A Comparison of Hypertonic to Isotonic Fluid in the Resuscitation of Brain Injury and Hemorrhagic Shock

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Submitted for publication April 12, 1990

We studied the early and late effects of hypertonic resuscitation (HR) on the injured brain using a porcine model of hemorrhagic shock and focal cryogenic brain injury. After shock, swine were randomly assigned to receive a bolus (4 cc/kg) of either Ringer's lactate (RL) or 7.5% hypertonic saline in 6% Dextran 70, followed by either RL or hypertonic sodium lactate to restore mean arterial pressure to baseline. All animals were studied for 24 hr after the start of resuscitation. Bolus HR improved cerebral blood flow (CBF) with a lower intracranial pressure (ICP) than RL. Continued hypertonic resuscitation prolonged the period of improved CBF and low ICP. At 24 hr CBF had deteriorated in the region of injury in all study groups and in the uninjured hemisphere in swine receiving RL. These data suggest that rapid resuscitation without increasing ICP for up to 6 hr as seen with hypertonic fluid could conceivably allow adequate time for surgical evacuation of mass lesions and effectively prevent secondary brain injury. This work underscores the importance of prolonged periods of study when evaluating brain resuscitation from traumatic shock.

INTRODUCTION

Resuscitation of the head-injured patient in shock is often complicated by the need to treat hypotension due to hemorrhage without exacerbating brain swelling. Ideally, one would prefer to administer a fluid that would rapidly restore perfusion and improve cerebral blood flow without increasing the intracranial pressure. Hypertonic fluids are capable of rapid volume expansion and improved perfusion following resuscitation from hemorrhagic shock in a variety of animal models [1–4] and in initial clinical trials [5]. In various types of head injury models, hypertonic resuscitation resulted in a lower intracranial pressure (ICP) and a lower cerebral water content compared to Ringer's lactate [6–9]. These studies were of short duration (<6 hr), however, and the early benefit of reduced ICP and water content may not persist since maximal brain swelling does not often occur until 12–18 hr after injury [10].

Since there have been no previous studies which evaluated the use of hypertonic fluid for prolonged periods after the initial resuscitation, we compared three different fluid regimens in a 24-hr porcine model of hemorrhagic shock and focal brain injury. We postulated that hypertonic fluid would restore systemic and cerebral perfusion more rapidly than isotonic fluids. We further hypothesized that the initial use of hypertonic fluid followed by additional resuscitation with isotonic fluid would eliminate any early benefits seen from the use of hypertonic fluid alone.

METHODS

Animal Preparation

Twenty-three mature swine averaging 40.3 ± 8.6 kg were fasted overnight but allowed free access to water. On the morning of the experiment, they were premedicated with ketamine (20 ml/kg) and atropine (0.5 mg) given intramuscularly along with cephalozin sodium (1 g) and gentamicin (80 mg). Anesthesia was induced with 2% halothane and oxygen by mask. The animals were endotracheally intubated and connected to a Harvard ventilator (Harvard Co., Chicago, IL), delivering a tidal volume of 10–14 ml/kg. Anesthesia was maintained with 0.5–1.0% halothane and a 2% succinylcholine drip at 1.5–2.0 mg/kg/hr for the duration of the experiment. A heating blanket was used to keep the temperature between 37 and 39°C. The femoral artery and vein were cannulated bilaterally under sterile conditions with polyethylene catheters (PE 200) for blood sampling and pressure monitoring. A quadruple lumen pulmonary artery catheter (VIP No. 93 A-831, 7.5 F, American Edwards Labs, Irvine, CA) was inserted through the femoral vein for determination of cardiac filling pressures and cardiac output by thermodilution, using a cardiac...
output computer (American Edwards, Model 9520A). Through a low midline laparotomy, the ureters were exposed and cannulated with silastic catheters which were brought out through a separate low midline stab incision and connected to an ultrasonic urine collection chamber (Vitalmetrics, San Diego, CA). All incisions were closed in layers and the animal was then carefully turned to the prone position. A midline cranial incision was made to expose the coronal and sagittal sutures (Fig. 1). An area on the left side adjacent to the confluence of the sutures was prepared for a focal cryogenic injury by removing the outer table of a small area of bone (3 cm in diameter) with an engraving drill bit. The inner table of bone was left intact. Fiberoptic brain tissue pressure transducers (Camino 420, Camino Labs, San Diego, CA) were inserted into each hemisphere through 2-mm twist drill holes [12]. On the lesioned side (left), the flow probe was inserted approximately 1 cm away from the area prepared for the lesion. The contralateral flow probe was inserted in a stereotactically similar position (Fig. 1). The hydrogen flow probes were connected to an amplifier and, along with the transduced hemodynamic pressures and ICP’s, were recorded on a Gould strip chart recorder (Gould Instruments, Cerritos, CA). Following surgical preparation, the animals were left undisturbed on halothane and succinylcholine for 60–90 min. Arterial PO₂ was maintained at >90 mm Hg and PCO₂ was kept between 35 and 45 mm Hg during all phases of the experiment by ventilator adjustments based on arterial blood gas analysis.

Study Variables

Following stabilization, the following baseline (BL) measurements were performed: mean arterial pressure (MAP), heart rate, cardiac output (CO), central venous pressure (CVP), ICP, and CBF. Serum sodium was measured on a standard serum chemistry analyzer (EASY ST Analyzer, EM Diagnostics, Gibbstown, NJ) and serum osmolarity was determined by vapor pressure changes (Advanced Wide-Range osmometer Model 3W2, Advanced Instruments, Inc., Needham Heights, MA). Fluid intake and urine output were measured and cumulative fluid balance was calculated. The animals were then injected with 0.5 cc/kg of a 2% Evan’s blue solution to stain areas of blood–brain barrier disruption and to allow measurement of lesion size at the time of postmortem examination.

The animals were then randomized to one of four groups. Control animals (Group 1, N = 5) were instrumented and studied under anesthesia for 24 hr to determine the effects of anesthesia on the study variables and to evaluate maintenance fluid requirements. Study animals all had a focal cryogenic brain lesion and a period of hemorrhagic shock prior to resuscitation with a specific fluid regimen. Following the BL measurements, the brain lesion was created by applying liquid nitrogen to the previously exposed inner table of the skull (Fig. 1). The liquid nitrogen was applied for 2 min via a polyethylene funnel with a 3-cm mouth attached by adhesive caulk to the 3-cm exposed area. Residual liquid nitrogen was aspirated at the end of the 2-min period. Study variables were measured 5 min after the completion of the brain lesion (T + 5 study period). The animals were hemorrhaged rapidly to a MAP of 50 mm Hg. The blood was collected in ACPD bags for preparation as packed cells to be returned to the animals later in the protocol. This level of hemorrhage was maintained for 45 min by allowing the animals to bleed by gravity into a collection bag whenever their blood pressure rose above 55 mm Hg.

Following measurement of the study variables (H + 45 study period), the animals were resuscitated with one of three regimens: Group 2 animals (RL/RL, N = 6) received Ringer’s lactate (RL) as an initial bolus (4 ml/kg) followed by constant infusion of RL to return MAP and CVP to BL values. Group 3 animals (HSD/RL, N = 6) received 7.5% hypertonic saline in 6% Dextran 70 as an initial bolus (4 ml/kg) followed by RL to restore MAP and CVP to BL values. Groups 4 animals (HSD/HSL, N = 6) received 7.5% hypertonic saline in 6% Dextran 70 as an initial bolus followed by hypertonic sodium lactate infusion (HSL) to restore MAP and CVP to BL values. The HSL was prepared by adding sodium chloride and sodium lactate to Ringer’s lactate, resulting in a solution of 250 mEq of sodium per liter (calculated osmolarity 500 mOsm/liter). Variables were measured after the initial bolus (RES), then at 30 and 60 min after the initial bolus (R + 30, R + 60, respectively). Shed blood was returned as packed red cells after the R + 60 study period. The animals were then studied 3, 6, 12, 18, and 24 hr after the initial bolus (R + 3H, 6H, 12H, 18H, and
sue by the platinum flow probes. Raw values were, therefore, converted to percentages of BL.

Differences within groups were evaluated using Student's t test with Bonferroni correction. Differences between groups were evaluated using ANOVA with correction for multiple comparisons. Significance was attributed to a P value of <0.05.

RESULTS

Hemodynamic Variables

There was no significant difference between the groups in CVP (data not shown) or in MAP at BL or following the brain lesion in Groups 2, 3, or 4 (Fig. 3). The MAP was significantly lower after hemorrhage in Groups 2, 3, and 4 compared to BL values and compared to the control animals (Group 1). There was no significant difference in the volume of hemorrhage between groups (34.7 ml/kg in Group 2, 37.0 ml/kg in Group 3, and 34.8 ml/kg in Group 4). Following the initial HSD bolus, MAP was significantly increased in Groups 3 and 4 (P < 0.05). The bolus of RL increased the MAP in Group 2, but the increase was not significant. After 30 min of additional fluid infusion the MAP in all the study groups had returned to BL and was not significantly different from that in the control group. The MAP was maintained at or near BL for the following 24 hr and there were no significant differences between groups after the initial resuscitation period (Fig. 3). Changes in CVP (data not shown) paralleled changes in MAP. With hemorrhage, CVP decreased significantly from BL but was restored to BL with resuscitation.
groups and significantly greater than BL ($P < 0.05$). The ICP in Groups 3 and 4 remained significantly lower than that in both control and Group 2 animals during this time. After 60 min of infusion of RL Group 3 animals (HSD/RL) demonstrated a progressive increase in ICP to greater than BL, but the difference was not statistically significant. The ICP in Group 4 (HSD/HSL) also rose but did not exceed BL until 6 hr after resuscitation, and the increase was not significant. By 24 hr postresuscitation, the ICP was higher in Groups 2 and 3 than in Groups 1 and 4, however, this difference did not reach statistical significance ($P = 0.07$). There was moderate variability in the ICP at 24 hr in the groups that received RL (Group 2: $25.8 \pm 8.8$; Group 3: $21.7 \pm 8.2$), but not in the controls (Group 1: $13.2 \pm 2.8$) or in the group receiving HSL (Group 4: $13.7 \pm 1.5$).

CBF in all animals ranged from 25 to 43 ml/100 g/min (average 32.3 ml/100 g/min). Because there was variability between animals due to probe location the values were converted to percentages of baseline for analysis (Table 1). The CBF increased initially in the control animals (Group 1) because of vasodilation associated with halothane [14]. The cryogenic lesion resulted in a reduction in CBF to both the lesioned and the nonlesioned hemispheres in the study animals (Groups 2, 3, and 4). The reduction in CBF was significant on the side of the lesion ($P < 0.05$). The CBF was further reduced by hemorrhage in Groups 2, 3, and 4 to approximately 50% of baseline values (Table 1). Bolus fluid infusion increased CBF in all animals. The CBF, however, remained significantly lower than BL in the RL group after hemorrhage and the bolus injection. Following resuscitation, the CBF in Group 2 rose slightly, but the increase was not significant. After this study period, there was no difference in CBF between the groups for the balance of the study period (Fig. 4).

Cerebral Variables

ICP was elevated slightly following the cryogenic lesion in the three lesioned groups (Groups 2, 3, and 4); however, hemorrhage was begun immediately following the brain lesion so any swelling or edema was accommodated by reductions in cerebral blood volume due to hemorrhage (Fig. 5). The ICP increased in Group 1 during this period as a result of cerebral vasodilatation and an associated increase in cerebral blood volume associated with the use of halothane [14]. As a result, the ICP was significantly higher in the control group immediately after hemorrhage and the bolus injection. Following resuscitation, the RL animals (Group 2) demonstrated a significant increase in ICP such that the ICP in Group 2 was significantly greater than that in any of the other groups prior to hemorrhage (t $P < 0.05$ vs Control, ANOVA). Continued infusion of HSL in Group 4 resulted in a CO which was significantly greater than BL ($tP < 0.05$, t test) and significantly greater than that in the other groups ($tP < 0.05$, ANOVA). (Study periods: BL, baseline; HEM, immediately after hemorrhage; RES, immediately after the 4 ml/kg bolus; R30, 30 min after RES; R3H, R6H, R12H, and R24H, 3, 6, 12, 24 hr after HEM.)

There was no significant difference between the groups in CVP at any time during the study.

Cardiac output was not significantly different between groups prior to hemorrhage (Fig. 4). Groups 2, 3, and 4 demonstrated a significant drop in cardiac output by the end of hemorrhage, falling to approximately 40% of prehemorrhage levels. The 4 ml/kg bolus of HSD increased the CO significantly in Groups 3 and 4, returning it BL within 5 min. The HSD/HSL group (Group 4) had a significantly higher cardiac output than the other groups for the first 60 min of resuscitation ($P < 0.05$). After the 4 ml/kg RL bolus, the CO in Group 2 rose slightly, but the increase was not significant. After this study period, there was no difference in CO between the groups for the balance of the study period (Fig. 4).
Fluid and Electrolyte Data

Serum osmolarity increased in Groups 3 and 4 within 30 min of resuscitation (Table 2). This increase was less pronounced in the Group 3 animals since they had received RL after the bolus injection of HSD. Serum osmolarity was highest in Group 4 animals at this time. Continued resuscitation with HSL in the Group 4 animals resulted in a serum osmolarity which was significantly greater than BL and significantly greater than the other groups at 24 hr (P < 0.05, Table 2). The animals receiving RL for the balance of the resuscitation (Groups 2 and 3) had serum osmolarities which were lower than BL but the decrease was not significant.

Changes in serum sodium paralleled those of serum osmolarity. The peak serum sodium in Group 3 was 153.8 ± 1.6 mEq/liter, occurring immediately after the bolus injection of HSD. The peak serum sodium in Group 4 was 156 ± 3.8 mEq/liter, occurring at 24 hr. At the conclusion of the experiment all animals were hemodynamically stable with urine outputs which exceeded 1 ml/kg/min. The net fluid balance in Group 4 at the end of the study was significantly lower than the net fluid balance in the other experimental groups (P < 0.05, Fig. 6). In addition, the net fluid balance in Group 4 was not significantly different from that in the control group.

### TABLE 1

Cerebral Blood Flow

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>Baseline</th>
<th>End of lesion</th>
<th>End of hemorrhage</th>
<th>Resuscitation</th>
<th>Resus + 30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Control)</td>
<td>Left CBF</td>
<td>100.0</td>
<td>118.2 ± 21.6*</td>
<td>113.9 ± 20.2*</td>
<td>106.7 ± 18.8</td>
<td>98.1 ± 13.8</td>
</tr>
<tr>
<td></td>
<td>Right CBF</td>
<td>100.0</td>
<td>111.4 ± 15.5</td>
<td>107.8 ± 15.4</td>
<td>101.4 ± 12.3</td>
<td>88.7 ± 10.0</td>
</tr>
<tr>
<td>(RL/RL)</td>
<td>Left CBF</td>
<td>100.0</td>
<td>63.2 ± 9.71</td>
<td>57.4 ± 7.11</td>
<td>68.5 ± 8.2†</td>
<td>108.9 ± 13.9</td>
</tr>
<tr>
<td></td>
<td>Right CBF</td>
<td>100.0</td>
<td>87.6 ± 9.8</td>
<td>65.2 ± 10.0†</td>
<td>68.1 ± 10.4†</td>
<td>113.2 ± 22.3</td>
</tr>
<tr>
<td>HSD</td>
<td>Left CBF</td>
<td>100.0</td>
<td>87.6 ± 9.8†</td>
<td>65.2 ± 10.0†</td>
<td>83.7 ± 11.1</td>
<td>90.0 ± 8.7</td>
</tr>
<tr>
<td></td>
<td>Right CBF</td>
<td>100.0</td>
<td>80.9 ± 9.0</td>
<td>50.6 ± 3.3†</td>
<td>96.1 ± 11.3</td>
<td>99.0 ± 12.6</td>
</tr>
<tr>
<td>[HSD, SI]</td>
<td>Left CBF</td>
<td>100.0</td>
<td>61.5 ± 11.3†</td>
<td>51.1 ± 8.4*</td>
<td>126.7 ± 16.7*</td>
<td>128.0 ± 12.9</td>
</tr>
<tr>
<td></td>
<td>Right CBF</td>
<td>100.0</td>
<td>83.2 ± 8.7</td>
<td>61.8 ± 12.5*</td>
<td>136.4 ± 28.8</td>
<td>145.1 ± 25.5</td>
</tr>
</tbody>
</table>

Note. CBF, percentage of baseline, mean ± SE* P < 0.05, ANOVA.
† P < 0.05 vs BL, t test.

(Groups 2). On the other hand, bolus injection of HSD significantly increased the CBF in Groups 3 and 4 (P < 0.05), returning it to near BL values (Table 1). CBF was greatest in Group 4 during this study interval (P < 0.05). Group 2 animals required additional fluid to return CBF to BL. Following an initial period of hyperemia, which occurred in all groups immediately after resuscitation, CBF decreased on the side of the lesion in all groups and was significantly less than BL at 24 hr. This was most pronounced in Group 3. The CBF of the uninjured (right) hemisphere was also significantly reduced from BL at 24 hr in Groups 2 and 3, but not in Group 4 (HSD/HSL).

### TABLE 2

Serum Osmolarity

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>End of hemorrhage</th>
<th>Resus + 30 min</th>
<th>Resus + 24H</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Control)</td>
<td>285.2 ± 2.0</td>
<td>284.2 ± 5.1</td>
<td>283.2 ± 3.4</td>
<td>282.8 ± 3.2</td>
</tr>
<tr>
<td>(RL/RL)</td>
<td>289.7 ± 4.2</td>
<td>293.5 ± 4.0</td>
<td>297.9 ± 10.2</td>
<td>272.0 ± 6.4</td>
</tr>
<tr>
<td>HSD</td>
<td>281.5 ± 2.4</td>
<td>285.8 ± 4.1</td>
<td>301.3 ± 6.0</td>
<td>279.5 ± 6.1</td>
</tr>
<tr>
<td>HSD/HSL</td>
<td>288.0 ± 3.1</td>
<td>281.5 ± 2.4</td>
<td>317.8 ± 24.7</td>
<td>286.7 ± 7.0</td>
</tr>
</tbody>
</table>

Note. Serum osmolarity (mOsm/liter), mean ± SE
* P < 0.05, ANOVA
† P < 0.05 vs RL

Cerebral Water Content

After sacrifice and removal of the calvarium the brain was carefully removed and the area of Evan’s blue staining was measured with calipers on the surface and on coronal and sagittal sections. In all animals the lesion was well circumscribed and easily measured (Fig. 7). The
Cortical cerebral water content (CWC) was significantly higher (lower specific gravity) in the left (lesioned) hemisphere of the study animals (Groups 2, 3, and 4) than in the controls ($P < 0.05$). There was no significant difference in cortical water content in the nonlesioned hemisphere between the groups (Fig. 8). The water content of the unlesioned white matter contained significantly less water than lesioned white matter (data not shown) in Groups 3 and 4 ($P < 0.05$), while in Group 2 (RL) there was no significant difference between the lesioned and unlesioned white matter. The unlesioned white matter in Group 4 animals contained the least water, although this difference was not statistically significant.

**DISCUSSION**

Despite significant improvements in modern trauma care, the combination of a severe head injury with hemorrhagic shock continues to have a high mortality rate [15]. While blood pressure can be restored with intravenous fluid, the effects of rapid fluid infusion on an evolving brain injury are poorly understood. The volume of asanguinous fluid necessary to restore blood pressure...
Hypertonic fluids have been shown to rapidly expand plasma volume and restore both blood pressure and cardiac output [1-5], but little is known about their effects on ICP and CBF. Shackford et al. [5], in a porcine model of hemorrhagic shock without brain injury, found that resuscitation with hypertonic sodium lactate solution was associated with a lower ICP than isotonic resuscitation with Ringer’s lactate. Prough and co-workers [16], using a canine model of hemorrhagic shock, also found a significantly lower ICP in animals resuscitated with hypertonic saline than in animals resuscitated with Ringer’s lactate. Gunar et al. found that 3% hypertonic saline resuscitation of hemorrhagic shock and a simulated head injury was associated with a lower ICP and less brain edema than resuscitation with isotonic fluid or colloid [6, 17]. Cerebral blood flow and brain water content were not measured in these studies. Wisner et al. [7], in an ovine model of traumatic shock and cryogenic brain injury, found no difference in either ICP or cerebral water content between animals resuscitated with colloid and those resuscitated with RL. Zornow and colleagues [8], in a rabbit model of isovolemic hemodilution and cryogenic brain injury without shock, found that the ICP in animals receiving RL was significantly greater than that in those receiving hypertonic sodium lactate. While the cerebral water content in the area of the injury did not differ between the groups, Zornow et al. found that the cerebral water content in the uninjured hemisphere was significantly lower in the group receiving hypertonic sodium lactate, suggesting that dehydration of normal brain might be a possible explanation for the lower ICP in the hypertonic group. Wisner et al. [9], in a rat model of shock and cryogenic brain injury, also noted significantly reduced cerebral water content in the uninjured hemisphere of animals resuscitated with hypertonic saline compared to those resuscitated with RL.

All of the studies examining resuscitation from shock and brain injury have been of relatively short duration (less than 6 hr). Such short study periods focus on the early effects of resuscitation when hemodynamic function is optimized, but do not allow an assessment of cerebral variables when brain swelling and ICP are maximal at 12–18 hr after injury [10]. Our study involved a 24-hr period of study following brain injury and hemorrhagic shock and included the measurement of cerebral blood flow and cerebral water content.

We used a focal cryogenic lesion to compare resuscitation regimens. While the cryogenic lesion lacks the rotation and shear forces of impact injury, it is very reproducible and results in a focal and uniform disruption of the blood–brain barrier which is similar in nature to that seen with cerebral contusion [18]. The model is similar in other respects to the clinical situation in which head-injured patients in shock are given asanguinous salt solution followed by blood to restore blood pressure and are often intubated, hyperventilated, sedated, and paralyzed to control ICP [19]. In order to exaggerate any detrimental effects that the study solutions might have on ICP, we chose not to hyperventilate the animals and we selected an anesthetic agent which produces cerebral vasodilation.

The control group (Group 1) had no brain injury, shock, or resuscitation but was instrumented and monitored to evaluate the stability of our model over the 24 hr of the experiment. The control group demonstrated stable hemodynamics, ICP, and CBF over the course of the experiment and had no evidence of brain edema or swelling at the completion of the study. Group 2 received isotonic fluid (RL) throughout the study period, both for bolus injection and for further resuscitation and maintenance of hemodynamic stability and urine output. Group 3 received a hypertonic bolus (HSD) followed by an isotonic fluid to complete the resuscitation and to maintain blood pressure and urine output. Group 4 received only hypertonic fluids, HSD for the bolus injection and HSL to complete the resuscitation.

Hemorrhage to 50 torr resulted in approximately a 50% blood volume deficit and a significant decrease in MAP and CO in all treatment groups. The HSD bolus in Groups 3 and 4 significantly improved MAP and CO, while the isotonic bolus in Group 2 did not significantly improve either parameter. Continued infusion of RL, however, returned both MAP and CO to BL values after 30 min of resuscitation. Continued hypertonic infusion
in Group 4 produced a transient rise in CO which was significantly greater than BL, while MAP was essentially unchanged. This enhancement of CO by hypertonic fluid has been observed by others [1–3] and is thought to be due to a combination of rapid volume expansion from the intracellular space, improved cardiac contractility, and systemic vasodilatation [1–3, 20].

Resuscitation and maintenance of blood pressure and urine output required significantly less fluid in Group 4 than in the other experimental groups and resulted in a significantly lower net fluid balance in the animals receiving only hypertonic fluid. Hypertonic resuscitation, however, resulted in significant increases in both serum sodium and serum osmolarity. These increases were greatest in Group 4 at the completion of the study period. Increases of similar magnitude in sodium and osmolarity have been observed in both animals and humans after hemorrhage and resuscitation with hypertonic fluid [4, 21, 22]. Hypernatremia and hyperosmolarity resolved without sequelae in those studies by renal mechanisms of increased osmolar clearance associated with a negative free water clearance over the 48 hr following resuscitation.

Cerebral blood flow was significantly reduced by hemorrhage in all experimental animals. A bolus injection of HSD rapidly restored CBF to prehemorrhage values without elevating the ICP. Since cerebral blood volume had to increase with increased flow, the ICP would be expected to increase unless the volume of brain tissue or the volume of cerebrospinal fluid was reduced. On the basis of our previous work (8) and that of others (9), we hypothesize that the hypertonic fluid reduced the brain volume by extracting water from uninjured cells across an intact blood–brain barrier. This cerebral dehydration allowed for accommodation of the increased volume due to reperfusion and edema without increasing the ICP. This is a very important finding since hypotension and reduced CBF associated with head injury and shock can lead to hypoxic damage and cytotoxic edema which can increase ICP and further reduce cerebral perfusion pressure, leading to a secondary injury of the brain [15]. The brain is particularly sensitive to hypoxic injury since it has a high energy requirement and no capability of storing substrate. Hence, interruption of oxygen delivery for even short periods (4–6 min) can result in irreversible ischemic change [23]. Animals resuscitated with RL did not have CBF restored to baseline until 30 min after resuscitation commenced, at which time ICP rose significantly and remained significantly above baseline for the duration of the study. Animals resuscitated with only hypertonic fluid had CBF restored rapidly and had the ICP maintained at baseline for up to 6 hr, subsequent to which there was a gradual rise. At 24 hr, however, ICP in this group (Group 4) was not significantly greater than baseline.

After a transient period of hyperemia, flow to the injured area deteriorated in all animals. In the animals receiving RL (Groups 2 and 3) flow also decreased to the uninjured hemisphere. We hypothesize that this reduction in flow was due to edema and swelling which compressed the microcirculation in the area of the flow probe. Edema was definitely present since the cortical water content in the area of the injury was significantly greater than that in the uninjured cortex in all experimental animals. There was, however, no difference in water content of uninjured cortex between the groups, suggesting that a mechanism other than edema reduction may be responsible for the improved flow to this area in the animals resuscitated with HSD/HSL. These changes in flow were most marked in Group 3 and are not explained by our data. While the reduced flow may have been due to endothelial swelling induced by a rapid reduction in serum osmolarity which occurred with infusion of the RL, we have no data to support this and it will require further investigation.

These data suggest that hypertonic resuscitation more rapidly restores CBF at a lower ICP than isotonic resuscitation in a model of focal cryogenic brain injury and shock. Moreover, improved flow and lower ICP persist for up to 3 hr in hypertonic resuscitated animals. A delay in the onset of raised intracranial pressure would conceivably allow adequate time for surgical evacuation of mass lesions and suggests to us that hypertonic resuscitation might prevent or reduce secondary brain injury in such cases. This study also demonstrates that significant changes in both CBF and ICP occur after 4–6 hr of study and suggests that prolonged periods of study are necessary when evaluating the effects of fluid resuscitation on the injured brain.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of Ms. Dale Rathe, Ms. Beni Twitchell, and Ms. Ann Rowan in the preparation of the manuscript and tables, and Mr. Anthony Quinn in the preparation of the figures.

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