The cardiovascular effects of intralipid as a rescue therapy for non-fatal bupivacaine toxicity

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**Background:** Lipid-emulsion therapy is now a widely recommended for treatment of acute life threatening local anaesthetic toxicity. However the differential effects on cardiac versus vascular systems remains poorly understood. The aim of this study was to investigate the cardiac and vascular effects of lipid-emulsion using pressure volume loops administered after a non-fatal dose of bupivacaine.

**Methods:** Male Sprague Dawley rats were anaesthetised and instrumented for pressure volume loops, using an open-chest preparation and conductance catheter method. Bupivacaine 2 mg.kg-1 was infused over 15 minutes via the jugular vein catheter, followed by infusion of saline (control), gelofusine or intralipid 30%. The volume administered was the same for each group and consisted of 5 ml.kg-1 bolus, then 1 ml.kg-1.min-1 for 2 minutes, then a further 5 ml.kg-1 bolus. Recovery was measured for a further 30 minutes. Comparisons were made between intralipid and saline and gelofusin and saline.

**Results:** 38 rats were included, 7 arrested during the bupivacaine infusion, and intralipid administered after arrest did not lead to successful resuscitation. In 13 rats the experiments were not completed due to inability to correctly position the catheter, non-evaluable loops, or equipment failure. Eighteen rats successfully completed the protocol (n=6 for each group). Systolic blood pressure was stable throughout the protocol and intralipid or gelofusine groups were not different from saline. Bupivacaine produced progressive bradycardia in all groups, with progressive recovery after cessation of the infusion. Neither intralipid nor gelofusin treatment differed from saline treatment. Neither contractility (PRWS) nor diastolic stiffness (EDPVR) were affected by either intralipid or gelofusin treatment compared to saline. Arterial elastance (Ea) significantly increased after intralipid treatment compared to saline, but gelofusin was not different to saline treatment. Stroke volume was significantly reduced in the gelofusin group compared to saline, with no difference between intralipid and saline. Left ventricular end diastolic volume and pressure were not difference between groups.

**Conclusions:** Lipid-emulsion therapy after non-fatal bupivacaine toxicity does not improve contractility, myocardial stiffness or heart rate, but does increase arterial elastance.

**Keywords:** Lipid-emulsion; Bupivacaine toxicity; Intralipid; Local anaesthetic Toxicity

( J Perioper Sci 2014, 1:1)

**Introduction**

Infusion of a lipid-emulsion is now a popular therapy for acute local anaesthetic systemic toxicity (LAST) [1,2]. Animal studies have shown that lipid-emulsion infusion can improve survival after cardiac arrest, as well as produce faster recovery of haemodynamic parameters [3-5]. Although there are no clinical trials investigating the effect of intralipid, there are a number of case reports which have demonstrated successful resuscitation [6]. Although caution should be exercised when making clinical decisions based on case reports, there is an accumulating body of evidence that lipid-emulsion therapy is probably not harmful [1] and may improve chances of survival in an often desperate situation [6]. This has also been shown for other lipid-soluble drugs such as overdose of beta-
blockers, calcium channel blockers, and tricyclic antidepressants [6,7].

Several mechanisms have been proposed including the "lipid sink" theory whereby lipid soluble drugs are captured within the lipid droplets, effectively removing them from cardiac and vascular tissues, and potentially enhancing delivery to the liver for elimination [8,9]. However, other authors have found contradictory results casting doubt on this mechanism [10,11]. Other mechanisms include improved fatty acid metabolism [12], alteration to binding of local anaesthetics at sodium channels [13], or even a cardioprotective event after ischaemia [14].

The clinical effect of bupivacaine toxicity is to reduce blood pressure and cardiac output leading to the cardiac arrest. Using a pressure-volume loop preparation in anaesthetised rabbits, we [15], identified that bupivacaine impairs contractility, reduces rejection fraction and cardiac index, but increases systemic vascular resistance as a sub lethal dose. It is unknown whether lipid-emulsion treatment effect contractility, heart rate, or vascular resistance when administered prior to a lethal dose administration.

The aim of this study was to investigate the cardiovascular effects of lipid-emulsion therapy following a non-fatal toxic dose of bupivacaine, using pressure volume loops.

Methods

The University of Melbourne Animal Ethics Committee approved the animal experiments, and in accordance with the Australian code of practice for the care and use of animals for scientific purposes (7th edition, 2004, National Health and Medical Research Council, Australian Government).

Male Sprague Dawley rats (300-500g) were placed into an induction chamber and anaesthetised with isoflurane 5% (Baxter Healthcare, NSW, Australia) in 100% oxygen. When anaesthetised, rats were given an intra-peritoneal injection of pentobarbitone 60 mg.kg⁻¹ (ilium, Troy Laboratories, NSW, Australia) to maintain general anaesthesia. Additional doses of 6 mg pentobarbitone were administered as required to prevent movement to deep paw pinch. Atropine 1 mg.kg⁻¹ (Sigma-aldrich, NSW, Australia) was also administered to help prevent bronchial secretions.

When surgical anaesthesia was achieved, rats were placed supine on a heated homeothermic heat blanket (Harvard Apparatus, Massachusetts, USA) to maintain body temperature at 38° Celsius. A small bolus of 1% lignocaine (Pfizer, NSW, Australia) was injected subcutaneously into the area above the trachea and an incision made. The muscle layers above the trachea were split and a tracheal tube inserted into a small hole made in the trachea. The tracheal tube was then connected to a ventilator (Ugo Basile, Italy) and the rat ventilated at a rate of ~70-80 breaths.min⁻¹ using a tidal volume of 6 ml.kg⁻¹. The left external jugular was isolated and a fluid filled cannula inserted for drug and fluid administration.

The right carotid artery was isolated and a 1.9F pressure-volume catheter (Scisense, London, Ontario, Canada) inserted into the carotid artery and passed retrogradely into the left ventricle. The catheter position along the long axis of the left ventricle was checked with transthoracic ultrasound. A small laparotomy was performed and a silastic sling positioned loosely around the inferior vena cava just below the liver, for later preload reduction manoeuvres.

After instrumentation, there was a 20 minute stabilization period prior to the commencement of baseline pressure volume loop recordings. No further anaesthetic doses were administered after commencement of the pressure volume loop recordings. Pressure volume loop measurements were performed during apnoea. Static loops were acquired, followed by an acquisition during acute preload reduction (by lifting the sling around the inferior vena cava to occlude it). Pressure volume loops were acquired at 5-minute intervals.

After a series of baseline recordings were complete, bupivacaine 2 mg.kg⁻¹ (Pfizer, NSW, Australia) was infused over 15 minutes via the jugular vein catheter. This dose regimen had been determined by a prior pilot study to produce near-fatal cardiovascular compromise. At the end of the bupivacaine infusion, 3 treatment groups were investigated:

1. Intralipid 30% (Pharmatel FreseniumKabi, Sweden) treatment (5 ml.kg⁻¹ bolus, then 1 ml.kg⁻¹.min⁻¹ for 2 minutes, the a further 5 ml.kg⁻¹ bolus) was administered via the jugular catheter. The recovery was then monitored for 30 minutes.
2. Gelofusine (B.Braun, NSW, Australia) was administered after bupivacaine at 5 ml.kg⁻¹ bolus, then 1 ml.kg⁻¹.min⁻¹ for 2 minutes, the a further 5 ml.kg⁻¹ bolus with the same volume and time
3. 0.9% saline was administered after bupivacaine at 5 ml.kg⁻¹ bolus, then 1 ml.kg⁻¹.min⁻¹ for 2 minutes,
the a further 5 ml.kg\(^{-1}\) bolus with the same volume and time.

The following measurements were obtained from a minimum of 10 sequential stable (non-reduction) loops: systolic blood pressure was recorded as the peak left ventricular pressure, left ventricular end diastolic pressures, heart rate, left ventricular end-diastolic volume, stroke volume, and arterial elastance (Ea). Preload recruitable stroke work (PRSW) was used as the load-independent measurement of contractility. The PRSW is the slope of the stroke work / end-diastolic pressure-volume relationship (mmHg), obtained from the first 10-15 beats following acute preload reduction. An \(R^2 > 0.9\) was used to determine an acceptable linearity of the PRSW measurement. The end-diastolic pressure-volume relationship (EDPVR) was obtained from the first 10-15 loops following preload reduction as a measurement of diastolic function (chamber compliance).

If rats arrested during the bupivacaine infusion they were immediately administered the intralipid infusion protocol but without active cardiac resuscitation.

**Statistical methods**

Data are presented for groups over time as mean ± standard error of the mean. The differences in profile between groups was compared to the saline group (comparisons were between intralipid and saline groups and gelofusin and saline groups), using two-way ANOVA with Bonferroni post hoc adjustment. \(P<0.05\) was considered significant. For PRSW and EDPVR, two-way ANOVA was not possible as there were missing data from non-evaluable pressure volume loops (acquired during preload reduction) in some animals. Rather, independent t-tests were used to compare groups against saline at each time, with Ryan-Holm Bonferroni correction if any \(P<0.05\). Analysis was performed on the raw data using SPSS version 21 (SPSS Inc., Illinois, USA) or GraphPad Prism version 5.0 (GraphPad Software Inc.; California, USA).

**Results**

A total of 38 rats were included in the experiments. Seven rats died during the bupivacaine infusion (1 at 5 minutes, 4 at 12 minutes and 1 at 15 minutes). Administration of intralipid was unsuccessful in resuscitating any of the rats. In 6 rats, the pressure volume loop catheter could not be satisfactorily inserted into the left ventricle to lie in the correct plane of the long axis. In 1 animal, the heat lamp short-circuited, causing power failure to the experimental system which could not be rapidly resolved. In 6 rats, the pressure volume loops were not evaluable due to arrhythmias, and the experiments were abandoned. This left 18 rats that successfully completed the protocol (n=6 for each group).

The haemodynamic and pressure volume loop data are presented in figure 1. Systolic blood pressure was stable throughout the protocol and intralipid or gelofusin groups not different from saline. Bupivacaine produced progressive bradycardia in all groups, with progressive recovery after cessation of the infusion. Neither intralipid nor gelofusin treatment differed from saline treatment. Neither contractility (PRWS) or diastolic compliance (EDPVR) were affected by either intralipid or gelofusin treatment compared to saline. Arterial elastance (Ea) significantly increased after intralipid treatment compared to saline, but gelofusine was not different to saline treatment. Stroke volume was significantly reduced in the gelofusin group compared to saline, with no difference between intralipid and saline. Left ventricular end diastolic volume and pressure were not difference between groups.

**Discussion**

Our study shows that the major cardiovascular effect of bupivacaine toxicity is to produce bradycardia and arrhythmia leading to cardiac arrest. Contractility was minimally reduced by bupivacaine but intralipid did not improve contractility compared to a saline control. Intralipid was not successful in facilitating resuscitation of animals once they had arrested. The only significant effect of intralipid was to increase arterial elastance. As heart rate and stroke volume did not differ between intralipid and saline, the increase in arterial elastance represents an increase in the vascular resistance.

Our study is the first to use pressure-volume loops to assess contractility in a load-independent manner. This preparation allows us to separate the cardiac from vascular effects in an in vivo model. Intralipid did not alter contractility, diastolic, or heart rate compared to either gelofusine or saline controls.
Cardiovascular effects are shown over time for a 5 ml.kg\(^{-1}\) bolus, then 1 ml.kg\(^{-1}\).min\(^{-1}\) for 2 minutes, then a further 5 ml.kg\(^{-1}\) bolus of intralipid 30% gelofusine, or saline, after 15 minutes of bupivacaine 2mg.kg\(^{-1}\) was infused over 15 minutes. * is P<0.05 for comparisons of gelofusine or intralipid against the saline group.

Any haemodynamic benefit was not due to volume affect of intralipid, as the same intravascular volume affect was administered by gelofusine, and would greater than the intravascular volume expansion with saline after redistribution to the extracellular compartment. There were no

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differences in the recovery profile between these three groups on cardiac parameters. Our finding that the major effect of intralipid was to increase vascular resistance, has also been demonstrated by Ok et al. [16], who showed that bupivacaine could reverse bupivacaine-mediated aortic ring vasodilation in an in vitro preparation. Melo et al. [17], also demonstrated an increase in systemic vascular resistance in anaesthetised pigs receiving bupivacaine after local anaesthetic toxicity.

We cannot explain why an increase in vascular resistance may improve survival noted in other studies or case report. Di Gregorio et al. [18] showed that intralipid was superior to vasopressin in a rat model of toxin –induced cardiac arrest, and Mayr et al. [19] found intralipid was superior to a combination of adrenaline and vasopressin in a porcine model of asphyxia arrest after administration of a toxic dose of bupivacaine. In both these studies vasopression should have increased vascular resistance. Other studies have investigated whether adrenaline can improve survival after local anaesthetic toxicity, which will augment both contractility and increase vascular resistance. The results are contradictory, with Mauch et al. [20] showing adrenaline to be superior to intralipid and Weinberg et.al. [4] showing that intralipid is superior to adrenaline. There may be a threshold level above which adrenaline is detrimental by inducing hyperlactaemia [21]. The absence of cardiac effects by intralipid shown in our study would support the use of an inotrope to augment contractility after cardiovascular collapse.

We were unable to resuscitate any rats with intralipid if they suffered cardiac arrest. Other authors have shown successful resuscitation with intralipid after cardiac arrest, with improved survival compared to other therapies [3,18]. In our study, we did not perform an active resuscitation protocol as the primary aim was to investigate the effects of intralipid in a non-fatal toxicity situation. It is possible that some animals could have been resuscitated if an acute cardiac life-support protocol had been instituted in addition to the administration of intralipid.

We used a bolus followed by infusion protocol to simulate guidelines proposed initially by Weinberg [22], and now promulgated by societies and educational websites. We used a 30% solution to reduce the volume load administered to animals. The protocol produced haemodynamic compromise particularly on heart rate. A number of animals arrested new the end of the bupivacaine infusion protocol, indicating that our dosing regimen produced significant local anaesthetic toxicity. It is possible that lipid-emulsion therapy could have different cardiac effects at lesser degrees of cardiac toxicity.

Conclusion

lipid-emulsion therapy after non-fatal bupivacaine toxicity does not improve contractility, myocardial stiffness or heart rate, but does increase arterial elastance.

Acknowledgements

We thank Linda Cornthwaite-Duncan for her assistance in conducting the animal experimentation. There are no conflicts of interest declared by the authors. The levosimendan was provided by Abbott Australia.

References


