Intravenous fluid tonicity: effect on intracranial pressure, cerebral blood flow, and cerebral oxygen delivery in focal brain injury

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An investigation into the role of intravenous fluid tonicity in determining intracranial pressure (ICP) after brain injury is described. The authors compare the results of infusion of a hypotonic fluid (Ringer's lactate, 270 mOsm/liter) to those of a hypertonic fluid (hypertonic sodium lactate, 500 mOsm/liter) in a porcine model of focal cryogenic brain injury. Hemodynamic parameters (ICP, regional cerebral blood flow (CBF), and oxygen delivery) and serum osmolarity were measured every 3 hours for 24 hours after injury. At sacrifice, the water content of the lesioned and nonlesioned cortex was determined by specific gravity. The cryogenic injury produced a significant increase in ICP and a significant decrease in CBF in all experimental groups. Maintenance infusion of hypertonic sodium lactate for 24 hours resulted in significantly lower ICP, higher CBF and oxygen delivery, and higher serum osmolarity than Ringer's lactate infusion. Cortical water content in the area of the lesion was similar in both groups, but in the uninjured hemisphere it was significantly lower in the hypertonic group. These data suggest that hypertonic maintenance fluid improves intracranial compliance by dehydrating uninjured cortex. Improved CBF in the hypertonic group may be due to dehydration of cerebrovascular endothelium and erythrocytes. By reducing ICP and improving CBF, hypertonic fluid administration may thus reduce secondary brain injury after head trauma.

KEY WORDS • brain injury • edema • fluid maintenance • osmolarity • hypertonic saline • pig

INJURY to the brain is often accompanied by cerebral edema and swelling that can lead to increased intracranial pressure (ICP), reduced cerebral blood flow (CBF), and a secondary ischemic injury.1,6,21,29 To lessen edema formation, fluid and salt restriction has been advocated,2,14 but there appears to be little support for this concept in the recent literature, which has shown no relationship between fluid balance and ICP or cerebral water content.18,30,31,33,34 Most experimental studies examining fluid therapy and head injury, however, have been of relatively short duration (<6 hours) and none has studied the effects of fluid tonicity on CBF or cerebral oxygen delivery.

We hypothesized that the administration of a hypotonic solution after brain injury would reduce cerebral compliance by increasing the water content of uninjured brain tissue, and that the administration of a hypertonic salt solution would have the opposite effect. Thus, hypotonic fluid administration would result in a greater increase in ICP than administration of a hypertonic fluid. We further postulated that a hypertonic solution would result in a greater CBF since this has been shown to improve capillary flow by reducing endothelial cell volume.9,10 To verify these hypotheses, we compared the results of hypotonic to those of hypertonic fluid infusion in a porcine model of focal brain injury over a period of 24 hours.

Materials and Methods

Animal Preparation

The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Vermont College of Medicine using guidelines for the humane care of animals developed by the National Institutes of Health. Mature swine (weight 35 to 50 kg) were fasted overnight but allowed free access to water. On the morning of the experiment, they were premedicated with an intramuscular injection of ketamine (20 mg/kg) and atropine (0.5 mg). Anesthesia was induced with 2% halothane and oxygen administered by mask; the animals were then endotracheally intubated.
and mechanically ventilated. Anesthesia was maintained with 1.0% halothane and a 0.2% succinylcholine drip at 1.5 to 2.0 mg/kg/hr for the duration of the experiment. A heating/cooling blanket was used to maintain body temperature between 37° and 38°C. The femoral artery and vein were cannulated bilaterally under sterile conditions for blood sampling, pressure monitoring, and fluid administration. A quadruple-lumen pulmonary artery catheter was inserted through the femoral vein for determination of body temperature, cardiac output (CO), and central venous pressure (CVP). Through a small lower-midline abdominal incision, the ureters were isolated and cannulated with intravenous tubing for recording hourly urine output.

After closure of the laparotomy incision, the animal was turned to the "sphinx" position with the head supported on a padded frame. A midline scalp incision was made to expose the coronal and sagittal sutures. An area on the left side adjacent to the confluence of the suture was prepared for a focal cryogenic injury by removing the outer table of a small area of the skull, 3 cm in diameter. Fiberoptic intracranial transducers were inserted into the subdural space through 2-mm twist-drill holes. Platinum electrodes for the measurement of regional CBF by the hydrogen clearance technique were inserted into the cortex of each hemisphere via 2-mm twist-drill holes. On the left side, the electrode was 10 mm away from the area prepared for the lesion. The right electrode was in a stereotactically similar position (Fig. 1).

Physiological Measurement

Following surgery, the animals were left undisturbed for 60 minutes. Arterial pCO₂ was maintained between 35 and 45 mm Hg by adjusting the ventilation rate and tidal volume based on end-tidal pCO₂ measurements and arterial blood gas analysis. Arterial pO₂ was maintained at a level greater than 70 mm Hg. After the animal was stabilized, the following baseline measurements were performed: mean arterial blood pressure (MABP), CVP, CO by thermodilution, ICP, CBF, arterial oxygen content by hemoximetry, serum osmolality, and serum sodium content. The amount of sodium infused was calculated by multiplying the volume administered by the concentration of sodium in the fluid. The cerebral perfusion pressure (CPP) was calculated as the difference between MABP and ICP. The cerebral oxygen delivery was calculated as the product of CBF and the arterial oxygen content.

After the baseline measurements were completed, the animals received an injection of 2.0% Evans blue solution (0.25 ml/kg) to stain the areas where the blood-brain barrier was disrupted.

Study Groups

The animals were then separated randomly into three groups of six animals. Control animals were instrumented and studied under anesthesia for 24 hours to determine the effects of anesthesia on the study variables and to determine the maintenance fluid requirement. Experimental animals had placement of a focal cryogenic lesion created by applying liquid nitrogen to the previously exposed inner table of the skull for 2 minutes (see lesion area, Fig. 1). Study variables were measured 5 minutes after induction of the brain lesion.

One group of experimental animals received Ringer's lactate infusion (sodium content 130 mEq/liter, osmolarity 274 mOsm/liter) and the other group was infused with hypertonic sodium lactate (sodium content 250 mEq/liter, osmolarity 500 mOsm/liter). Fluid was administered to keep the CVP within ± 3 torr of baseline value and urine output at 0.5 to 1.0 ml/kg/hr. All measurements were repeated at 1, 3, 6, 12, and 24 hours after the brain lesion.

Postmortem Examination

At the end of the experiment, each animal was sacrificed using sodium pentobarbital. The calvaria was opened rapidly and the brain carefully removed. The surface area of the lesion was measured and the area of injury was cut transversely and longitudinally to measure its length and depth. Since our previous work had determined that the focal injury produced in this model was roughly conical, lesion volume was calculated using the formula for the volume of a cone, substituting lesion width for diameter and lesion depth for height (volume = \( \frac{1}{3} \pi \times (\text{width}^2) \times \text{depth} \)). Small tissue samples (1 cu mm) were taken from the cortex of both
Intravenous fluid tonicity in focal brain injury

FIG. 2. Graph showing intracranial pressure (ICP) changes during the 24-hour study period. The ICP increased significantly in the experimental animals after injury and continued to increase in the group receiving Ringer's lactate (RL) during the remainder of the experiment; however, ICP decreased in the group receiving hypertonic sodium lactate (HSL), resulting in a significant difference between the experimental groups at 6, 12, and 24 hours postinjury. In the RL group, ICP was significantly greater than its control group (C) for all measurements after 5 minutes postinjury. In the HSL group, ICP was significantly greater than control at 5 minutes (TS) and at 1 and 3 hours, but was not significantly different at 6, 12, and 24 hours. Abbreviations: BL = baseline; H = hours after lesion.

FIG. 3. Graph showing cerebral perfusion pressure (CPP) during the 24-hour study period. The CPP remained stable throughout the experiment and showed no significant difference either between or within groups at any time. Abbreviations: BL = baseline; T5 = 5 minutes after lesion; H = hours after lesion; RL = Ringer's lactate group; HSL = hypertonic sodium lactate group; C = control group.

animals, and there were no significant differences in these parameters either within or between groups during the study (data not shown).

Intracranial and Cerebral Perfusion Pressure

There was no significant difference between the groups in ICP at baseline. The cryogenic brain lesion rapidly increased the ICP in the experimental groups (p < 0.001 vs. control group, Fig. 2). The ICP in the group receiving Ringer's lactate continued to increase with maintenance fluid infusion such that it was significantly greater at 6 hours after injury than in either the control or the hypertonic fluid animals (p < 0.05). Conversely, the ICP in the hypertonic fluid group decreased with maintenance fluid infusion such that this group showed no significant difference in this regard from the control group at 24 hours.

The CPP was lowest at 24 hours in the group receiving Ringer's lactate (Fig. 3), but was not significantly different from the CPP in the other groups and was well above the ischemic threshold.

Cerebral Blood Flow

The mean CBF (averaged raw values of all 18 animals) was 42 ± 2 ml/100 gm/min at baseline. A transient initial increase in CBF was observed in control animals, which was attributed to the vasodilatory effects of halothane anesthesia (Table 1). The animals with lesions exhibited significantly decreased regional CBF in both hemispheres compared to baseline and to the control group; this decrease was most pronounced in the area adjacent to the lesion. The CBF to the area adjacent to the injury remained significantly lower in the group with Ringer's lactate compared to both the control and the hypertonic fluid groups (p < 0.05); at 24 hours after injury it was lowest in the Ringer's lactate group. The CBF in both hemispheres at 24 hours in the

Data Analysis

Data were recorded on prepared forms at the time of the experiment and were entered later into a commercially available data base using a personal computer. Statistical analysis was performed using a commercially available software program. Differences within groups were evaluated using Student's t-test and differences between groups were evaluated by means of analysis of variance with correction for multiple comparisons. Significance was attributed to p < 0.05. Data are expressed as means ± standard error of the means.

Cerebral blood flow measurements demonstrated variability in all groups due to the slightly differing positions and depths of the electrodes. Therefore, raw CBF data were converted to a percentage of baseline values before statistical analysis was performed. Similarly, raw cerebral oxygen delivery data were converted to a percentage of baseline.

Results

Hemodynamics

All animals remained hemodynamically stable throughout the 24-hour study period. The MABP, CO, and CVP were maintained with fluid infusion in all

the lesioned area and the injured hemisphere for determination of water content by the specific gravity technique.

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§ MRTOD developed by Retriever Data Systems, Seattle, Washington.
hypertonic fluid group was not significantly different from that in the control group.

**Oxygen Delivery**

Changes in oxygen delivery to the area near the lesion were similar to changes in the CBF (Fig. 4). This would be expected since there was no significant difference in arterial oxygen content between the groups (data not shown). The oxygen delivery decreased after injury in the group with Ringer's lactate and continued to decrease for the duration of the study. Oxygen delivery in the hypertonic fluid group was maintained at baseline levels and was not significantly different from that in the control group at any time during the study. Beginning at 3 hours after injury, oxygen delivery in the Ringer's lactate group was significantly lower than in the hypertonic group (p < 0.05) and remained so for the balance of the study.

**Fluid Data**

Fluid data were collected during the entire experiment and included not only the 24-hour period of study, but also the 4 to 6 hours of preparation (anesthesia induction, laparotomy, skull preparation, and instrumentation), observation, and stabilization. The fluid required to maintain the CVP within ±3 torr of baseline and the urine output at 0.5 ml/kg/hr or above, as well as to administer succinylcholine and measure CO, was significantly less in the group with hypertonic fluid than in either the control or the Ringer's lactate group (p < 0.05, Fig. 5). Similarly, net fluid balance was significantly lower in the hypertonic fluid group (p > 0.05). The amount of sodium administered, however, was significantly greater in the animals infused with hypertonic fluid (hypertonic fluid group 703 ± 46 mEq; Ringer's lactate group 574 ± 34 mEq; p < 0.05).

There was no difference between the groups in serum osmolarity or sodium content at baseline (Table 2). At 24 hours, both levels in the hypertonic fluid group were significantly greater than in the other groups and significantly greater than baseline (p < 0.05).

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**TABLE 1**

| Cerebral blood flow in head-injured pigs receiving hypo- and hypertonic fluid replacement therapy* |
|---------------------------------|---------|---------|---------|---------|---------|
| Group & Side                    | Time After Lesion |
|------|---------|---------|---------|---------|---------|
|      | 5 Min   | 1 Hr    | 6 Hrs   | 12 Hrs  | 24 Hrs  |
| control rt | 113 ± 15† | 100 ± 10 | 85 ± 7  | 83 ± 9  | 95 ± 11 |
| Ringer's lactate rt | 108 ± 11† | 91 ± 5   | 81 ± 4  | 76 ± 9  | 89 ± 10 |
| Ringer's lactate lt | 68 ± 6   | 71 ± 7†  | 55 ± 4† | 51 ± 5† | 43 ± 6† |
| Ringer's lactate rt | 84 ± 4   | 78 ± 6   | 70 ± 4  | 73 ± 3  | 69 ± 4  |
| hypertonic saline lt | 66 ± 4   | 89 ± 5‡  | 84 ± 8‡ | 91 ± 9‡ | 82 ± 9‡ |
| hypertonic saline rt | 80 ± 2   | 95 ± 7   | 95 ± 15 | 90 ± 10 | 91 ± 9‡ |

* All measurements are expressed as percentage of baseline values.
† Significance of difference: p < 0.05 as calculated by analysis of variance.
‡ Significance of difference: p < 0.05, Ringer's lactate vs. hypertonic saline group, as calculated by Student's t-test.

**TABLE 2**

<table>
<thead>
<tr>
<th>Serum osmolarity (mOsm/liter) and serum sodium (mEq/liter)*</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td></td>
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<tr>
<td>control</td>
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<tr>
<td>Ringer's lactate</td>
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<td>Hypertonic fluid</td>
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*Abbreviations: So = serum osmolarity; SNa = serum sodium.
† Significance of difference: p < 0.05 as calculated by analysis of variance.
Intravenous fluid tonicity in focal brain injury

FIG. 6. Postmortem photograph of porcine brain in situ after the focal cryogenic injury and 24 hours of intravenous fluid therapy. Note the area of the injury stained with Evans blue dye, as well as the swollen convolutions in both the injured and noninjured hemispheres and the dilated pial vessels in the area of the lesion.

The lesion produced in the experimental animals was uniform (Fig. 6). The volume of Evans blue staining was greater in the hypertonic fluid group (4168 ± 723 cu mm) than in the group receiving Ringer's lactate (3397 ± 284 cu mm), but this difference was not significant.

Cortical biopsy samples taken from the area of injury (left hemisphere of the experimental animals) contained significantly greater water (significantly lower specific gravity) than did those taken from the uninjured left hemisphere of the control animals (p < 0.05, Fig. 7). The uninjured cortex (right hemisphere) of the Ringer's lactate-infused animals had significantly more water than did the uninjured cortex in the hypertonic fluid group (p < 0.05).

Discussion

Conventional Fluid Therapy

Vasogenic and cytotoxic edema contribute to the raised ICP associated with most forms of head injury, especially those in which there is a focal contusion or disruption of the blood-brain barrier. Conventional management of such patients has been directed at controlling or decreasing the ICP and attempting to reduce edema formation.

It has become increasingly apparent that vasogenic edema formation is driven by the capillary hydrostatic pressure acting at the site of the disrupted blood-brain barrier. Intravenous fluid restriction has been advocated as a means of controlling edema formation by maintaining or reducing the capillary hydrostatic pressure. In fact, some authors have advocated actively dehydrating the patient as a means of achieving this. Fluid restriction, while of theoretical benefit, has not been shown to be effective in reducing either ICP or edema formation in the laboratory and there are no controlled clinical trials demonstrating its efficacy in reducing cerebral edema or ICP. Furthermore, fluid restriction is often not possible in patients with multiple injuries who require large volumes of asanguinous fluid and blood to treat intravascular fluid volume deficits.

Salt restriction has also been advocated in head-injured patients since retention of sodium might lead to promotion of edema formation; however, no studies have documented that salt restriction either decreases edema formation or reduces ICP. On the contrary, Bakay and coworkers showed that administration of an isotonic salt solution (0.9%) lowered the cerebrospinal fluid pressure by 30% to 50% in patients in chronic coma, while a hypotonic salt solution (0.45%) caused no change. The administration of fluid without ionizing solute (dextrose in water) resulted in a 14% to 100% increase in the cerebrospinal fluid pressure.

Hypertonic Fluid Therapy

Recent laboratory studies using various head-injury models, with and without associated hemorrhagic shock, have failed to show a relationship between the amount of sodium or fluid administered and either the cerebral water content or the ICP. In fact, the use of hypertonic fluids (1.8% to 3%) to treat laboratory models of head injury has been associated with a significantly lower ICP and a significantly lower cerebral water content than treatment with either hypotonic or isotonic fluids. These studies, however, have been of short duration and have not examined the effects of fluid administration on CBF and cerebral oxygen delivery. These two parameters are...
particularly important when determining the efficacy of fluid therapy in head injury since ischemia plays such a major role in secondary brain injury.11

Comparison of Hypertonic Saline to Ringer’s Lactate

In this study, fluid was administered to maintain MABP, CVP, and urine output, parameters that are used clinically in the fluid management of trauma patients.19 There were no differences in MABP, CVP, and CO between the groups during the study. To maintain these parameters at appropriate levels required significantly more fluid in the Ringer’s lactate group, but significantly more sodium in the hypertonic fluid group. This is similar to the findings in our previous studies using hypertonic fluid in the resuscitation of patients undergoing major aortic reconstruction.20,21

Less fluid is required to maintain hemodynamic stability with hypertonic solutions because water is extracted from cells down an osmolar gradient to replenish the intravascular space.9,23 The primary sources of this water appear to be the erythrocytes and the muscle cells, with the result that the extraction of water reduces erythrocyte size and decreases pressure in the intramuscular compartment.24

The animals receiving Ringer’s lactate had a significantly greater ICP and a significantly lower CBF and oxygen delivery than animals receiving hypertonic saline. These changes could not have been due to greater vasogenic edema formation or to the greater volume of fluid administered in the group with Ringer’s lactate infusion since there were no significant differences between the groups in vascular hydrostatic pressures (CVP and MABP). Furthermore, the groups did not differ significantly in the water content of cortical biopsy samples taken near the area of injury. Rather, we attribute the differences in ICP, CBF, and oxygen delivery to the difference in toxicity of the two solutions and its effect on intracellular volume. Ringer’s lactate is slightly hypotonic and contains approximately 100 ml/liter of “free” (solute-free) water. The administration of this free water will reduce serum osmolarity and result in movement of water into cells during the process of osmolar equilibration. This will lead to swelling of endothelial and parenchymal cells and to an increase in tissue pressure, especially in those tissues that are compartmentalized, such as muscle and brain. Swelling of endothelial cells can reduce the capillary lumen and decrease blood flow.16 An increase in tissue pressure can also compress tissue capillaries, further reducing blood flow. Hypertonic sodium lactate, on the other hand, moves water out of cells, reducing tissue pressure and cell size, and resulting in a decrease in intracompartmental pressure (that is, in ICP) and a reduction in cerebral water content in the uninjured hemisphere. Hypertonicity should also improve blood flow, not only by decreasing endothelial cell volume and increasing the diameter of the capillary lumen, but also by decreasing erythrocyte size.

Hypertonicity and Edema Formation

Concerns about potential increases in edema formation due to hypertonic fluid resuscitation have been raised by Gunnar and coworkers;7 they noted more intense staining of Evans blue dye on the side of epidural balloon inflation in animals resuscitated from hemorrhagic shock with a 3% sodium chloride solution. Similar concerns were raised by Waters, et al.,32 who studied the effects of parenteral nutrition in a cryogenic model of brain injury. They also found a greater volume of Evans blue staining in animals receiving hyperosmolar solutions, leading them to suggest that edema formation is enhanced by increases in serum osmolarity which accelerate the bulk flow of edema through white matter. It is interesting to note in their work, however, that the cerebral water content was less in the animals receiving hyperosmolar solutions. They also found that the water content in the uninjured hemisphere decreased in hyperosmolar animals. Unfortunately, Waters and colleagues did not measure ICP or CBF, and the duration of their study was only 6 hours.

We also found an increase in the volume of Evans blue staining in the animals receiving hypertonic saline. Although this difference in volume was not significant when compared to the animals receiving Ringer’s lactate, the depth (one of the parameters used to calculate the volume) of Evans blue staining was consistently greater in the animals with hypertonic fluid infusion (lesion depth averaged 18.3 ± 1.7 mm compared to an average depth of 15.9 ± 0.9 mm in the Ringer’s lactate group). This confirms the observations of Gunnar, et al.,7 and Waters, et al.,32 and supports the concept that hyperosmolar solutions increase the bulk flow of edema through the white matter. This appears logical since the hyperosmolar fluid would decrease the intracellular volume of uninjured cells surrounding the lesion, thereby reducing the resistance to bulk flow. The role of cellular volume in edema spread has been demonstrated by Reulen,16 who induced intracerebral edema with hexachlorophene and found that edema spread was impeded. If cellular swelling impedes edema spread, then cell shrinkage should facilitate it. We suggest that cerebral dehydration and cell shrinking decrease the resistance to bulk flow and that this facilitates edema resolution rather than edema formation. Hypotonic fluids would have the opposite effect by increasing cellular volume. We therefore attribute the observed increase in Evans blue staining in the hypertonic animals in our study to the more expeditious movement of edema through the white matter toward the ventricle. Rapid edema resolution may represent another mechanism by which ICP is controlled by the administration of hypertonic or hyperosmolar fluids.

Conclusions

Intravenous fluid therapy for a focal brain injury with a slightly hypertonic solution (1.8% saline) resulted in a significantly lower ICP and a significantly greater
Intravenous fluid tonicity in focal brain injury

CBF and cerebral oxygen delivery than did similar treatment with a slightly hypotonic solution. We attribute the beneficial effects of hypertonic fluid to a reduction in the cellular volume of uninjured brain parenchyma, endothelial cells, and erythrocytes mediated by extraction of water from these cells down an osmolar gradient. The reduction in the cellular volume of uninjured brain tissue surrounding the lesion may also hasten edema resolution. The adverse effects of increased ICP and decreased CBF and cerebral oxygen delivery observed in the animals receiving the hypertonic fluid suggest to us that administration of hypertonic solutions to head-injured patients may contribute to secondary brain injury. Hypertonic fluids, on the other hand, may limit or abrogate secondary injury and may be the intravenous fluid of choice for maintenance therapy after head injury.

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