

Hemodynamic changes in lipid emulsion therapy (SMOFlipid) for bupivacaine toxicity in swines¹

Alterações hemodinâmicas na terapia por emulsão lipídica (SMOFlipid) na intoxicação por bupivacaína em suínos

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ABSTRACT

PURPOSE: To evaluate the hemodynamic changes following SMOFlipid emulsion therapy with after bupivacaine intoxication in swines.

METHODS: Large White pigs were anesthetized with thiopental, tracheal intubation was performed and mechanical ventilation was 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 then randomly divided into two groups and received 4 ml.kg⁻¹ of saline solution or 4 ml.kg⁻¹ of SMOFlipid emulsion 20%. 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. SMOFlipid emulsion therapy was able to improve blood pressure mainly by increasing vascular resistance since the cardiac index had no significant improvement in our study. Hemodynamic results of the use of lipid emulsion in bupivacaine intoxication were better than the control group.

CONCLUSION: The SMOFlipid emulsion is a option for reversing hypotension in cases of intoxication by bupivacaine.

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

RESUMO

OBJETIVO: Avaliar as alterações hemodinâmicas da terapia lipídica com SMOFlipid após intoxicação com bupivacaína em suínos.

MÉTODOS: Suínos da raça Large White foram anestesiados com tiopental, realizada intubação traqueal e mantidos em ventilação mecânica. As variáveis hemodinâmicas foram registradas através de pressão invasiva e cateterização da artéria pulmonar (cateter de Swan-Ganz). Após período de 30 minutos de repouso, 5 mg.kg⁻¹ de bupivacaína foram injetados por via endovenosa e novas medidas hemodinâmicas foram realizadas 1 minuto após; os animais foram então aleatoriamente divididos em dois grupos e receberam 4 ml.kg⁻¹ de solução salina ou 4 ml.kg⁻¹ da emulsão tipo SMOFlipid a 20%. As alterações hemodinâmicas foram reavaliadas aos 5, 10, 15, 20 e 30 minutos.

RESULTADOS: A intoxicação pela bupivacaína causou queda da pressão arterial, índice cardíaco e do trabalho sistólico dos ventrículos principalmente sem importantes alterações das resistências vasculares. A terapia com a emulsão SMOFlipid foi capaz de melhorar a pressão arterial através, principalmente, do aumento das resistências vasculares uma vez que o índice cardíaco não apresentou melhora expressiva em nosso estudo. Os resultados hemodinâmicos com o uso da emulsão lipídica na intoxicação pela bupivacaína foram melhores que no grupo controle.

CONCLUSÃO: A emulsão SMOFlipid é uma opção para reverter a hipotensão em caso de intoxicação pela bupivacaína.

Descritores: Anestesia Local. Bupivacaína. Lipídeos. Hemodinâmica. Emulsões Gordurosas Intravenosas. Suínos.

Introduction

Locoregional anesthesia may require high doses of local anesthetics and there is always a potential risk of toxic reactions due to inadvertent intravascular injection. Bupivacaine is still the most widely used agent, owing to its good quality of anesthesia and prolonged duration of action^{1,2}. However, in 1979, an editorial of Anesthesiology³ on the severe cardiovascular effects produced by accidental intravascular injections led to a search for new agents with lower toxicity and antidotes to combat their effects. Intravascular bupivacaine injection may result in severe toxicity of the central nervous and cardiovascular systems⁴ which are the main targets. Damage to the nervous system precedes cardiac compromise with signs and symptoms including tinnitus, metallic taste, visual disturbance, perioral numbness, loss of consciousness, convulsions and death. Cardiotoxicity is characterized by a decrease in ventricular contractility, loss of vasomotor tonus, cardiovascular collapse, arrhythmia and asystole⁵. Until 1981 the incidence of systemic toxicity was 100 per 10,000 epidural anesthetics⁶; safety measures such as frequent aspiration before injection, use of a test dose and epinephrine began to be adopted in an attempt to reduce complications⁶. In a review study conducted in 1995, Brown *et al.*⁷ reported a rate of 1.2 complications per 10,000 epidural anesthetics, similar what was found by Auroy *et al.*⁸ in France. New local anesthetics of long duration were synthesized and launched in the market such as ropivacaine and levobupivacaine which would be safer alternatives⁹. In 1998, Weinberg *et al.*¹⁰ demonstrated that a lipid emulsion (LE) was efficient in the treatment of local anesthetic cardiotoxicity, increasing by 50% the mean lethal dose of bupivacaine, however these solutions had been used for parenteral nutrition since 1961! Rosenblatt *et al.*¹¹ and later Litz *et al.*¹² were the first to publish the successful use of LE in the treatment of cardiac arrest due to local anesthetics, when conventional resuscitative techniques had failed. There are now reports of the successful use of LE to treat toxicity due to these agents^{13,14}. The aim of this study was to evaluate the hemodynamic changes after intravenous bupivacaine injection as a clinical scenario of toxicity and treatment with a 20% lipid solution named SMOFlipid^{15,16} (Soybean oil + Medium-chain triglycerides + Olive oil + Fish oil).

Methods

After approval from the Animal Experimentation Ethics Committee of the Biology Institute of UNICAMP, in compliance with the Council for International Organization of Medical Sciences (CIOMS) ethical code for animal experimentation, 20

Large-White pigs weighing between 19.5 and 23.5 kg were fasted overnight with free access to water. On the morning of the study the animals were weighed and body surface area was calculated by the formula¹⁷ $BS (m^2) = (9 \times \text{weight in grams}^{2/3}) \times 10^{-4}$ introducing the results on the Engstrom AS/3 hemodynamic monitor for index calculation. Venipuncture was performed in the animal ear and anesthesia was induced with 2.5 % sodium thiopental 25 mg.kg⁻¹. After intubation, the animals were maintained under controlled ventilation in a partial rebreathing system, tidal volume of 15 ml.kg⁻¹ and adequate respiratory rate to obtain $P_{ET}CO_2$ between 32 and 34 mmHg. The pigs were ventilated with an air and O₂ mixture maintaining hemoglobin saturation higher than 97%, measured by a sensor placed on the tongue. A cardioscope was also used in DII lead. Isoflurane 1% expired fraction was used for maintenance of anesthesia. Local anesthesia with 5 ml of 1% lidocaine without vasoconstrictor was administered to the internal portion of the pig thigh for dissection of the femoral artery and vein for continuous measurement of arterial blood pressure and introduction of the 7F Swan-Ganz catheter located in a branch of the pulmonary artery by the morphologic aspect of the pressure curve obtained. The following variables were measured: cardiac output, heart rate, mean arterial blood pressure, central venous pressure, mean pulmonary artery pressure and pulmonary capillary pressure. The monitor, using classical formulas calculated vascular resistances, ventricular work and all their indexes. After 30 minutes of stabilization and rest, baseline standard hemodynamic measurements were taken (T_0), followed by 5 mg.kg⁻¹ of intravenous bupivacaine injection. One minute later, new hemodynamic measurements were taken (T_1). The animals were then randomly divided into two groups. In the first group 4 ml.kg⁻¹ of saline solution were injected immediately after T_1 (CTRL group) and in the other 4 ml.kg⁻¹ of SMOFlipid (SMOF group) were injected. New hemodynamic measurements were taken at 5, 10, 15, 20 and 30 minutes after toxicity (T_5 to T_{30}). The numerical variables measured in a single time point were compared by the Student's t test. To study numerical variables in various time points Analysis of Variance for repeated measurements (ANOVA) was used, Duncan's test was used to compare the groups in each time point and the contrast profile test to analyze the progression between time points in each group. The significance level adopted was 5% ($p < 0.05$).

Results

Table 1 shows mean and standard deviations of weight and body surface areas. There were no statistic differences.

TABLE 1 – Weigh and body surface area.

Group	Weight ± SD (Kg)	BSA ± SD (m ²)
CTRL	21.15 ± 1.29	0.64 ± 0.03
SMOF	22.2 ± 0.67	0.66 ± 0.01

P>0.05

There were no differences in hemodynamic parameters at rest as well.

Mean arterial blood pressure

As shown in Figure 1, after bupivacaine injection there was a significant and similar decline in mean arterial pressure in both groups. Immediately following injection of the lipid, pressure increased in SMOF and remained higher than CTRL until the end (p<0.001). In CTRL, pressure increased progressively until 15 minutes. After this time and until the end of the experiment, values returned to levels similar to those in T₀ (p<0.001). In SMOF, pressures increased significantly in each time period until T₁₅ and remained similar after that and always higher than at T₀.

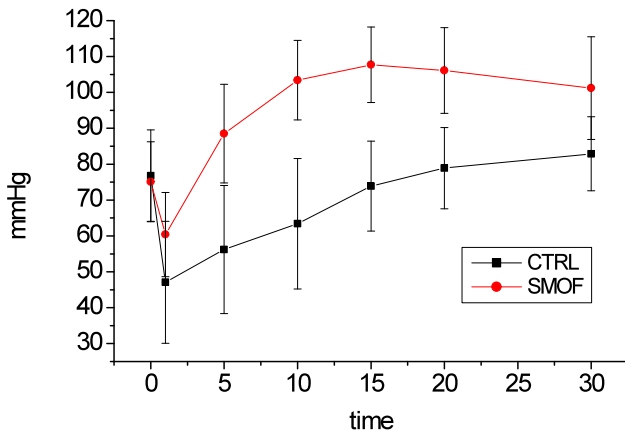


FIGURE 1 - Mean arterial pressure.

Heart rate

As shown in Figure 2 there was no changes in SMOF but the heart rate declined in CTRL and was lower than SMOF until T₅ (p=0.006). In CTRL values remained lower than T₀ till the end but increased from T₁ to T₁₀ (p=0.001).

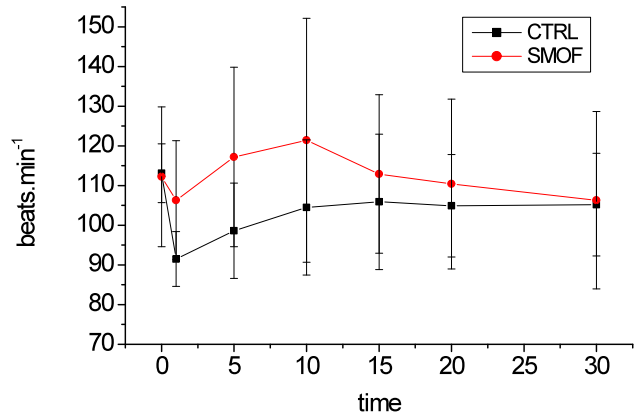


FIGURE 2 - Heart rate.

Central venous pressure

As seen in Figure 3, there was an increase in values in both groups, in SMOF they were higher than CTRL until T₂₀ (p<0.001). In both groups the results did not return to levels similar at rest until the end of the experiment, although in SMOF results were successively different from previous values (p<0.001).

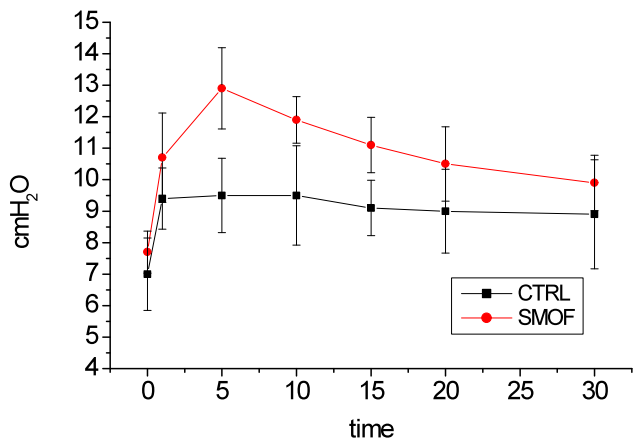


FIGURE 3 - Central venous pressure.

Mean pulmonary artery pressure

As observed in Figure 4, mean pulmonary artery pressure differed between groups after toxicity and until the end of the experiment (p<0.001). In SMOF, it increased significantly and remained higher than rest till the end with differences between T₁ and T₅ in addition to T₂₀ and T₃₀. In CTRL, there were no differences relative to T₀ (p<0.001).

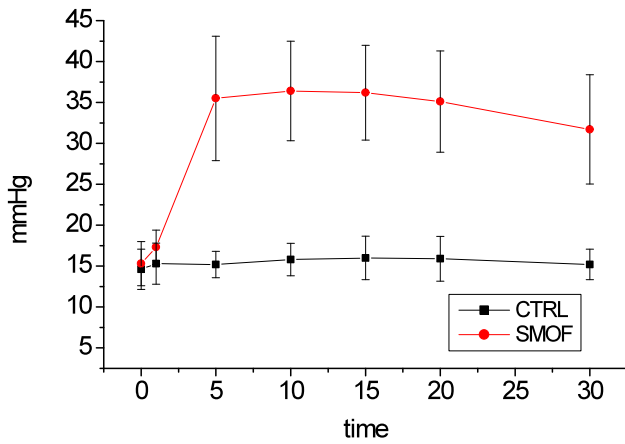


FIGURE 4 - Mean pulmonary arterial pressure.

Pulmonary capillary wedge pressure

As observed in Figure 5, in SMOF values were higher than CTRL from T₁ to T₁₅ (p=0.002). In both groups, pressure values in all time periods were higher than in T₀. However, in SMOF T₅ and T₁₅ were also higher than the values immediately prior to those time periods (p<0.001).

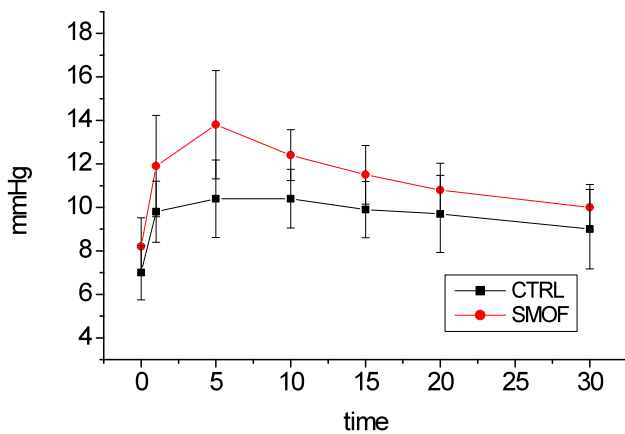


FIGURE 5 - Pulmonary capillary wedge pressure.

Cardiac index

As shown in Figure 6, the cardiac index decreased equally in both groups (p=0.004). In CTRL values only returned to those similar to rest in T₃₀ and T₁₀ was lower than T₁₅. In SMOF, values did not return to levels similar to T₀, although they increased from T₂₀ to T₃₀ (p<0.001).

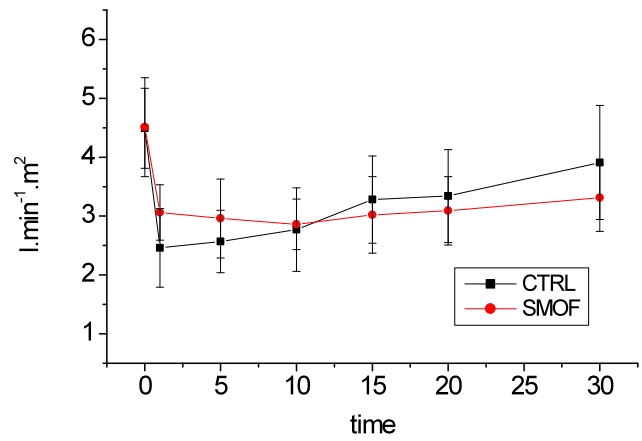


FIGURE 6 - Cardiac index.

Systemic vascular resistance index

As observed in Figure 7, the systemic vascular resistance index in SMOF was higher than in CTRL beginning at T₅ till the end (p<0.001). In CTRL there was an increase from T₁₀ to T₃₀ and T₁ was lower than T₅. In SMOF all results were higher than T₀ and exhibited significant increases in T₅, T₁₀ and T₃₀ compared to previous time (p<0.001).

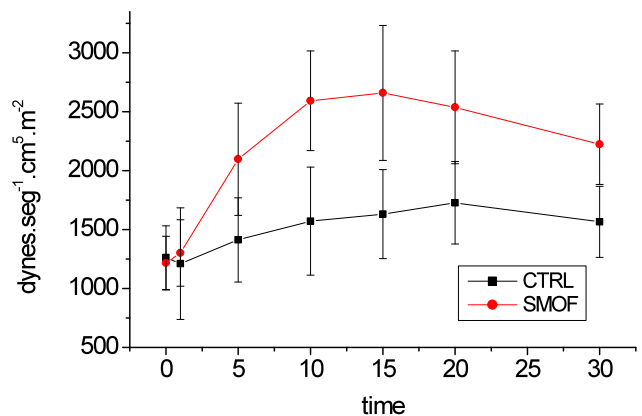


FIGURE 7 - Systemic vascular resistance index.

Pulmonary vascular resistance index

As shown in Figure 8, there was a significant increase in pulmonary vascular resistance in SMOF that remained higher than in CTRL from T₅ to T₃₀ (p<0.001). In CTRL, there were no differences between time periods; in SMOF all values were higher than those at rest, T₁ was lower than T₅ and T₂₀ higher than T₃₀ (p<0.001).

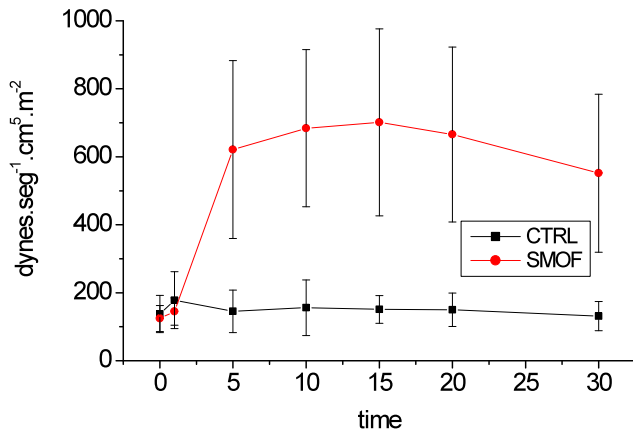


FIGURE 8 - Pulmonary vascular resistance index.

Left ventricular systolic work index

As observed in Figure 9, left ventricle systolic work index had a significant decline in both groups and this was more striking in CTRL until T₁₅ (p=0.049). In CTRL all values remained lower than standard levels until T₂₀ and T₁₅ and T₃₀ were higher than the previous values; in SMOF there was a progressive increase in T₅, T₁₀ and T₂₀ when values returned to similar at rest (p<0.001).

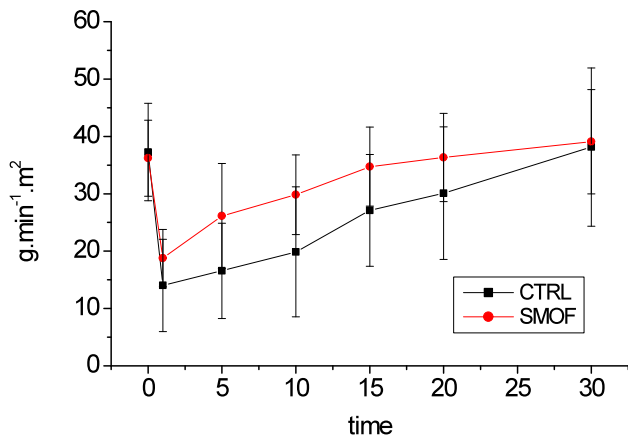


FIGURE 9 - Left ventricular stroke work index.

Right ventricular systolic work index

As observed in Figure 10, the right ventricular systolic work index had a significant decrease in both groups, however, in SMOF values recovered and remained higher than CTRL from T₅ till the end (p<0.001). In CTRL, values returned to those similar to rest in T₁₅ and remained constant until the end. In SMOF, after T₅ and until the end these values were higher than those at rest (P<0.001).

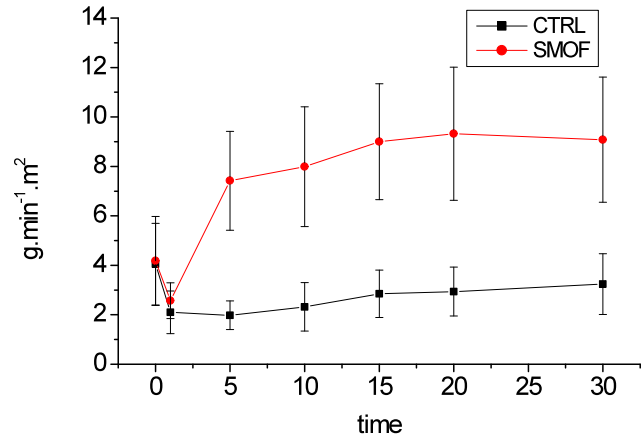


FIGURE 10 - Right ventricular stroke work index..

Discussion

Cardiotoxicity of local anesthetics is still a concern for anesthesiologists. Until recently, it was a devastating complication without any specific treatment. Since 2006, with a publication on the successful use of lipid emulsion^{11,12} to treat cardiotoxicity due to intravascular injection of local anesthetics, several formulations have been suggested for this purpose¹³. We chose to use the 20% SMOFlipid solution because there are few cases describing its use for this type of complication. Three hypotheses on the mechanism of action of lipids in local anesthetic toxicity have been formulated. The first theory, known as ‘lipid sink’, suggests the establishment of new pharmacokinetics, with expansion of the lipemic phase that would sequester local anesthetic molecules, decreasing the free fraction and consequently toxicity of these agents¹⁸. This is a well-accepted theory since it was observed that toxicity of other lipophilic drugs, as some antipsychotics, barbiturates, antidepressants, organophosphates and antihypertensives, also responds to a lipid infusion. In corroboration with this theory, Turner-Laurence and Kerns demonstrated in vitro the binding capacity of lipid emulsions to local anesthetics in buffer solutions¹⁹. In the plasma, bupivacaine binds to alfa-1 glycoprotein and albumin. The affinity for alfa-1 is greater than that for albumin, although albumin is more abundant. The binding capacity of lipid emulsions to bupivacaine is important, a 1% solution is equivalent to 1.5 to 4 times the binding capacity of human plasma. Thus 100 ml of a 20% lipid emulsion would have the same binding capacity to albumin contained in 7 to 12 liters of plasma²⁰. The second theory states that lipid emulsions would overcome by mass effect, or by some other unknown mechanism, bupivacaine inhibition of carnitine-acetyltransferase. This enzyme is essential for fatty acid transportation into the mitochondria where they are used

as substrate for energy production by the myocardium and other tissues²¹. And finally, the third theory states that an increase in fatty acids would increase the calcium levels in cardiac myocytes, promoting a positive inotropic effect²². In our study, we observed a rapid and significant improvement in arterial blood pressure in animals treated with SMOFlipid after local anesthetic toxicity. We can infer that the reasons for this improvement may be an extraction of bupivacaine molecules by the lipid emulsion and an increase in the systemic and pulmonary vascular resistance indexes, since we did not observe great changes in cardiac index. In 2011, Ok *et al.*²³ published the first study demonstrating that LE reverses vasodilation caused by local anesthetics in the isolated rat aorta, they suggested that the mechanism of this reversal may be blunting of inhibition mediated by local anesthetics in the calcium voltage-dependent channels in smooth vascular muscles and partially by endothelial release of nitric oxide²³. It is worth noting that, if the reason for restoration of arterial blood pressure was only an increase in vascular resistance and the lipid emulsion did not exert this type of influence, the same results should have been achieved when vasoconstrictors were used. However, cardiac arrest due to this type of complication is often resistant to adrenergic therapy and may even lead to severe pulmonary edema after the use of epinephrine²⁴. Weinberg studied cardiac arrest caused by bupivacaine toxicity in rats. The same author reported better results when LE rather than epinephrine was used for treatment²⁵. Concerning the heart rate, in SMOF it was more stable than CTRL, a result similar to that found by Chen *et al.*²⁶. We also observed a significant increase in pulmonary artery pressure in SMOF compared to CTRL. This alteration was described as one of the side effects of LE when a dose higher than 100 mg.kg⁻¹.h was used or when LE was given to patients with previous pulmonary disease²⁷. Finally, other side effects of lipid emulsions have been described: risk of infection, allergic reactions especially in soy oil emulsions, thrombophlebitis, increased amylase, hyperlipidemia, hemolytic anemia, thrombocytopenia and fat embolus¹⁹.

Conclusion

The SMOFlipid emulsion proved to be efficient in the reversal of hemodynamic alterations due to bupivacaine toxicity in pigs, suggesting that the early use of this lipid solution may help to prevent or mitigate the cardiotoxicity of local anesthetics.

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