in RVSWI in T_1 in all groups. In the CTRL group, values remained lower than T_0 until T_{15} and then achieved baseline values. In contrast, from T_5 to T_{15} LCT values were higher than in T_0 and then became equal; $T_0=T_5$ in MCT and the remaining values were all higher than baseline values ($p<0.001$). Between groups, significant differences were noted: CTRL<LCT and MCT from T_5 to T_{30} and LCT<MCT in T_{20} and T_{30} ($p=0.001$).
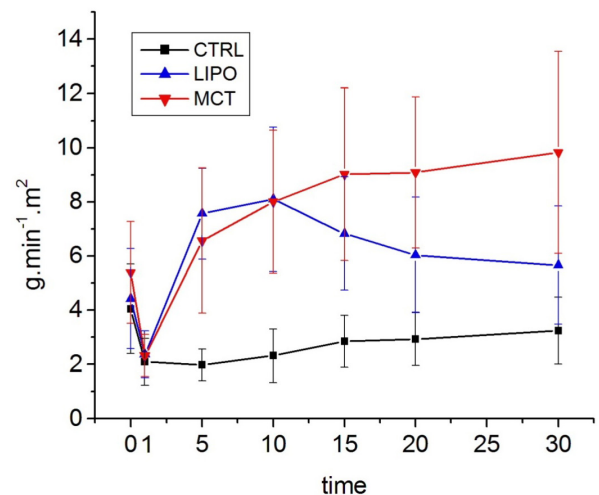

FIGURE 10 - Right ventricular stroke work index.

Discussion

Locoregional anesthesia has aroused great interest in the past years. Concomitant administration of locoregional anesthesia with general anesthesia in a multimodal approach has enabled the use of significantly lighter planes of general anesthesia. It is well-known that general anesthesia has negative cardiopulmonary repercussions. However, local anesthetic cardiotoxicity in case of inadvertent intravascular injection remains a concern for healthcare professionals, despite the implementation of newer drugs and techniques used for neural blocks. In 2006, the use of lipid emulsions for treatment of local anesthetic toxicity was proposed in humans. Three mechanisms were proposed to explain the effects of these agents. The first mechanism suggests a pharmacokinetic balance between the lipid plasma expansion phase, reducing the free fraction of lipophilic drugs in the plasma, and hence toxicity. This effect known as the "lipid sink" is obtained by chelation of LA molecules[22] which led to the use of this solution for treatment of toxicity from a number of other lipophilic drugs. The second mechanism is based on the concept that local anesthetics are known for inhibiting carnitine-acetyltransferase, essential for the transportation of fatty acids into mitochondria[23]. LE could overcome this inhibition and metabolic effect of the toxic substance through a "mass effect" alone or through another unknown mechanism. The third mechanism is based on the known fact that fatty acids can increase calcium levels in cardiac myocytes and may thus activate a direct inotropic route[22,24]. The hypothesis that long-chain triglyceride lipid emulsions *in vitro* would be more effective[16,17] motivated to conduct this study. The purpose of the study was to evaluate hemodynamic repercussions in swines with bupivacaine-induced toxicity and find the best solution in case this complication occurred. In this experiment, we did not observe any significant differences in the main hemodynamic variables using LE with long-chain triglycerides and a mixture of long-chain and medium-chain triglycerides. Hemodynamic parameters improved secondary to increased systemic vascular resistance and pulmonary vascular resistance in animals treated with lipid emulsions, a result similar to that found by Stojiljkovic *et al*.[25] who studied hemodynamic variations due to lipid infusion in humans, but contrary to Kearney *et al*.[26]. In this study, an increase in resistance was mostly noted in the pulmonary circulation. However, no greater differences were observed with both types of solutions used. There was no improvement in cardiac index, a result similar to that obtained by Litonius *et al*.[27] investigating bupivacaine and mepivacaine toxicity in pigs. However, these findings differed from results described by Stehr *et al*.[28] who reported a positive inotropic effect on the isolated rat heart. In this study, arterial blood pressure improved with lipid emulsions after toxicity, but solutions with long-chain triglycerides and those with a mixture of medium-chain and long-chain triglycerides did not achieve different results of interest. The use of lipid emulsions needs to be further investigated. However, the lack of adverse effects until recently[29] has been encouraging and these solutions are even recommended in case of accidents during obstetric anesthesia[30].

Conclusions

Lipid emulsions with long-chain or a combination of long-chain and medium-chain triglycerides have proven to be efficient at reversing hypotension due to bupivacaine toxicity in pigs. It has been suggested that the early use of lipid emulsions may help to attenuate local anesthetic cardiotoxicity. Nevertheless, no significant differences were observed when either solution was used.

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Correspondence
Artur Udelsmann
Av. Prof. Atílio Martini, 213
13083-830 Campinas – SP Brasil
Tel.: (55 19)99838-8049
au1849@gmail.com