Pretreatment with Hypertonic Saline Outperforms Sodium Bicarbonate In Rodent Bupivacaine Toxicity

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Abstract
Bupivacaine is a commonly used local anesthetic agent with a significant cardiac adverse effect profile. Powerful experimental evidence has recently been published showing an effect for lipid emulsions in bupivacaine toxicity. Other studies have provided evidence of an effect for hypertonic sodium solutions. There is no evidence on whether the effects of lipid emulsion and hypertonic sodium solutions are additive.

This preliminary study aims to establish which hypertonic sodium solution is most effective and create a model for future study.

24 female rats were divided into groups and pretreated with gelofusine® (control), hypertonic saline (HS) or sodium bicarbonate (NaBic) solution. Subjects were then infused with bupivacaine 0.75%. Outcomes were time to death and percent QRS duration prolongation two minutes into the infusion.

HS pretreated animals survived bupivacaine infusion longer than NaBic (5.3+/−0.7 vs. 4.25+/−1.7 mins, p<0.05). Neither group was significantly different to controls for time to death. A protective effect for HS and NaBic on percent QRS prolongation 2 minutes into infusion occurred (8.8+/−6.1%(HS) and 1.2+/−10.1% (NaBic) vs. 22.8+/−15.0% p<0.05) with no significant difference between the 2 solutions.

Increased lethal dose of bupivacaine in the HS group versus NaBic made it the most successful pretreatment. While no protective effect was found on time to death for either HS or NaBic, both had a protective effect on QRS duration prolongation 2 minutes into infusion, suggesting benefit. This variable can be included in future studies a priori.

INTRODUCTION
Bupivacaine is a commonly used local anesthetic agent with a significant cardiac adverse effect profile. Powerful experimental evidence has recently been published showing an effect for lipid emulsions in bupivacaine toxicity. Weinberg et al resuscitated a group of 6 dogs 10 minutes into bupivacaine induced cardiac arrest using intralipid®, with all 6 control animals dying (1). Previous studies have provided evidence of an effect for hypertonic sodium solutions in bupivacaine toxicity (2,3). There is no evidence on whether the effects of lipid emulsion and hypertonic sodium solutions are additive.

The aims of this study are to determine whether HS or NaBic is the most effective solution to trial further with lipid emulsion by investigating the effect of both versus control, and to establish a model for future research.

MATERIALS AND METHODS
This experiment was approved by the Ruakura Animal Ethics Committee. A total of 26 female rats (Rattus norvegicus, Ruakura Agresearch, Hamilton, New Zealand), raised in single sex conditions with no possibility of pregnancy were used. Weights ranged from 200-300 grams. There was no significant difference in weight between control, NaBic and HS groups (t test). Animals were anesthetised with 50mg/kg ketamine and 0.1 mg/kg xylazine intraperitoneally. Following anesthesia rat tail veins were cannulated using 24g insyteN® cannulae. Oxygen via nose cone was administered at one liter per minute. ECG samples were taken prior to and after pretreatment, and every two minutes during bupivacaine infusion.

The control group were pretreated with 4% succinylated gelatin solution (gelofusine®), 8 ml/kg. The HS group were pretreated with 5ml/kg 7.5% HS (7.5 meq/kg). The NaBic
group were pretreated with 8.4% NaBic at 5 ml/kg (5 meq/kg). All pretreatment solutions were infused over 5 minutes and flushed with 0.5 ml 0.9% saline.

After pretreatment rats were infused with bupivacaine 0.75% at 15 ml/kg/hr. This was calculated to administer the rat LD50 IV for bupivacaine over 10 minutes (\(\text{LD50} \))

Rhythm strips were taken and scanned at 120 pixels/cm. These were then magnified until pixelation, each pixel representation 0.00167 sec. QRS durations were analysed prior to pretreatment, after pretreatment, and 2 min into the bupivacaine infusion. Presence of respiratory effort was checked every 30 sec. The primary study variable was time to death defined as absence of a cardiac rhythm > 4 sec or cessation of respiratory effort. Percent change in QRS duration at 2 min was chosen as an outcome post hoc.

Subjects were allocated to the three pretreatment groups sequentially, with initial plans for 10 in each group. As 2 control animals received inadvertent overdoses of anesethesic and died before the experiment, there were 8 in the control group. When a significant difference was found between HS and NaBic in time to death, the study was stopped at 6 NaBic subjects.

Data were analysed using Instat3® software. Statistical significance was set at a 2 - tailed p value <0.05. Students t tests were used for percent changes in QRS duration. Paired t tests were used to compare changes in post pretreatment QRS duration with baseline. The Mann-Whitney test was used for time to death.

**RESULTS**

The mode of death was universally respiratory arrest in all treatment groups. The mean times in min were 4.5 +/- 1.7 (control)(n=8), 5.3 +/- 0.7 (HS)(n=10) and 4.3 +/- 0.5 (NaBic)(n=6). The difference between HS and NaBic was significant (p=0.014, Mann Whitney). There was no significant difference between control and HS (p=0.158) or NaBic (p=0.75).

Means and 95% confidence intervals for percent QRS duration prolongation at 2 minutes were: control 22.8 +/- 15.0; HS 8.8 +/- 6.1; NaBic 1.6 +/- 10.1. There was a significant difference between controls and both NaBic (p=0.038, t test) and HS (p=0.044). No significant difference was seen between HS and NaBic (p= 0.179).

Effects of pretreatment QRS duration were not significant for any of the groups (p=0.67 control, 0.38 HS, 0.08 NaBic, paired t test).

**DISCUSSION**

A significant effect favouring HS over NaBic in time to death was found. There was no difference found between either pretreatment group and controls. Significant protective effect on QRS duration prolongation at 2 min was found for both agents. While this represents post hoc analysis, it supports a protective action.

QRS prolongation in bupivacaine toxicity is believed to be caused by reduced sodium flux in phase 0 of the cardiac action potential, resulting in slower conduction along and between myocytes. Increased QRS duration is caused by an increase in time to depolarisation of the ventricular mass through delayed conduction(\(\text{d} \)). There are alternative explanations for the QRS duration prolongation. Thomas et al demonstrated QRS duration prolongation with intramedullary injection of bupivacaine in rats (\(\text{i} \)). A potential central contribution in this study could change the hypothesized site of action of pre-treatment, but would not detract from effect.

The mode of death in all animals was respiratory arrest. Two minutes was chosen as the time of QRS analysis as it was early in the infusion thus minimising any effects of respiratory depression. Hypoxia and hypercapnoea could still have contributed to QRS prolongation.

This study has some methodologic limitations. As it is new research, pre-experiment power analysis was not able to be undertaken. The investigator was not blinded though end points were objective, minimizing potential for bias. Study groups were unequal in number for reasons previously outlined. However, given this is a preliminary experiment the aim of which is to find which agent to use in future experiments, group size did not detract from this goal.

**CONCLUSION**

Increased lethal dose of bupivacaine in the HS group made it the most successful pretreatment in this experiment. While no protective effect was found on time to death for either HS or NaBic, both had a protective effect on QRS duration prolongation 2 min into infusion, suggesting benefit. This variable can be included in future studies a priori.

A further study is planned using the model in this study to assess whether the effects of HS are additive to those of lipid emulsion in bupivacaine toxicity.
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