Evaluation of the Maintained Effect of 3% Hypertonic Saline Solution in an Animal Model of Intracranial Hypertension

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Current clinical treatment methods for refractory intracranial hypertension include elevation of the decubitus, ventilation adjustment, and use of hypertonic solutions such as hypertonic saline and mannitol solutions. Previous studies have shown that hypertonic solutions are particularly effective. Although several concentrations of saline solution have been proposed, a 3% solution is the most widely used. The aim of this study was to evaluate the maintained efficacy of a 3% hypertonic saline solution in an experimental model of intracranial hypertension.

Material/Methods: A porcine model of reversible intracranial hypertension was created by inserting a balloon catheter into the brain parenchyma, which was inflated and deflated to simulate intracranial hypertension and its surgical correction. The experiment included 3 groups of animals (A, B, and C) with different balloon inflation volumes. In group B, balloons were inflated 2 times to simulate reexpansion. A 20 mL/kg bolus of 3% saline solution was infused using a pump 90 minutes after the start of balloon inflation, and the effects of intracranial pressure were evaluated 60 minutes after infusion.

Results: No increases outside of the normal range were observed in mean serum sodium concentrations (p=0.09). In addition, we identified no differences within each group in serum sodium levels measured during hypertonic saline infusion (p=0.21). No significant reductions in intracranial pressure were observed in any of the 3 groups.

Conclusions: Bolus infusion of 3% hypertonic saline solution with the aid of a pump does not significantly reduce intracranial pressure in an animal model of intracranial hypertension.

MeSH Keywords: Intracranial Hypertension • Intracranial Pressure Saline Solution, Hypertonic

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Background

Elevated and refractory intracranial pressure (ICP) resulting from acute hemorrhagic brain injury leads to tissue changes, cerebral ischemia, hernias, and damage to vital brain structures. The use of osmotically active substances is a fundamental component of neurocritical care protocols and is recommended by current guidelines for the treatment of intracranial hypertension [1–4]. Mannitol and hypertonic saline solutions (HSS) are most commonly used and have gained wide acceptance, despite the lack of high-quality clinical studies demonstrating their effectiveness [5,6]. In the absence of definitive evidence of an optimal treatment, there is significant variation in both the choices and usage of such agents [7]. Methods of HSS administration vary considerably, including bolus infusion of a 2% or 3% solution and continuous or bolus infusion of 5%, 7.5%, or 23.4% solutions [8–11]. Results of a recent meta-analysis have suggested that HSS (3%) may be more effective than mannitol for controlling sharp increases in ICP [12]; however, no previous studies have evaluated its long-term capacity to control ICP. In our experience, continuous infusion of 3% HSS is effective in reducing ICP during the treatment of intracranial hypertension. Several possible mechanisms may account for the reduction of intracranial hypertension by treatment with HSS [13–15]. Accordingly, this study analyzed the effects of 3% saline solution infusion 1 hour after simulation of ICP elevation in an animal model of intracranial hypertension.

Material and Methods

Animals

Twenty-nine hybrid pigs of the Landrace, Duroc, and Pietrain breeds (approximately 20 kg each) were used in this study, under general anesthesia, duly assisted with ventilation and hemodynamic monitoring. Of these, 1 animal was excluded because of anemia, with a hemoglobin level of 6.7 (only animals with hemoglobin levels greater than 9.0 were used), and 1 animal was excluded because of hyponatremia, which may influence ICP and therefore compromise our results. The study procedures were approved by the Animal Research Ethics Committee (number 0520/09) and by the Department of Neurology (Faculty of Medicine) at the University of São Paulo. All experiments were carried out according to the ethical principles for the use of laboratory animals adopted by this institution. We attest that the animals were not subjected to conditions of suffering or pain in any step of the experiment.

### Animal preparation, anesthesia, and monitoring

The pigs were subjected to 12 h of fasting with free access to water until 1 h before the experiment. Prior to anesthesia

induction, ketamine (5 mg/kg; Ketamin-S; Cristália®, Itapira, Brazil) and midazolam (0.25 mg/kg; Dormire; Cristália®) were administered intramuscularly. After 15 min, the marginal ear vein was catheterized with a 20- or 22-gauge Insyte vascular catheter (BD, Franklin Lakes, New Jersey, USA). After venous access was established, anesthesia was induced intravenously (i.v.) using propofol (5 mg/kg; Provive 1%; Claris, Ahmedabad, India). Anesthesia was maintained with propofol (3 mg/kg/h), and analgesia was maintained with fentanyl (Fentanest; Cristália) at a starting dose of 5 µg/kg, followed by continuous i.v. infusion at 0.4 µg/kg/min. Neuromuscular blockade was achieved by administration of pancuronium (Pancuron; Cristália) at a starting dose of 0.1 mg/kg i.v., followed by continuous i.v. infusion at 0.02 mg/kg/h. Animals also received an initial i.v. infusion of saline solution (20 mL/kg, 0.9% NaCl) to compensate for volume loss due to fasting, and received supportive fluid therapy with 0.9% NaCl at a rate of 5 mL/kg/h throughout the procedure.

After endotracheal intubation with a Portex 6.0 mm tube (Smiths Medical, Rockland, Massachusetts, USA), the animals received volume-cycled controlled mechanical ventilation (Dixtal 5010 ventilator; Dixtal Biomédica, São Paulo, Brazil) with a tidal volume of 10 mL/kg, fraction of inspired oxygen of 0.50, and positive end-expiratory pressure of 5 cm H_2O. Ventilation parameters were adjusted to maintain the partial pressure of CO_2 between 35 and 45 mm Hg, the partial pressure of O_2 between 100 and 150 mm Hg, and the pH between 7.35 and 7.45. In order to monitor and maintain sufficient ventilation, both the final pressure of expired CO_2 and peripheral hemoglobin saturation were continuously measured using pulse oximetry. The right femoral artery was catheterized to monitor the mean invasive blood pressure. Arterial blood gas analysis was performed using 0.3 mL samples collected at the beginning of the procedure in order to establish ventilation parameters and after the interventions described below. Hemodynamic data were collected using a multi-parameter monitor (Monitor Portal DX 2020; Dixtal).

Experimental procedure

An intracerebral expansive process was simulated in the right hemisphere. A frontotemporal incision was performed, and bone trepanning was performed on the right hemisphere 1 cm lateral to the sagittal suture and 1 cm anterior to the coronal suture. A NEUROVENT-P intraparenchymal catheter with a multisensor that analyzes ICP and brain temperature (Raumedic, Helmbrechts, Germany) was inserted into the white matter of the right frontal lobe at a depth of approximately 10 mm. Right posterior temporal trepanning and insertion of a NEURODUR-P ICP epidural monitoring catheter (Raumedic®) was also performed. Bone trepanning 1 cm lateral to the sagittal suture and 1 cm posterior to the coronal suture (3 mm in diameter) allowed the insertion of an 8 French pediatric urethral catheter at a 20° lateral inclination and a depth of 2 cm, targeting
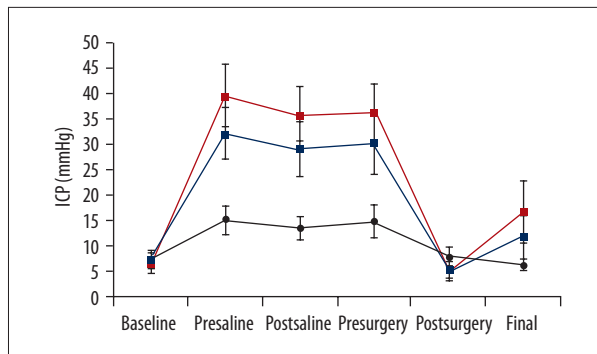
Figure 1. Intracranial pressure in the three experimental groups. The "pre" measurements were performed immediately before each intervention. The "post" measurements were performed 1 hour after each intervention. A significant ICP control was identified only with the deflation of the balloon ("surgery") in the three groups. Black line indicates group A (4 mL); blue line indicates group B (4 mL +3 mL); red line indicates group C (7 mL).

Figure 2. Distribution of average values of intracranial pressure in each group as measured by the ICP parenchymal monitoring in mm Hg during evaluation of the delayed effect of hypertonic saline at 3% one hour after infusion.

the right frontal subcortical white matter. Balloon inflation was performed over a 15 min period using an infusion pump (B Braun Medical, Woburn, Massachusetts, USA). This fluid system was tested prior to insertion. A hypertonic solution of 3% NaCl (5.3 mL/kg) was infused 30 min after the start of the final balloon inflation. The effects on ICP control was measured 60 minutes after saline solution infusion
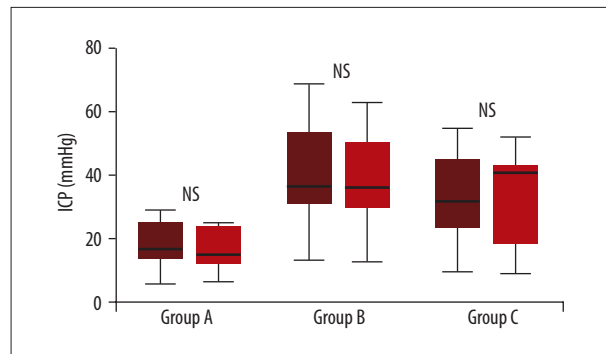
The 27 animals included in the study were divided into 3 groups (n=9 per group). In group A, the balloons were inflated to 4 mL in order to simulate mild to moderate hypertension. In group B, the balloons were initially inflated to 4 mL and were inflated by an additional 3 mL after 1 h, simulating expansion. In group C, an intracranial hematoma model with balloon with a volume of 7 mL was performed. The animals were sacrificed at the end of the experiment by means of an intravenous dose of propofol (20 mg/kg) and fentanyl (10 mg/kg), followed by 40 mL of 19.1% potassium chloride solution. After the experiment, the animals were placed in vivarium plastic bags with labels clearly identifying their origin and content and the researcher in charge. They were then transported for incineration.

Sample size

We used a convenience sample; and as this study was exploratory (there's no study, as far as we know, that used this model to evaluate the use of hypertonic solutions), we defined a total of 30 pigs as being sufficient for a first analysis.

Statistical section

Continuous variables were reported as means and standard deviations. To evaluate the ICP following the interventions

(balloon inflation and hypertonic saline infusion) we used a paired student's t test or Wilcoxon rank-sum test according to normality of the data with significance at p=0.05.

Results

Twenty-seven animals were included in the study (14 female and 13 male), with 9 in each experimental group. The mean weight of the animals was 19.74±1.12 kg, with no differences between groups. All animals included in the study completed the experiments.

ICP measurements in each group confirmed the effectiveness of the intracranial hypertension model. In group A, balloon inflation to a volume of 4 mL using an infusion pump generated a moderate increase in ICP. We also observed an increase in ICP in group B, which represented an early reexpansion model of intracranial hematoma. In group C, there was a marked increase in ICP that remained higher when compared to the other two groups. In the evaluation of increased ICP, it was confirmed that the model was suitable to generate an increase in ICP and that the increases in the mean ICP between three groups were statistically significant (p<0.001) (Figure 1).

We observed no increases in the mean serum sodium concentration beyond the normal range (p=0.09). In addition, no differences were identified in the serum sodium level measured during HSS infusion within each group (p=0.21). There was no effect of significant pressure reduction in any of the 3 groups (Figure 2). Group C showed an increase in ICP with saline infusion; however, this increase was immediate but not statistically significant and therefore did not represent a rebound effect.

Discussion

The saline solution used in our experiment was a 3% NaCl solution, and the calculation for infusion was 5.3 mL/kg. In the present study, we did not observe reductions in intracranial pressure following HSS infusion in any of the experimental groups. Animals in group C, in which extreme hypertension was simulated, showed an increase in ICP following HSS treatment, and the animals remained stable during this period. Cerebral perfusion pressure also did not change significantly with the administration of saline solution in any of the groups. Zornow described the effects of 3.2% HSS infusion in a rabbit model of cryogenic brain injury, which included acute effects of pressure reduction with a continuous late increase in ICP [16]. By contrast, Qureshi et al. reported no beneficial effects of 3% HSS on regional cerebral blood flow or cerebral metabolism rates in a canine model of intracranial hypertension [17].

Although HSS is widely administered, there is no definitive protocol for its use. It has been suggested as a treatment option by different studies and guidelines, but there is no clear consensus regarding its specific uses [18–21]. We did not find that a bolus HSS infusion was effective for controlling ICP. There are indications that the use of HSS at higher concentrations (for instance, 23.4% NaCl at a dosage of 0.7 mL/kg) may be a more appropriate strategy.

The present study analyzed only the acute effects of HSS infusion, and no immediate complications were identified. There are numerous theoretical adverse effects associated with the use of HSS, although these are likely not of great clinical relevance. Electrolyte disturbances are among the most commonly observed findings, specifically hypernatremia and an associated hyperosmolar state. The significance of these findings has yet to be clearly defined, as HSS exerts its effects on ICP reduction in hypernatremic patients suffering from hyperosmolar conditions. Potential complications associated with hypernatremia include central pontine myelinolysis and acute renal failure. Acute renal failure is a known adverse effect of mannitol therapy; however, with the exception of a few case reports, its importance for HSS treatment is not well elucidated. It was also demonstrated that HSS might be effective when used in patients with renal failure.

Other potential adverse effects include rebound increases in ICP. However, in our patients we did not observe this rebound increase. We observed an increase in ICP after 1 hour of HSS infusion in group C, which modeled more severe hypertension; however, this increase was not statistically significant. Nau suggests that the risk of developing rebound ICP increases with repeated administration of HSS, the degree of damage to the blood-brain barrier, and the position of the patient on the ICP-volume curve [22]. However, the existence of this phenomenon remains a matter of debate. The animals used in this study received a single dose of HSS; therefore, the effects of repeated HSS infusions were not tested.

Limitations of the study

This study has some limitations. First of all, the concentration and the type of infusion vary among studies. Also, the use of 3% hypertonic saline as a continuous infusion may not be the ideal dose to cause a decrease of ICP in our model. Moreover, we did not check serum osmolarity after HSS infusion. Additionally, the mechanism of action of hypertonic saline has been classically attributed to reduction of the water content of the interstitial space in a broken blood-brain barrier, a fact that could partially justify our results. However, we believe that the area surrounding the balloon would cause rupture of axons and the blood-brain barrier, causing immediate inflammatory changes that contribute to ICP increase and, consequently, are amenable to be treated with hypertonic saline. Considering all these points together, the present results should be analyzed with caution. However, this experimental study was done in a controlled environment where was possible to identify a consistent increase of ICP over the different groups, showing, at least, that this model could be used to evaluate the different types of clinical and surgical interventions to reduce ICP.

Conclusions

This study identified a consistent increase of ICP according to the different volumes of balloon inflation, showing that this model may be used to evaluate clinical and surgical treatments to decrease ICP. However, we did not see any effect of HSS following balloon inflation in any of the three groups.

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