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Effects on Brain Edema of Crystalloid and Albumin Fluid Resuscitation after Brain Trauma and Hemorrhage in the Rat

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ABSTRACT

Background: It has been hypothesized that resuscitation with crystalloids after brain trauma increases brain edema compared with colloids, but previous studies on the subject have been inconclusive. To test this hypothesis, the authors compared groups resuscitated with either colloid or crystalloid.

Methods: After fluid percussion injury, rats were subjected to a controlled hemorrhage of 20 ml/kg and were randomized to 5% albumin at 20 ml/kg (A20), isotonic Ringer's acetate at 50 ml/kg (C50), or 90 ml/kg (C90). After 3 or 24 h, water content in the injured cortex was determined using a wet/dry weight method. Blood volume was calculated from plasma volume, measured by ^{125}I-albumin dilution, and hematocrit. Oncotic pressure and osmolality were measured with osmometers.

Results: At 3 h, blood volume was equal in the A20 and C90 groups and lower in the C50 group. Oncotic pressure was reduced by 35–40% in the crystalloid groups and unchanged in the albumin group. Cortical water content in the A20 group was lower than in the C90 group (81.3 ± 0.5% *vs.* 82.1 ± 1.1%, $P < 0.05$), but it was not different from the C50 group (81.8 ± 1.1%). At 24 h, oncotic pressure and blood volume were normalized in all groups, and cortical water content was significantly lower in the albumin group than in the crystalloid groups. Osmolality and arterial pressure were equal in all groups throughout the experiment.

Conclusions: When given to the same intravascular volume expansion, isotonic crystalloids caused greater posttraumatic brain edema than 5% albumin at 3 and 24 h after trauma.

What We Already Know about This Topic

- Hypovolemia after brain trauma may worsen neurologic outcome, and fluid resuscitation is often needed
- Whether crystalloid or colloid is preferable to reduce brain edema in this setting is controversial

What This Article Tells Us That Is New

- In rats with traumatic brain injury and hemorrhage, colloid resuscitation resulted in less brain edema than crystalloid

HYPOVOLEMIA occurs frequently in patients with brain trauma not only because of blood loss from associated injuries but also because of a general increase in microvascular permeability, resulting in loss of plasma volume to the interstitium.[1] Several studies have shown that prolonged hypotension is associated with poor outcome after brain trauma.[2,3] Independent of blood pressure, hypovolemia may adversely affect brain microcirculation and outcome because of a baroreceptor-mediated increase in cerebral vascular resistance.[4,5] Therefore, restoration of normovolemia is of fundamental importance in patients with brain trauma, but the choice of the resuscitation fluid is still under debate.

The normal blood–brain barrier (BBB) has a low permeability to solutes, and filtration of fluid will rapidly create a

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counteracting crystalloid osmotic gradient, which terminates further fluid shifts.[6] It has been proposed that an increased permeability of the BBB to crystalloids after trauma will increase the importance of plasma oncotic pressure as an opposing force to fluid filtration and that edema formation could be counteracted by the maintenance of the plasma oncotic pressure under these conditions.[7,8] Several carefully conducted experimental studies have tested the hypothesis that colloid resuscitation after brain injury induces less brain edema than crystalloid resuscitation.[7,9–15] The results have been contradictory, which may be explained by differences in the design of these studies. Although widely used to simulate the development of brain edema, the freeze lesion model used in several studies[9–12] may not be representative of a traumatic brain injury, as it induces more severe BBB damage than that obtained from mechanical injury models.[16] Furthermore, in all the previous studies, the volume of crystalloids was only two to three times the volume of colloids, which would result in a relatively smaller degree of plasma volume expansion, considering that the crystalloid solution is distributed to the whole extracellular space of the body.

The objective of this study was to compare the effects of 5% albumin solution and isotonic Ringer's acetate solution on cerebral edema formation after traumatic brain injury and hemorrhage, when the resuscitation fluids were given in doses that would result in equal plasma volume expansion. The study was performed on rats subjected to brain injury by lateral fluid percussion, followed by controlled hemorrhage. The influence of the different fluids on the development of brain edema and blood volume were investigated at 3 and 24 h after trauma.

Materials and Methods

Experimental Protocol

The study was approved by the Ethics Committee for Animal Research of Lund University (Lund, Sweden), and the animals were treated in accordance with the Guide for the Care and Use of Laboratory Animals of the National Academy of Science (United States). One hundred thirty-three male Sprague Dawley rats (Scanbur BK, Sollentuna, Sweden) weighing 383 ± 41 g were used. The study involved three groups of animals:

1. To characterize the neurologic outcome in the trauma model, composite neuroscore at 24 h after brain trauma was investigated by comparison with a sham procedure.
2. To investigate whether BBB permeability in this trauma model was compatible with increased importance of oncotic pressure for fluid exchange, the changes in microvascular permeability to the small hydrophilic molecule ^{51}Cr-EDTA (0.34 kDa) and to ^{125}I-albumin (69.3 kDa) at 3 and 24 h after brain trauma were investigated.
3. In the main group, we analyzed cortical water content in the injured and uninjured hemisphere at 3 and 24 h after brain trauma combined with hemorrhage and resuscitation with either a colloid (A20) or a crystalloid in two different volumes (C50 and C90). Cortical water content was also analyzed in a sham-operated nonhemorrhage group (control group) and in a sham-operated hemorrhage group resuscitated with crystalloids at 90 ml/kg (sham C90). An overview of the experimental protocol for these groups is given in figure 1.

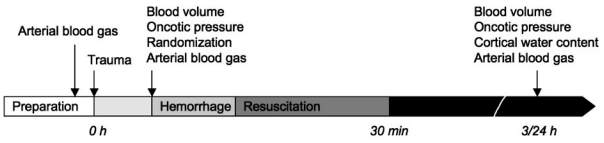

Fig. 1. Schematic illustration of the experimental protocol in the hemorrhage groups.

Anesthesia and Surgical Preparation

The animals were anesthetized with sodium pentobarbital given intraperitoneally at a dose of approximately 60 mg/kg (Apoteket AB, Stockholm, Sweden). The supplementary doses of 3–6 mg were given as required to maintain adequate depth of anesthesia. Body temperature was maintained at 37.2°–37.5°C with a feedback-controlled heating pad.

Lateral fluid percussion traumatic brain injury was produced as described previously.[17] Briefly, the head was placed in a stereotactic frame, the scalp was infiltrated with 10 mg/ml lidocaine (Astra Zeneca, Södertälje, Sweden), and the skull was exposed bilaterally through a midline incision. A 5-mm left-sided craniotomy was performed, centered on the parietal bone. A metal screw was anchored in the frontal bone, and a plastic luer-lock connector was fitted to the craniotomy with Histoacryl (Braun, Tuttingen, Germany) to provide a tight seal. The luer-lock connector was cemented to the skull and the anchoring screw using dental cement (Dentalon Plus; Heraeus Kulzer GmbH, Hanau, Germany). The animals were removed from the stereotactic frame, and anesthesia was continued using 0.6–1.5% isoflurane (Schering-Plough, Farum, Denmark) with spontaneous mask ventilation.

The right internal jugular vein and the left femoral artery were cannulated with saline-filled polyethylene catheters. The jugular vein catheter was used for the measurement of central venous pressure (CVP) and fluid administration. The arterial catheter was used for the measurement of mean arterial pressure (MAP) and heart rate (HR) and for blood sampling for measurements of Pa_{O_2}, Pa_{CO_2}, pH, Na, K, hematocrit (i-STAT; Abbot Scandinavia AB, Stockholm, Sweden), and blood glucose levels (Glucosure; HaeMedic AB, Munka-Ljungby, Sweden).

Baseline MAP, CVP, HR, Pa_{O_2}, Pa_{CO_2}, pH, Na, K, hematocrit, and blood glucose levels were measured under stable conditions. The luer-lock was connected to a fluid percussion injury device (Amscien Instruments, Richmond, VA), and a trauma of approximately 2.4 bars was induced. The connector device was removed, and the rats were again placed on the heating pad. The dura was inspected, and the rats with dural tears were excluded from further study. Sham-operated animals were subjected to the same surgical prepa-

ration, including craniotomy and positioning for fluid percussion injury, but with no trauma.

Hemorrhage and Resuscitation

After trauma, the rats in the hemorrhage group were bled a total volume of 20 ml/kg body weight (including blood sampling) for 10 min, and the blood samples for analysis of oncotic pressure, osmolality, and plasma volume were obtained. The animals were then randomized to receive an infusion of 5% albumin at 20 ml/kg (A20: n = 16 in the 3 h group, n = 9 in the 24 h group), crystalloid at 50 ml/kg (C50: n = 10 in the 3 h group, n = 9 in the 24 h group), or crystalloid at 90 ml/kg (C90: n = 16 in the 3 h group, n = 9 in the 24 h group). The A20 and C50 groups were resuscitated for 10 min. The C90 group received half the volume during 5 min and half during the next 10 min to avoid fluid overload and pulmonary edema. The sham C90 groups (n = 4 in the 3 h group, n = 4 in the 24 h group) were bled and resuscitated as in the C90 groups but were not subjected to trauma for confirming that the crystalloid solution did not cause edema in the uninjured brain. The C50 groups were included to verify the postulated lower blood volume after crystalloid resuscitation with only 2.5 times the volume of the shed blood. A control group that was sham operated but not bled was also included to ascertain that the bleeding itself did not alter brain water content (n = 6).

The albumin infusion consisted of 200 mg/ml of albumin (Behring, Marburg, Germany) and Ringer's acetate (Fresenius Kabi, Halden, Norway) *quantum satis* to an albumin concentration of 50 mg/ml. Osmolality was adjusted to 296–300 mOsm, as measured with an osmometer (see Osmolality and oncotic pressure), by adding concentrated NaCl (4 mmol/ml; Fresenius Kabi, Uppsala, Sweden). The crystalloid infusion was prepared similarly by adding 400 μl of NaCl (4 mmol/ml) to 100 ml of Ringer's acetate to give a measured osmolality of 296–300 mOsm.

Twenty minutes after completion of the resuscitation, MAP, CVP, and HR were again recorded. The arterial catheter was removed, and the vessel was ligated. The animals were allowed to wake up with free access to food and water.

Cortical Water Content

Approximately 2.5 or 23.5 h after volume resuscitation, the animals were weighed and reanesthetized with 4% isoflurane in a closed chamber. The femoral artery catheter was reinserted. After tracheotomy, the animals were mechanically ventilated (Ugo Basile Animal Ventilators, Comerio, Italy) to an end-tidal carbon dioxide concentration of 4.5–5.5% (Capstar-1000; CWE, Ardmore, PA). After 10 min of equilibration to 1.5% isoflurane, plasma volume, MAP, CVP, HR, Pa_{O_2}, Pa_{CO_2}, pH, Na, K, hematocrit, and blood glucose levels were measured. After decapitation, the brains were rapidly harvested and transferred to a chilled plastic tray. A 4-mm coronary section including the lesion was cut using a rodent brain matrix. The injured and contralateral cortical tissues were dissected as shown in figure 2. The specimens were then weighed on preweighed squares of aluminum foil and weighed again after drying at 100°C for 24 h. Cortical water content was calculated as ([wet tissue weight − dry tissue weight]/wet tissue weight) × 100.

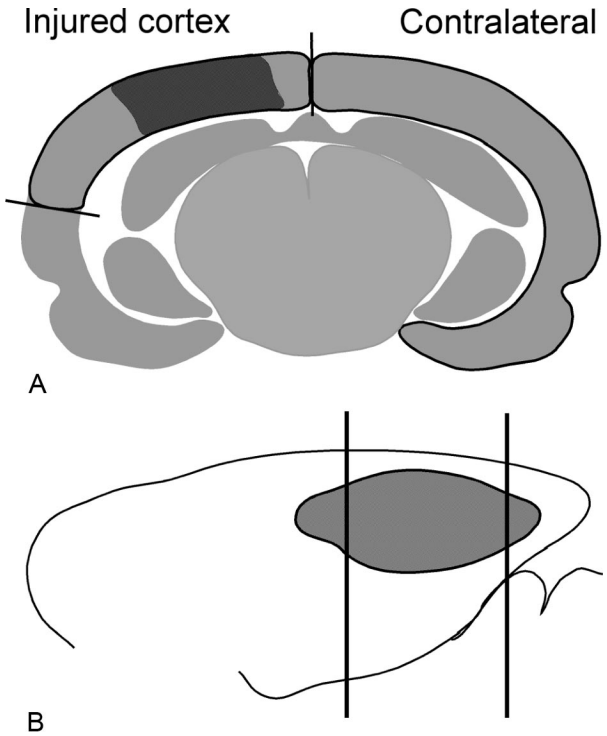

Fig. 2. Coronal (*A*) and sagital (*B*) views of the sampling sites for measurement of cortical water content and blood-brain barrier permeability. The *darker area* represents the contusion.

Osmolality and Oncotic Pressure

Plasma oncotic pressure was measured at baseline and at the end of the experiments with a 10-kDa cutoff membrane (Osmomat 050; Gonotec, Berlin, Germany), and plasma osmolality was measured by the freeze-point method (Micro-Osmometer Model 210; Fiske Associates, Norwood, Massachusetts). With the purpose of investigating whether rapid clearance of acetate could cause an early and transient decrease in crystalloid osmotic pressure, osmolality was measured before hemorrhage and 30 min, 1 h, and 2 h after hemorrhage and resuscitation with 90 ml/kg of isotonic Ringer's acetate solution in separate experiments (n = 4). No change in osmolality could be detected.

Blood Volume

In the hemorrhage experiments, plasma volume was determined at baseline and at the end of the experiments using an albumin dilution technique, by dividing a known amount of ^{125}I-albumin injected intravenously by the subsequent increase in plasma concentration 5 min later. The remaining radioactivity in the syringe and vials was subtracted from the prepared dose. ^{125}I activity was assessed with a gamma

counter (1480 Wizard; Wallac Sweden AB, Sollentuna, Sweden). Unbound iodine was less than 1% as measured after trichloroacetic acid precipitation. Hematocrit was measured using a conductometric technique (iStat; Abbot Scandinavia AB). Total blood volume was calculated as plasma volume/(1 − hematocrit).

Effects of Brain Trauma on Neurologic Outcome

To determine the severity of the trauma, motor function was evaluated in a separate series of animals using the composite neuroscore test (0–28) as described in detail previously.[17,18] Composite neuroscore tests were performed before induction of anesthesia and 24 h after fluid percussion injury or sham operation (n = 6 in each group). An investigator who was blinded to the treatment status of the animals performed all scoring.

Effect of Brain Trauma on BBB Permeability

The effect of brain trauma on BBB permeability in the injured cortex was investigated in separate experiments. Blood-to-brain transfer constants for solutes (K_i) reflect capillary permeability at an unchanged surface area available for fluid exchange.[19] K_i for ^{125}I-albumin and ^{51}Cr-EDTA was measured at 3 and 24 h after trauma and at 3 h after sham trauma to investigate posttraumatic permeability changes to small and large molecules (n = 36 in total). For comparison, K_i for albumin was also measured in the skeletal muscle of sham animals. The methodology has been described in detail elsewhere.[20] Briefly, the animals were subjected to a fluid percussion injury or a sham procedure as described earlier (see Anesthesia and Surgical Preparation), with the exception that no arterial or venous catheters were inserted before the trauma. Either 2.5 h or 23.5 h after trauma, rats were connected to a ventilator, and the venous and arterial catheters were inserted as described earlier (see Anesthesia and Surgical Preparation). The animals received an intravenous bolus dose of the tracer ^{51}Cr-EDTA or ^{125}I-albumin, followed by a constant-rate infusion of ^{51}Cr-EDTA or saline, respectively. Plasma concentration of the respective tracer was measured at regular intervals, and the animals were decapitated after 40 min (Cr-EDTA) or 60 min (albumin). Tissue plasma volume was determined with an intravenous bolus dose of either ^{125}I-albumin or ^{131}I-albumin, which was allowed to circulate for the last 4 min of the experiment, and tissue uptake of the tracer was calculated as tissue activity minus regional plasma activity. K_i for ^{51}Cr-EDTA or ^{125}I-albumin was then calculated according to the following equation[19]:

$$K_i = B / \int_0^T C_a(t)\,dt \quad (1)$$

Where B is the amount of tracer in the tissue, C_a is the concentration of the tracer in arterial plasma as a function of time, and T is the duration of the experiment.

Statistical Analysis

One-way ANOVA was used for the analysis of blood volume at 3 and 24 h. Within-group analysis of plasma osmolality and oncotic pressure before and after hemorrhage or resuscitation was performed with paired *t* tests. Between-group differences were analyzed with one-way ANOVA. MAP, CVP, HR, and K_i data for each tracer were analyzed with one-way ANOVA. The Student-Newman-Keul's *post hoc* test was used when applicable. Ordinal data from the composite neuroscore test were analyzed with the Mann–Whitney U test. All analyses were performed using GraphPad Prism version 5.0a for Macintosh (GraphPad Software, San Diego, CA). *P* values of <0.05 were considered statistically significant. Parametric data are expressed as mean ± SD.

Results

Physiologic Variables in the Hemorrhage Groups

MAP, CVP, and HR did not differ between the groups at any of the time points. After resuscitation, MAP returned to pretrauma levels (within a range of ± 15%) in all groups (table 1). Osmolality, Na, K, and arterial blood gases were similar before and after trauma and did not differ between the groups. All groups showed a marked increase in blood glucose level, with no differences between the groups (table 2). At 3 h, body weight was significantly lower in the albumin group than in the crystalloid groups. At 24 h, all groups showed marked weight loss compared with baseline, with no differences between the groups (fig. 3).

Neurologic Outcome and Brain Trauma Intensity

Median composite neuroscore (0–28) at baseline was 27.3 and 28 in the trauma and sham groups, respectively, and it was 13.5 and 27.5 at 24 h, respectively ($P < 0.05$; fig. 4). There was no difference in trauma intensity between the hemorrhage groups; it was 2.4 ± 0.2 bar, 2.3 ± 0.1 bar, and 2.3 ± 0.1 bar in the A20, C50, and C90 3-h groups, respectively, and 2.3 ± 0.1 bar in all 24-h groups. There were no differences in trauma intensity in the neuroscore and permeability groups compared with the hemorrhage groups. Mortality in the animals exposed to brain trauma was approximately 15%, and death usually occurred within the first 5 min and always within 30 min of trauma. The cause of death was either neurogenic pulmonary edema or respiratory arrest.

Permeability to ^{125}I-Albumin and ^{51}Cr-EDTA after Brain Trauma

In sham animals, K_i for ^{51}Cr-EDTA was 0.03 ± 0.03 $\mu l \cdot min^{-1} \cdot g^{-1}$ in the cortex, when compared with 1.6 ± 0.06 $\mu l \cdot min^{-1} \cdot g^{-1}$ in the traumatized cortex at 3 h and 0.7 ± 0.3 $\mu l \cdot min^{-1} \cdot g^{-1}$ at 24 h ($P < 0.05$). The corresponding values for K_i for ^{125}I-albumin were 0.01 ± 0.009 $\mu l \cdot min^{-1} \cdot g^{-1}$ in sham animals, 0.13 ± 0.03 $\mu l \cdot min^{-1} \cdot g^{-1}$ at 3 h, and 0.09 ± 0.09 $\mu l \cdot min^{-1} \cdot g^{-1}$ at 24 h ($P < 0.05$). K_i for ^{125}I-albumin in

Table 1. Hemodynamic Data

	A20 3 h	C50 3 h	C90 3 h	Sham 3 h
HR (per min)				
Pre FPI	385 ± 54	387 ± 46	371 ± 47	380 ± 50
Hem	364 ± 72	334 ± 60	344 ± 82	293 ± 39
Resusc	364 ± 71	403 ± 42	392 ± 42	389 ± 30
End exp	365 ± 35	368 ± 38	364 ± 63	332 ± 19
MAP (mmHg)				
Pre FPI	98 ± 13	98 ± 13	98 ± 11	99 ± 15
Hem	39 ± 12	43 ± 15	41 ± 14	28 ± 5
Resusc	96 ± 8	87 ± 16	86 ± 20	82 ± 19
End exp	82 ± 14	78 ± 17	79 ± 16	80 ± 16
CVP (mmHg)				
Pre FPI	1 ± 0.7	0.9 ± 0.8	1.3 ± 0.7	1.8 ± 1.1
Hem	0 ± 0.7	0 ± 1.3	0 ± 1.0	0.8 ± 1.7
Resusc	1.5 ± 0.8	1.4 ± 0.8	0.9 ± 1.0	1.6 ± 1.1
End exp	2.7 ± 0.8	2.5 ± 1.3	3.0 ± 1.8	4.1 ± 1.0
	A20 24 h	**C50 24 h**	**C90 24 h**	**Sham 24 h**
HR (per min)				
Pre FPI	389 ± 43	397 ± 37	389 ± 23	355 ± 29
Hem	334 ± 74	342 ± 72	315 ± 28	310 ± 24
Resusc	386 ± 31	372 ± 47	399 ± 38	378 ± 67
End exp	355 ± 37	350 ± 48	345 ± 31	356 ± 28
MAP (mmHg)				
Pre FPI	98 ± 16	109 ± 13	99 ± 11	91 ± 1
Hem	33 ± 7	40 ± 10	50 ± 14	30 ± 12
Resusc	95 ± 8	81 ± 23	87 ± 19	76 ± 15
End exp	80 ± 18	96 ± 12	83 ± 23	88 ± 7
CVP (mmHg)				
Pre FPI	1.1 ± 0.6	1.2 ± 0.7	0.9 ± 0.6	0.8 ± 1
Hem	−0.3 ± 1	0 ± 0.6	0 ± 1.0	0 ± 0.5
Resusc	2.2 ± 0.4	1.6 ± 0.9	1.5 ± 0.7	0.8 ± 0.8
End exp	2.0 ± 1.1	3.9 ± 1.4	3.6 ± 0.9	1.7 ± 0.8

There were no significant hemodynamic differences between the groups before trauma, after hemorrhage, after resuscitation, or at the end of the experiment. A20 is the albumin group after 3 h and 24 h. C50 is the crystalloid group given 50 ml/kg after 3 h and 24 h, and C90 is the crystalloid group given 90 ml/kg after 3 h and 24 h.

CVP = central venous pressure; End exp = end of the experiment; Hem = after hemorrhage; HR = heart rate; MAP = mean arterial pressure; Pre FPI = before trauma; Resusc = after resuscitation.

the abdominal rectus muscle was $0.07 \pm 0.04\ \mu l \cdot min^{-1} \cdot g^{-1}$ in the sham group (fig. 5).

Blood Volume and Oncotic Pressure

Prehemorrhage blood volumes were 61 ± 4 ml/kg, 62 ± 3 ml/kg, 61 ± 3 ml/kg, and 66 ± 6 ml/kg in the 3-h A20, C50, C90, and sham groups, respectively. The corresponding values for the 24-h groups were 65 ± 5 ml/kg, 67 ± 6 ml/kg, 64 ± 7 ml/kg, and 67 ± 3 ml/kg.

At 3 h, blood volume deficit in the A20 and C90 groups was 10.5 ± 9.9% and 10.2 ± 9.2%, respectively, as opposed to 18.7 ± 9.6% in the C50 group ($P < 0.05$), with no significant differences between the groups at 24 h (fig. 6).

Prehemorrhage plasma oncotic pressures in the 3-h groups were 15 ± 2 mmHg, 16 ± 5 mmHg, 15 ± 2 mmHg, and 15 ± 1 mmHg in the A20, C50, C90, and sham groups, respectively. Prehemorrhage plasma oncotic pressures in the 24-h groups were 16 ± 2 mmHg, 17 ± 1 mmHg, 18 ± 2 mmHg, and 15 ± 1 mmHg in the A20, C50, C90, and sham groups, respectively. At 3 h, plasma oncotic pressure was significantly lowered by 34 ± 8%, 38 ± 7%, and 41 ± 4% compared with baseline in the C50, C90, and sham groups, respectively, and it returned to prehemorrhage values at 24 h. Plasma oncotic pressure was unchanged in the A20 group throughout the experiment (fig. 7).

Cortical Water Content

At 3 h, cortical water content in the injured cortex was lower in the A20 group than in the C90 group (81.3 ± 0.5% and 82.1 ± 1.1%, respectively, $P < 0.05$), but it was not significantly different from that in the C50 group (81.8 ± 1.1%). Cortical water content in the sham C90 animals and in control animals (sham-operated but not bled) was 79.8 ± 0.5% and 80.0 ± 0.3%, respectively, and it was lower than in the traumatized groups ($P < 0.05$) (fig. 8A). Cortical water content in the contralateral cortex at 3 h was 80.4 ± 0.5%, 80.4 ± 0.4%, and 80.6 ± 0.4% in the A20, C50, and C90 groups, respectively, with no difference between the groups, and it was lower than in the contusion area in all groups ($P < 0.05$). Cortical water content of the contralateral cortex in

Table 2. Summary of Blood Chemistry

	A20 3h	C50 3h	C90 3h	Sham 3h
Pa_{O_2} (mmHg)				
Pre FPI	67 ± 8	65 ± 8	65 ± 4	67 ± 5
End exp	75 ± 8	72 ± 7	83 ± 11	82 ± 6
Pa_{CO_2} (mmHg)				
Pre FPI	53 ± 6	57 ± 4	53 ± 4	54 ± 3
End exp	40 ± 6	38 ± 5	38 ± 5	36 ± 2
Osmolality (mOsm/kg)				
Pre FPI	303 ± 4	303 ± 7	303 ± 5	307 ± 1
End exp	303 ± 7	302 ± 3	298 ± 4	303 ± 2
pH				
Pre FPI	7.38 ± 0.03	7.37 ± 0.03	7.36 ± 0.03	7.39 ± 0.02
End exp	7.49 ± 0.04	7.49 ± 0.05	7.46 ± 0.06	7.50 ± 0.03
Hematocrit (%)				
Pre FPI	45 ± 3	45 ± 2	45 ± 3	43 ± 2
End exp	25 ± 2	25 ± 2	24 ± 2	22 ± 2
Na (mM)				
Pre FPI	137 ± 2	138 ± 1	137 ± 2	138 ± 2
End exp	138 ± 1	137 ± 2	136 ± 2	136 ± 2
K (mM)				
Pre FPI	4.7 ± 0.3	4.5 ± 0.3	4.7 ± 0.3	4.6 ± 0.6
End exp	4.5 ± 0.3	4.1 ± 0.3	4.8 ± 0.5	4.1 ± 0.5
Glucose (mM)				
Pre FPI	7 ± 1	7 ± 1	9 ± 2	7 ± 1
End exp	18 ± 3	16 ± 3	17 ± 4	17 ± 4
	A20 24h	C50 24h	C90 24h	Sham 24h
Pa_{O_2} (mmHg)				
Pre FPI	64 ± 6	65 ± 9	64 ± 9	70 ± 5
End exp	72 ± 8	78 ± 8	83 ± 11	77 ± 6
Pa_{CO_2} (mmHg)				
Pre FPI	52 ± 4	54 ± 5	53 ± 3	50 ± 5
End exp	38 ± 4	35 ± 3	35 ± 2	37 ± 3
Osmolality (mOsm/kg)				
Pre FPI	303 ± 5	301 ± 3	300 ± 5	304 ± 5
End exp	302 ± 3	297 ± 5	300 ± 4	297 ± 5
pH				
Pre FPI	7.41 ± 0.02	7.39 ± 0.03	7.39 ± 0.02	7.39 ± 0.01
End exp	7.49 ± 0.05	7.50 ± 0.03	7.49 ± 0.03	7.52 ± 0.01
Hematocrit (%)				
Pre FPI	43 ± 4	45 ± 2	44 ± 1	43 ± 1
End exp	25 ± 2	25 ± 2	24 ± 2	25 ± 2
Na (mM)				
Pre FPI	137 ± 2	138 ± 2	138 ± 1	136 ± 1
End exp	137 ± 2	135 ± 1	136 ± 1	136 ± 1
K (mM)				
Pre FPI	4.5 ± 0.3	4.5 ± 0.5	4.4 ± 0.4	4.9 ± 0.1
End exp	4.1 ± 0.3	4.4 ± 0.5	4.5 ± 0.2	4.4 ± 0.4
Glucose (mM)				
Pre FPI	8 ± 2	8 ± 1	7 ± 1	8 ± 2
End exp	16 ± 3	18 ± 3	18 ± 3	16 ± 3

There were no significant differences in arterial partial pressure of oxygen (Pa_{O_2}), arterial partial pressure of carbon dioxide (Pa_{CO_2}), B-glucose, osmolality, or hematocrit before trauma (Pre FPI) or at the end of the experiment (End exp). A20 is the albumin group after 3 h and 24 h. C50 is the crystalloid group given 50 ml/kg after 3 h and 24 h, and C90 is the crystalloid group given 90 ml/kg after 3 h and 24 h.

the sham C90 and control groups was 80.5 ± 0.5% and 80.4 ± 0.4%, respectively, and it was not different form the corresponding values for the trauma groups.

At 24 h, brain water content in the injured cortex in the C50 and C90 groups was higher than in the A20 group (83.4 ± 0.8% and 83.5 ± 0.9%, respectively, *vs.* 82.8 ± 0.5%; $P < 0.05$). Cortical water content in the sham C90 and control groups was 79.7 ± 0.3% and 80.0 ± 0.2% respectively, which was less than in all other groups ($P < 0.05$; fig. 8B). The corresponding values for the contralateral cortex were lower in all trauma groups (80.2 ± 0.4%, 80.2 ± 0.3%, and 80.2 ± 0.4% in the A20, C50, and C90 groups,

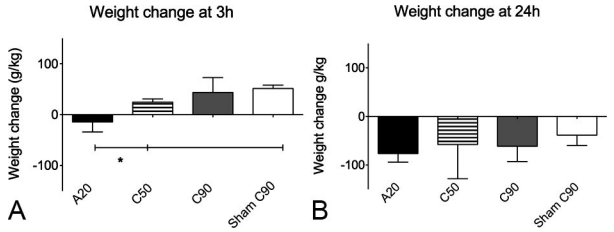

Fig. 3. The change in the body weight at 3 h (*A*) and 24 h (*B*) presented as g/kg initial body weight. There was a significant difference between the A20 group and the other groups at 3 h. At 24 h, there were no differences between the groups (* $P < 0.05$).

respectively), with no differences between the groups. In the contralateral cortex of the sham C90 and control animals, water content was 80.5 ± 0.2% and 80.4 ± 0.5%, respectively, and these values were not different from the corresponding values for the traumatized groups.

Discussion

The current study on the rat has shown that after an experimental traumatic brain injury combined with a major hemorrhage, brain edema is greater after resuscitation with an isotonic crystalloid than after resuscitation with 5% albumin solution.

Trauma Model

The lateral fluid percussion model of traumatic brain injury has been widely used in several species for the past 20 years, and it has many characteristics in common with human brain trauma in terms of histologic, physiologic, and behavioral posttraumatic changes.[21] We have previously shown that trauma of similar magnitude as used in the current study results in a contusion volume of approximately 10% of total cortical volume from bregma and caudally.[17] The observed mortality and reduction in neuroscores after trauma are in agreement with the results of previous studies using similar intensity of trauma intensity,[17,18] and taken together, the data suggest that the intensity of the trauma is in the moderate-to-severe range.[18]

Plasma Volume and K_i Measurements

The ^{125}I-albumin dilution technique for plasma volume measurement is used both clinically and in laboratory experiments under normal and inflammatory states with highly reproducible results.[22] The potential errors in the technique, such as effects of poor mixing of the tracer in plasma and effects of transcapillary escape during the 5-min mixing period have been discussed previously and found to be small.[23] The method used to determine K_i for albumin and Cr-EDTA has been used in several studies, and the current K_i values are similar to the previously reported values for the normal brain cortex and skeletal muscle.[20,24,25]

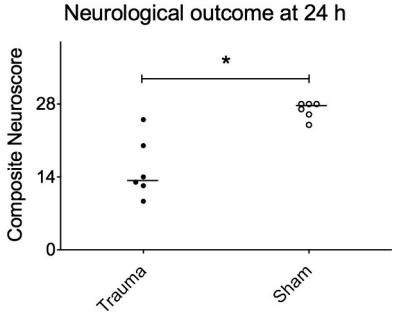

Fig. 4. Neurologic outcome at 24 h after trauma or sham procedure alone. Baseline medians were 27.3 and 28 for the trauma and sham groups, respectively (* $P < 0.05$).

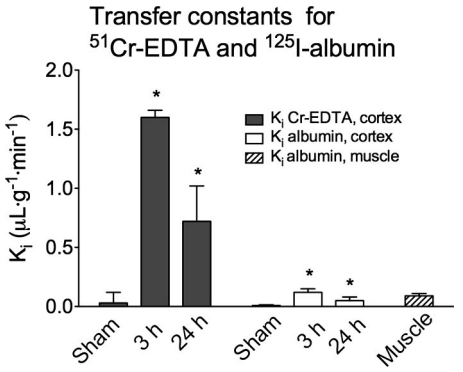

Fig. 5. Transfer constants (K_i) in the injured cortex for ^{51}Cr-EDTA and ^{125}I-albumin at 3 h and 24 h after trauma or after sham procedure. For comparison, K_i for albumin in the normal skeletal muscle was in the same range as K_i for albumin in the injured cortex (* $P < 0.05$ compared to sham).

Fluid Composition

The rationale for using Ringer's acetate solution and not saline was to avoid the high chloride load of normal saline, which may result in metabolic acidosis. Ringer's acetate solution was modified to avoid hypotonicity and possible development of hypoosmolar brain edema.[7,9,26] As intended, measured plasma osmolality did not vary between or within the groups, either before or after trauma, and there was no metabolic acidosis. At the end of the experiments, there was a slight respiratory alkalosis, which was equal in all groups and could not, therefore, have influenced the results.

We used 5% albumin solution as colloid because it is commonly used in patients with brain trauma, and it has been shown to expand plasma volume in the rat to approximately the same degree as the infused volume, with relatively long duration.[22] The decrease in plasma oncotic pressure by 30–40% in the crystalloid groups at 3 h, including the sham

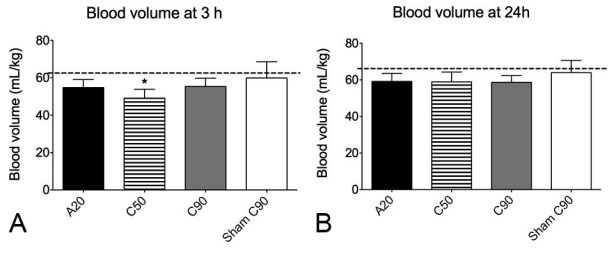

Fig. 6. Blood volume at 3 h (*A*) and at 24 h (*B*). The *dashed line* represents mean values before hemorrhage for all groups. Blood volume in the C50 group at 3 h was lower than in all other groups (* $P < 0.05$).

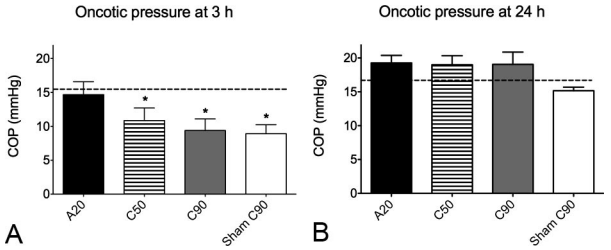

Fig. 7. Plasma oncotic pressure (COP) at 3 h (*A*) and 24 h (*B*). The *dashed line* represents mean values before hemorrhage for all groups. At 3 h, values for the C50, C90, and sham C90 groups all differed significantly from that for the A20 group (* $P < 0.05$).

C90 group, is consistent with plasma volume expansion with crystalloids after major hemorrhage and corresponds well with reported albumin concentrations as low as 20 g/l in patients with brain trauma.[27] The return to baseline values at 24 h indicates *de novo* synthesis of proteins, compensating for the decrease in oncotic pressure.

Intravascular Volume and Brain Trauma

Hypovolemia will increase cerebral vascular resistance as a result of sympathetic activation, with release of catecholamines from the adrenal glands, thus overriding the vasodilatory autoregulatory response to hypotension.[5] Such an increase in vascular resistance in the vulnerable penumbra zone of a brain contusion may aggravate the secondary ischemic insult. In a retrospective analysis of data from the National Acute Brain Injury Study: Hypothermia, Clifton *et al.*[4] found that a negative fluid balance was independently associated with worse outcome after brain trauma. It is reasonable to believe that restoration of blood volume after brain trauma is crucial for optimal treatment of these patients, especially in the states of increased intracranial pressure.[4,5]

When comparing different plasma volume expanders, "equipotent" doses, that is, doses giving the same plasma volume expansion, should be used. The use of 4.5 times greater volume in the C90 group than in the A20 group was based on the fact that a crystalloid solution is distributed to the whole extracellular space, whereas albumin initially remains in the intravascular compartment. That such a relationship of volumes represents "equipotent" doses is supported by equal blood volumes at 3 h in the A20 and C90 groups and from previous studies with or without hemorrhage.[28,29] The C50 group, which received only 2.5 times the shed blood volume of crystalloid, consequently showed a significantly lower blood volume at 3 h than the A20 and the C90 groups.

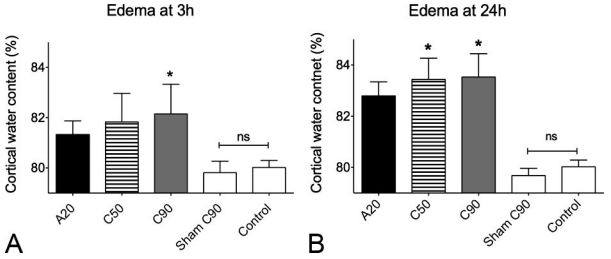

Fig. 8. Cortical water content in the injured cortex at 3 h (*A*) and at 24 h (*B*). Edema in the C90 group was significantly higher than in the A20 group at 3 h. Edema in the C50 group and in the C90 group was significantly higher than in the A20 group at 24 h (* $P < 0.05$ compared with the A20 group). There were significant differences between all the traumatized groups and the sham C90 and control groups.

Transcapillary Fluid Exchange in the Brain

Water flux across the cerebral capillaries, and thus brain volume, is normally regulated by the very low permeability of the BBB not only to the large molecules but also to the electrolytes.[6] Any fluid filtration or absorption across the barrier will immediately create a balancing osmotic gradient, opposing further fluid flux. An increase in permeability of the BBB after traumatic brain injury may, therefore, alter regulation of water flux into the brain.[7,20] During these conditions, it has been suggested that fluid flux across the cerebral capillaries of the contused brain is dependent on the balance between the transcapillary hydrostatic and oncotic pressures, as the osmolality on either side of the BBB will be rapidly equalized.[8]

The 50-fold increase in the K_i for Cr-EDTA after trauma suggests an increased permeability for the smaller and osmotically important molecules such as sodium across the disrupted BBB. This is in agreement with a clinical study showing that hypertonic saline reduces brain water content in the uninjured but not in the injured brain tissue; that is, an osmotic gradient is rapidly equalized in the contused parts of the brain.[30] The K_i presented for albumin after trauma is in the range of that in normal skeletal muscle, suggesting that a transvascular oncotic gradient can be maintained in the injured brain. This hypothesis is further supported by the low protein concentrations in the cerebrospinal fluid[31] and brain tissue,[32] even in patients with severe head injury.

These observations indicate that the use of a colloid as plasma volume expander could result in less brain edema than the use of a crystalloid solution because of a stronger transcapillary absorbing force.[7,8,33] Furthermore, when the cerebral capillaries are permeable to small solutes, a crystalloid solution will be distributed to the whole extracellular space of the brain, by analogy with the rest of the body, and an increase in brain edema regardless of plasma oncotic pressure. Both these physiologic mechanisms may have contributed to the higher water content of the injured cortex in the C90 group than in the A20 group at 3 h. It is unlikely that any differences in hydrostatic capillary pressure in the brain would have contributed to the observed difference in brain edema, as there was no difference in MAP between any of the groups. The distribution effect may explain the observation that edema in the C50 group did not differ significantly from that in the A20 group at 3 h (fig. 8), as there was less fluid to be distributed to the injured brain with the lower total volume of crystalloid. The relative hypovolemia in this group had no adverse effect on edema formation at 3 h, but it may have contributed to the increased edema at 24 h. Brain water

content in the sham C90 groups was not different from that in control animals or from values given in previous studies,[20] which confirms that a reduced plasma oncotic pressure in the brain with intact BBB does not induce brain edema.[6,8,34]

Comparable Studies

Previous studies have investigated the effects of fluid resuscitation and plasma oncotic pressure on cerebral edema formation in different brain injury models, but with contradictory results. Thus, after freeze injury, resuscitation with either colloids or crystalloids was not found to cause any differences in edema formation.[9–12] The reason for the negative results in the studies using the freeze-injury model is likely to be related to a more pronounced increase in BBB permeability than after mechanical brain trauma.[9,16] If permeability is sufficiently high, colloids will enter the brain with ease, and transcapillary oncotic pressure will be markedly reduced.

Studies using mechanical head trauma models have also failed to consistently demonstrate any beneficial effects of colloids on brain edema. Chorny *et al.*[13] studied the effect of hypervolemic hemodilution on brain edema and brain tissue necrosis volume after a closed head trauma in the rat using 20% albumin, 10% hydroxyethyl starch, or saline. They found no difference in edema formation 72 h after trauma, although brain tissue necrotic volume was lower in both colloid groups. These results do not, however, exclude the possibility of an early difference in brain edema contributing to the better histologic outcome observed in the colloid groups. In another study by the same group, Eilig *et al.*[14] compared colloid and crystalloid fluid resuscitation after brain trauma and uncontrolled hemorrhage, but the positive effect of colloids could not be reproduced. However, the infused volumes of the study fluids, the widely different postresuscitation hemoglobin levels, and the difference in cumulative blood loss between the normal saline and the colloid groups indicate that the groups were not comparable regarding intravascular volume. Furthermore, as suggested by the high cortical water content, the trauma resulted in a severe injury, which may have made it difficult for oncotic pressure and the distribution of crystalloids to influence edema. By using a cortical contusion injury model of brain trauma in the rat, Elliot *et al.*[15] reported the beneficial effects on brain edema after early but not late administration of 4% albumin compared with hypertonic saline with or without additional albumin. The authors speculated that the time course of BBB impairment in the cortical contusion injury model is rapid and may account for the results presented.[15,16] Furthermore, fluids were given to normovolemic animals at doses that resulted in different degrees of hypervolemia, making the results difficult to interpret in relation to clinical practice; they are not directly comparable with the current hemorrhage model.

In the study by Drummond *et al.*,[7] less brain edema was reported with hydroxyethyl starch than with normal saline as plasma volume substitution at 4 h after fluid percussion injury in the rat. The authors used a plasma exchange technique in which hematocrit levels remained at baseline throughout the experiment, but normal saline was given only in approximately 1.6 times the volume of hydroxyethyl starch. In the normal saline group, 83% of the animals required phenylephrine to maintain an MAP of more than 75 mmHg; the corresponding figure in the hydroxyethyl starch group was 16%. The difference in pharmacologic treatment and intravascular volume may have influenced the results by a difference in cerebral blood flow, according to the studies showing that ischemia and hypoxia aggravate cellular edema after brain trauma.[35–37] The results of the current study indicate that the conclusions of the study by Drummond *et al.* are valid despite these methodologic considerations, and taken together, these studies suggest that all colloids may counteract edema formation by their mainly intravascular distribution and by maintenance of plasma oncotic pressure. In addition, the increased edema in both the crystalloid groups compared with the albumin group at 24 h in the current study illustrates that the initial fluid resuscitation may also have long-term consequences for intracranial pressure.

In a small, randomized clinical study, Tomita *et al.* showed that pericontusional brain edema was less, and clinical outcome was better when plasma oncotic pressure was increased with 25% albumin infusions than in the controls treated in a standard way.[33] In contrast, a subgroup analysis of patients with head injury in the study on saline *versus* albumin fluid evaluation revealed a higher 28-day mortality in the group resuscitated with 4% albumin than in the saline group,[38] but the incidence of intracranial hypertension and the number of deaths attributable to traumatic brain injury showed no difference between the groups. Our study also suggests that these results cannot be explained by an edema-promoting effect of albumin. Considering that albumin did not increase mortality in other patient categories included in the original study on saline *versus* albumin fluid evaluation, it is not unlikely that the increased mortality after traumatic brain injury was related to a combination of albumin and other aspects of the treatment specific to traumatic brain injury patients, such as high doses of vasopressors.[39]

In conclusion, the current study suggests that resuscitation after brain trauma and hemorrhage using 5% albumin results in less edema formation than resuscitation with a crystalloid to the same blood volume. From a physiologic point of view, this effect may be put down to a difference in plasma oncotic pressure and to greater distribution of the crystalloid solution to the brain interstitium, but other mechanisms may also be involved. Future randomized and prospective trials are clearly needed to clarify the net effect of albumin and other colloids on outcome in patients with brain trauma.

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