Differential effects of isotonic and hypotonic 4% albumin solution on intracranial pressure and renal perfusion and function

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Intravenous fluids are frequently used in intensive care units (ICUs) to resuscitate patients with trauma.[1] Although the appropriate use of fluids in ICUs may have benefits, there is increasing awareness of the potential risks in trauma patients. In particular, in patients with traumatic brain injury (TBI), resuscitation with commercially available 4% albumin solution has been associated with increased mortality.[2]

It was proposed that an increase in intracranial pressure (ICP) following infusion of the hypotonic commercial 4% albumin solution used in the Saline or Albumin for Fluid Resuscitation in Patients with Traumatic Brain Injury (SAFE-TBI) study explained such increased mortality in patients with TBI.[2] An increase in ICP with albumin administration was subsequently confirmed in a follow-up of the SAFE-TBI study, involving patients with ICP monitoring.[3] However, it remains unclear whether the increase in ICP seen in the SAFE-TBI study was due to the albumin molecule itself or to the hypotonicity of the solution containing 4% albumin.[3] Moreover, although albumin may be used as a volume expander in response to oliguria, a relatively common complication of trauma, and of trauma with TBI, the effects of the commercially available 4% albumin solutions on renal blood flow and function have never been studied.

We performed an experimental study in conscious, chronically instrumented sheep to test the hypothesis that infusion of commercial 4% albumin solution would increase ICP, even in healthy animals, and that a modified albumin solution with a tonicity similar to that of normal saline, or the infusion of saline itself, would prevent such an increase in ICP. Because the effects of tonicity of an albumin solution and of albumin itself on systemic haemodynamics, renal blood flow and renal function are unclear, we also studied the effects of infusion of the three experimental fluids on these variables.

Methods

Animal preparation

Experiments were conducted on six healthy adult Merino ewes (mean bodyweight, 43.1 kg [SD, 3.7 kg]) housed in individual metabolic cages, fed 800 g of oaten chaff per day and given water ad libitum.

Experimental procedures were approved by the Animal Ethics Committee of the Florey Institute of Neuroscience

ABSTRACT

Objectives: Albumin is used to resuscitate trauma patients but may increase intracranial pressure (ICP). Its effects on renal blood flow and function are unknown. Our aim was to examine the effects of hypertonic albumin on ICP and renal function, and if any effects are due to the hypotonicity of the solution containing albumin or to albumin itself.

Design, setting and subjects: Cross-over, randomised controlled experimental study of six adult Merino ewes in the animal facility of a research institute.

Method: Sheep were implanted with flow probes around the pulmonary and renal arteries and an ICP monitoring catheter in a lateral cerebral ventricle. Conscious sheep received normal saline, commercially available hypotonic 4% albumin solution (4% Albumex [278 mOsm/kg]) or a novel isotonic 4% albumin solution (288 mOsm/kg), with at least 48 hours between each intervention.

Results: Commercial hypotonic albumin solution increased ICP (by 8.5 mmHg [SEM, 2.1 mmHg]; $P < 0.01$), but neither isotonic albumin solution nor saline significantly changed ICP. The increase in ICP with hypotonic albumin solution was associated with an increase in central venous pressure (CVP) (by 5.4 mmHg [SEM, 0.6 mmHg]; $P < 0.001$), but no significant changes in cardiac output or stroke volume. None of the infusions changed renal blood flow, plasma creatinine level, creatinine clearance or plasma or urinary electrolyte levels.

Conclusion: Compared with saline or isotonic albumin solution, hypotonic albumin solution increased ICP and CVP, but did not alter arterial pressure, cardiac output renal blood flow or renal function. Our findings support the view that the tonicity of the albumin solution, rather than the albumin itself, is responsible for increasing ICP.

under guidelines laid down by the National Health and Medical Research Council of Australia.

Sheep underwent two sterile surgical procedures under general anaesthesia. In the first, a carotid arterial loop was created to facilitate arterial cannulation and a 20 mm transit-

time flow probe (Transonics Systems) was implanted on the pulmonary artery to measure cardiac output (CO).[4] After 2 weeks, a 4 mm transit-time flow probe was implanted on the left renal artery. The sheep were then placed in a stereotactic apparatus and, in an aseptic operation, stainless steel guide tubes (17G) were implanted, with the tips about 2 mm above the lateral ventricles.[5] Pre-surgical and post-surgical antibiotics and analgesia were given as previously described elsewhere.[4]

A 14-day recovery period from the second surgery was allowed before experimentation started. The day before experimentation, a cannula was inserted into a carotid artery to monitor blood pressure and sample blood, and two cannulae were inserted into a jugular vein for infusion of albumin solutions or saline and measurement of central venous pressure (CVP).[4] To measure ICP, a 20G probe that projected 5 mm below the tip of the ventricular guide tube was inserted. The probe, connected to a Tygon cannula (1 mm internal diameter; 1.5 mm external diameter) filled with artificial cerebrospinal fluid (CSF), was held in place with a luer-lock. It was confirmed that the needle tip was located in the lateral cerebral ventricle by raising and lowering the catheter and checking that artificial CSF flowed into and back from the catheter, respectively. The catheter was connected to a pressure transducer that was tied to the wool on the back of the head at the level of the brain. The location of the needle in the cerebral ventricle was further confirmed by demonstrating that ICP pulsed together with the arterial pulse. Throughout the experimental period, artificial CSF was infused at 0.6 mL/h.

Analogue signals for mean arterial pressure (MAP), heart rate (HR), CO, renal blood flow (RBF), CVP and ICP were recorded at 100 Hz on a computer with a micro1401 interface and Spike2 software (Cambridge Electronic Design). Blood and urine samples were obtained for measurement of creatinine, sodium, and potassium levels. Creatinine clearance, as a measure of glomerular filtration rate, and fractional excretion of sodium were calculated according to standard formulae. Arterial blood was obtained simultaneously for blood oximetry and measurement of lactate levels (ABL system 625; Radiometer Medical).

Experimental protocol

Study design

All experimental animals received normal saline, hypotonic commercially available albumin solution (4% Albumex, CSL Behring [Australia]) as used in the human trial, or an experimental, custom-made isotonic, isochloraemic 4% albumin formulation (CSL Behring [Australia]) (Table 1). Albumin solutions were given in random order, within 2 days of each other to avoid development of an immune response

Table 1. Composition of the hypotonic and isotonic albumin solutions and normal saline

Parameter	Hypotonic albumin	Isotonic albumin	Normal saline
Protein (%)	3.95%	4.05%	0
Sodium (mM)	140.0	145.75	154
Chloride (mM)	132.5	100.50	154
Caprylate (mM)	6.6	6.7	0
Sodium gluconate (mM)	0.0	19	0
Potassium (mM)	0.0	5	0
Sodium acetate (mM)	0.0	19	0
Measured osmolality (mOsm/kg)	278	288	286

to the second dose of human albumin. The saline infusion was given either 2 days before or 2 days after the infusions of 4% albumin. Following a baseline recording period of 1 hour, 500 mL of each solution was infused over 15 minutes, to simulate acute resuscitation in trauma patients, after which recordings were continued for 24 hours. Arterial blood samples were collected for measurement of levels of arterial blood gases, sodium and potassium, immediately before the infusions and at 1, 2, 4, 8 and 24 hours after the start of the infusions.

Statistical analysis

Data are shown as means with standard errors of means (SEMs), and all analysis was performed using Prism, version 6.0 (GraphPad). Statistical analysis was performed on baseline values and data collected at 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hours after the start of solution infusion. Comparisons were made between the groups using two-way, repeated-measures analysis of variance with the factors treatment ($P_{treatment}$:commercial 4% albumin solution or a modified experimental albumin solution or saline), time (P_{time}) and their interaction ($P_{interaction}$). These analyses were conducted on absolute values or the change from 0 to 24 hours after the start of solution infusion. All reported P values are two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Baseline values

The levels of ICP, MAP, HR, RBF, CO, CVP, plasma electrolytes and arterial lactate were not significantly different between the 1 hour baseline periods on each of the 3 days before infusion of standard human albumin solution, isotonic human albumin solution or saline. No sheep experienced an immune response after the albumin infusions.

Figure 1. Change in intracranial pressure, mean arterial pressure and central venous pressure in conscious sheep during a 1-hour baseline period (Time 0) and up to 24 hours after infusion of study fluids (*n* = 6)
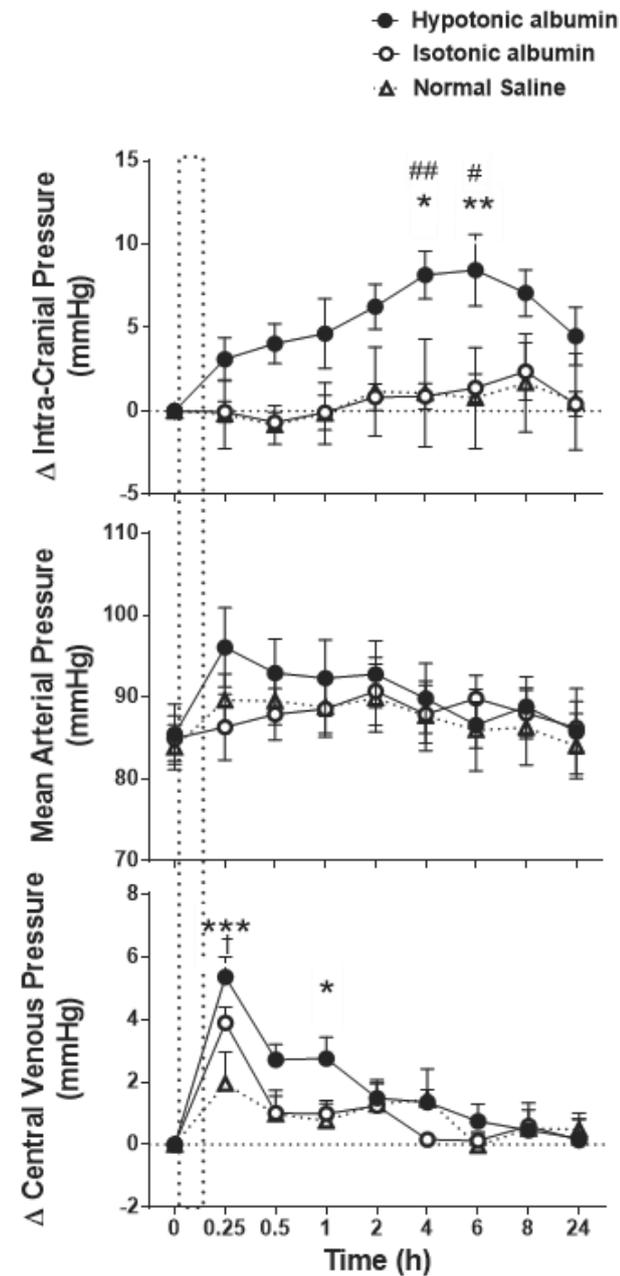
The dotted rectangle indicates the time the solutions were infused. Results are means with standard error of means (SEMs). *P* values represent treatment–time interactions from a 2-way, repeated-measures analysis of variance from 0 to 24 hours after study solution infusion. # *P* < 0.05 and ## *P* < 0.01: significant differences between hypotonic albumin and isotonic albumin. * *P* < 0.05, ** *P* < 0.01 and *** *P* < 0.001: significant differences between hypotonic albumin and saline. † *P* < 0.05, significant differences between isotonic albumin and saline.

Changes in ICP after albumin infusions

The mean basal levels of ICP before the infusion of commercial hypotonic albumin, isotonic albumin and normal saline, were 6.7 mmHg (SEM, 1.0 mmHg), 10.2 mmHg (SEM, 1.7 mmHg) and 6.9 mmHg (SEM, 2.0 mmHg), respectively. After infusion of hypotonic 4% albumin solution, mean ICP progressively increased to a maximum of 8.5 mmHg (SEM, 2.1 mmHg) above the baseline value after 6 hours, and it remained increased at 8 hours before slowly declining over 24 hours (Figure 1). In contrast, after infusion of isotonic 4% albumin solution or normal saline, there were no significant increases in ICP above baseline levels over 24 hours after the infusions (Figure 1).

Systemic haemodynamic effects of albumin infusions

During the baseline period, MAP was 85.5 mmHg (SEM, 3.7 mmHg) and following infusion of commercial hypotonic 4% albumin solution it reached a maximum value of 96.1 ± 4.8 mmHg at the end of the 15-minute infusion, but this increase was not statistically significant (Figure 1). Infusion of either of isotonic albumin solution or normal saline had no significant effects on MAP (Figure 1). At the end of the 15-minute infusion of commercial hypotonic 4% albumin solution, CVP was significantly increased by 5.4 ± 0.6 mmHg (*P* < 0.001), compared with the change during normal saline (+1.9 ± 1.0 mmHg), following which CVP declined toward baseline levels (Figure 1). There was a smaller increase in CVP after infusion of isotonic albumin solution (+ 3.9 ± 0.5 mmHg, *P* < 0.05). Following all infusions there was a similar trend for HR to decrease, reaching a minimum after 4–6 hours, but these changes were not significant (Figure 2). There were no significant changes in CO, stroke volume or total peripheral conductance with any of the infusions (Figure 2).

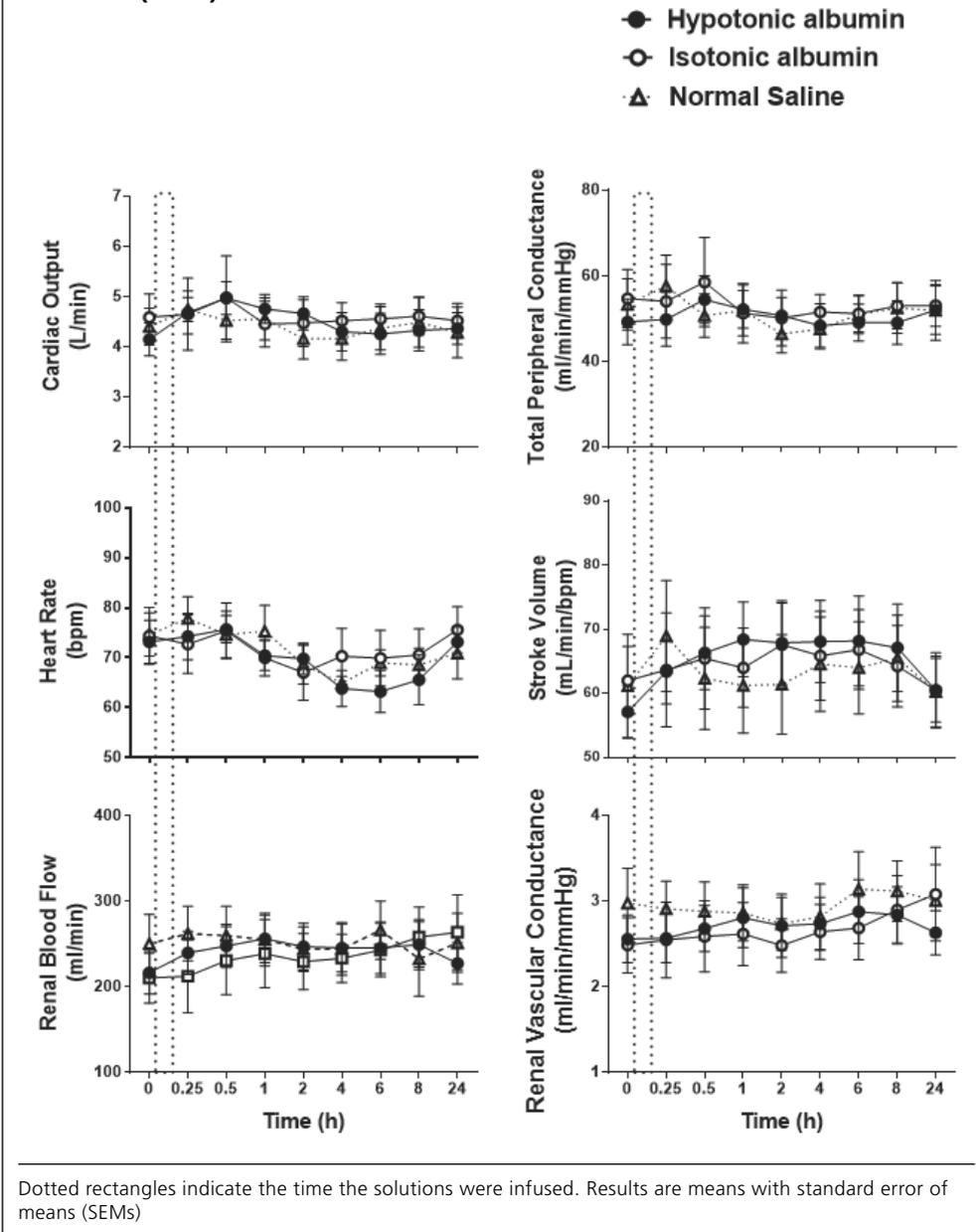## Renal and electrolyte changes after albumin infusions

There were no significant changes in RBF or renal vascular conductance after either albumin infusion compared with the changes after infusion of normal saline (Figure 2). The levels of plasma creatinine, creatinine clearance and plasma and urinary electrolytes were not significantly affected. During the study there were also no significant changes in plasma creatinine, creatinine clearance, and fractional excretion of sodium or in plasma levels of sodium or chloride (Figure 3).

Discussion

Key findings

We performed an experimental study in conscious instrumented sheep to test whether a commercial hypotonic 4% albumin solution (4% Albumex), used in the Saline

Figure 2. Cardiac output, total peripheral conductance, heart rate, stroke volume, renal blood flow and renal vascular conductance during a 1-hour baseline period (Time 0) and then up to 24 hours after infusion of study solutions (*n* = 6)

Dotted rectangles indicate the time the solutions were infused. Results are means with standard error of means (SEMs)

of a commercial hypotonic solution caused a substantial and sustained increase in ICP. Moreover, we found a greater increase in CVP with the commercial albumin solution, but no significant differences in the responses of other haemodynamic variables. Finally, we found no specific effect of albumin on RBF or renal function.

Relationship to previous findings

The mechanism of the effect of albumin on ICP as seen in the SAFE-TBI study has been unclear, but was hypothesised to be due either to the albumin molecule itself or to the low tonicity of the electrolyte solution containing albumin. Our study found that once the tonicity of the fluid containing albumin was modified to more closely simulate the tonicity of plasma, the increase in ICP was prevented and the ICP changes were the same as those seen with saline administration. This finding accords with the conclusion of the SAFE-TBI investigators, who suggested that a possible cause of the increase in ICP was due to rapid decreases in tonicity,[3] because the albumin preparation used in the SAFE study (4% Albumex) is hypotonic (260 mOsmol/L) and about 26 mOsmol/L less than 0.9% saline and normal plasma.[6] The current consensus statement on the use of colloid volume therapy in critically ill patients recommends that solutions other than albumin should be used in patients with head injury.[7] However, such recommendations do not take into account the nature and tonicity of the solution containing albumin. In fact, the most likely mechanism of increased mortality in these patients after resuscitation with albumin was the acute increase in ICP with albumin therapy that occurred

versus Albumin Fluid Evaluation (SAFE) study[1] and assessed in the SAFE-TBI study,[2] would increase ICP in healthy animals, and whether this effect would be prevented if the same albumin was given in a near isotonic solution or saline was given instead. We also simultaneously assessed the systemic haemodynamic effects of administration of a bolus of such albumin preparation fluid. Finally, we assessed the renal effect of albumin resuscitation compared with saline. We found that infusion of an isotonic albumin solution or saline caused no increase in ICP, but infusion

during the first week, as shown in a detailed post hoc analysis of ICP changes in monitored patients.[3] Consistent with this proposal, our study showed that infusion of hypotonic albumin solution caused a prolonged and sizable (8.5 mmHg) increase in ICP in normal animals, but there was no increase in ICP with isotonic albumin.

It is unlikely that either the tendency for arterial pressure to increase, or the significant increase in CVP after infusion of hypotonic albumin, played a role in determining the increase in ICP, because the time courses of these changes were entirely different. After infusion of hypotonic albumin solution, ICP gradually increased to reach a peak at 6–8 hours, but MAP and CVP reached maximum values at the end of the 15-minute infusion and then decreased. Changes in CVP and MAP in association with volume expansion with albumin administration are consistent with clinical experience and the findings of the SAFE study.[1]

Finally, to our knowledge, we are the first to report the effects of human albumin on RBF and renal function in a controlled experimental study in large animals. Our study does not support the use of albumin or saline to increase RBF or renal function in non-hypovolaemic states, as might be the case in insolated TBI.

Implications of findings

Our study implies that the increase in ICP in patients with TBI during the SAFE study using a commercially available hypotonic 4% albumin solution was not due to the albumin in the solution, but rather to the hypotonic nature of the solution. Moreover, our study implies that, even in a healthy brain, a modest decrease in the tonicity of fluid can cause major increases in ICP. Such increases are logically likely to be much more dramatic in the presence of TBI. In the aggregate, our observations suggest that even other relatively hypotonic fluids such as Hartmann's solution should be avoided in patients with TBI. Finally, our study implies that in non-hypovolaemic states, as might be seen in patients with isolated TBI, additional volume expansion with albumin or saline does not have discernible effects on RBF or renal function.

Strengths and limitations

Our study has several strengths. It addresses and resolves a phenomenon of clinical relevance that has not been fully explained. Studies were completed in conscious animals, without the confounding effects of anaesthesia. The infusion volume and rate (500 mL over 15 minutes) were clinically relevant.[1]

Our study has several limitations. There was a wide variation in baseline levels of

Figure 3. Plasma sodium and chloride, plasma creatinine and creatinine clearance, and urine flow and fractional excretion of sodium in conscious sheep during a 1-hour baseline period (Time 0) and then up to 24 hours after infusion of study solutions (n = 6)
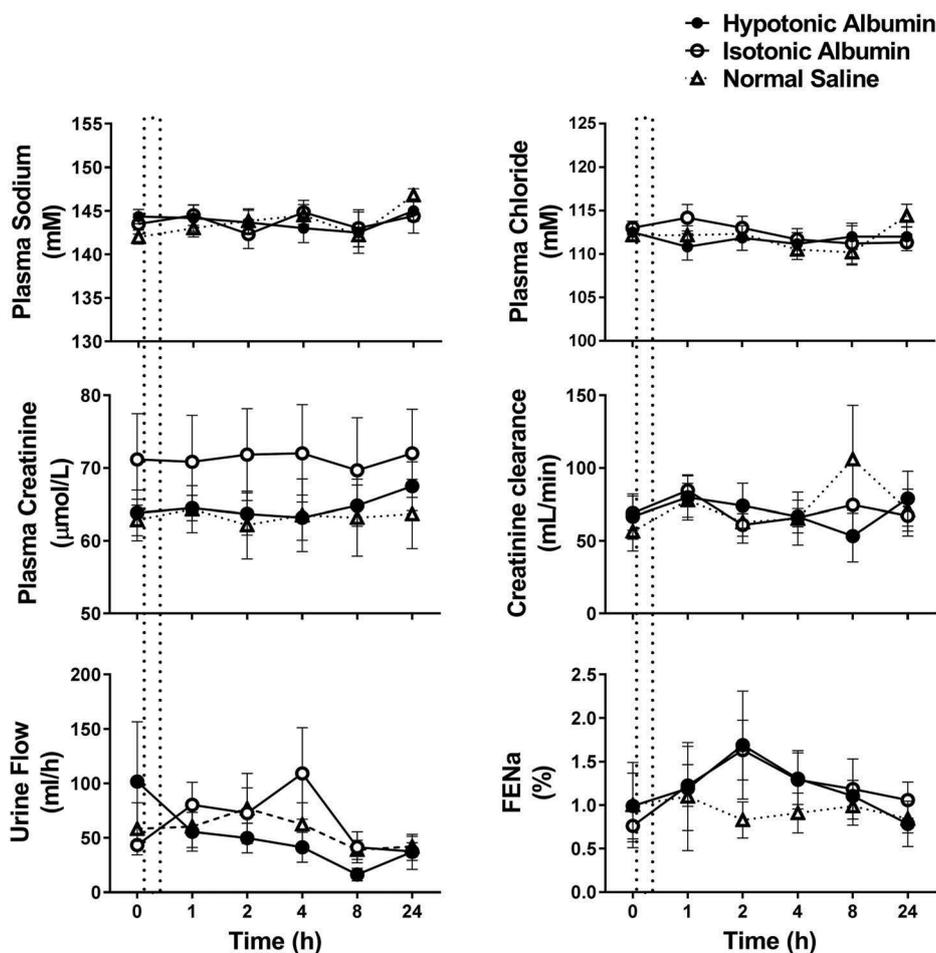
Dotted rectangles indicate the time the solutions were infused. Results are means with standard error of means (SEMs)

ICP (from 2.2 mmHg to 13.9 mmHg in individual animals), but this was similar to a study in healthy human subjects in which ICP varied from 7 mmHg to 15 mmHg.[8] This wide range was also found in the SAFE-TBI study, in which mean ICP in the albumin-treated group was 15.0 mmHg (SD, 12.9 mmHg) and in the saline group it was 12.4 mmHg (SD, 7.2 mmHg). Our study was conducted in healthy sheep; in critically ill patients there may be breakdown of the blood–brain barrier, which will lead to greater increments in ICP after infusion of hypotonic albumin solution. However, such a state of injury would only serve to magnify the effect seen in healthy animals. Finally, our observation of the effect of albumin administration on haemodynamics and renal perfusion and function were also seen in healthy animals, and may not apply to hypovolaemic trauma patients. However, they may apply to patients with isolated TBI.

Conclusions

This study shows that a commercial hypotonic albumin solution increased ICP in healthy animals, but infusion of an isotonic solution of 4% albumin or of saline did not increase ICP. However, neither albumin solution significantly increased cardiac output, mean arterial pressure or renal perfusion and did not affect renal function. Our findings support the notion that it was the tonicity of the albumin solution, rather than the albumin molecule itself that was responsible for the increased ICP and increased mortality seen in the SAFE-TBI study. Thus, in non-hypovolaemic states, such as might be seen in isolated TBI, albumin-based volume expansion does not carry physiological benefits.

Acknowledgements

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