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ORIGINAL ARTICLE

Randomized Controlled Trial Comparing the Effect of 8.4% Sodium Bicarbonate and 5% Sodium Chloride on Raised Intracranial Pressure after Traumatic Brain Injury

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Abstract
Background Hypertonic sodium chloride solutions are routinely used to control raised intracranial pressure (ICP) after traumatic brain injury but have the potential to cause a hyperchloremic metabolic acidosis. Sodium bicarbonate 8.4% has previously been shown to reduce ICP and we have therefore conducted a randomized controlled trial to compare these two solutions.
Methods Patients with severe traumatic brain injury were randomly allocated to receive an equiosmolar dose of either 100 ml of sodium chloride 5% or 85 ml of sodium bicarbonate 8.4% for each episode of intracranial hypertension. ICP and blood pressure were measured continuously. Arterial pCO_2, sodium, chloride, osmolality, and pH were measured at intervals.
Results We studied 20 episodes of intracranial hypertension in 11 patients. Treatments with 8.4% sodium bicarbonate and 5% sodium chloride reduced raised ICP effectively with a significant fall in ICP from baseline at all time points ($P < 0.001$). There was no significant difference in ICP with time between those episodes treated with 5% sodium chloride or 8.4% sodium bicarbonate, $P = 0.504$. Arterial pH was raised after treatment with 8.4% sodium bicarbonate.
Conclusions An equiosmolar infusion of 8.4% sodium bicarbonate is as effective as 5% sodium chloride for reduction of raised ICP after traumatic brain injury when infused over 30 min.

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Keywords Traumatic brain injury · Brain edema · Intracranial hypertension · Sodium bicarbonate · Saline solution · Hypertonic · Acidosis

Introduction

Hypertonic saline solutions are well established in the treatment of raised intracranial pressure (ICP) after severe traumatic brain injury (TBI) [1]. In a previous study, we demonstrated that hypertonic 8.4% sodium bicarbonate was effective at reducing raised ICP after severe TBI [2]. In this randomised controlled trial we compared the effects of an equiosmolar dose of 8.4% sodium bicarbonate with our standard treatment of 100 ml of 5% sodium chloride for the treatment of raised ICP after TBI.

Materials and Methods

This study was performed in the intensive care unit of a tertiary neurosurgical Ethics Committee for Wales (09/MRE09/34), and the Medicines and Healthcare Regulatory authority approved the use of 8.4% sodium bicarbonate solution in the study (Eudract 2009-012199-29).

Patients

Patients were recruited to the trial if they had suffered TBI requiring sedation, ventilation, and ICP monitoring. They were excluded if it was anticipated that they would be extubated or require surgical intervention within 24 h. Personal legal representatives gave assent for entry into the study. All patients were over 16 years old. Patients with established renal failure (creatinine >150% predicted), or

respiratory disease (history of chronic obstructive pulmonary disease) were not eligible for the study. Patients were also excluded if they developed acute lung injury (PaO_2/FiO_2 <200 mmHg).

After enrolment patients were treated in accordance with our institutional protocol for the management of raised ICP after TBI. Briefly, this includes sedation (Ramsay score 6) and ventilation, maintenance of cerebral perfusion pressure (60–70 mmHg), and then 4 sequential stages: Stage 1: use of osmotherapy (hypertonic saline, frusemide); Stage 2: hypothermia (down to 34°C as needed); Stage 3: hyperventilation (down to a PCO_2 of 4 kPa as needed); Stage 4: either thiopentone infusion and/or decompressive craniectomy. We do not routinely use transcranial Doppler, jugular venous oxygen saturation, or cerebral microdialysis and this data was therefore not collected in this study.

Intervention

For each episode of intracranial hypertension requiring osmotherapy (unprovoked ICP >20 mmHg for >5 min) patients were randomised to receive either hypertonic saline (100 ml 5% saline) or sodium bicarbonate (85 ml 8.4% sodium bicarbonate) each given via a central venous catheter over 30 min. The randomisation sequence was determined in blocks of 10 (5:5) and treatment allocations were kept in sealed opaque envelopes. The investigators were not aware of the treatment sequence. Blinding was not possible due to the volume difference.

Patients were studied for 6 h after each dose, monitoring ICP, mean arterial pressure (MAP), and cerebral perfusion pressure (CPP). Serial arterial blood samples measured pH, pCO_2, pO_2, sodium, chloride, and osmolality.

If patients failed to respond to a single dose they could receive a second dose (same allocation) within 6 h. If they failed to respond to a second dose they were removed from the study. If after 24 h patients required further intervention they were re-randomised to further treatment. The primary outcome measure was change in ICP after treatment. Secondary outcomes included changes in arterial pH, sodium, chloride, and venous osmolality.

Based on our previous work with 8.4% sodium bicarbonate we calculated that a total of 20 treatment episodes would need to be studied to reach statistical power of 80% at a significance level of 0.05 for changes in ICP. The study was not powered to compare clinical outcomes.

We used two way ANOVA for repeated measures for ICP comparisons between those episodes treated with 5% hypertonic saline and those treated with 8.4% sodium bicarbonate. We calculated a mean delta ICP (baseline ICP–ICP at 60 min post dosing) and compared this between groups with a *t* test. Data was analyzed using the SPSS package.

Results

Between October 2009 and May 2010, we obtained assent from 11 consecutive eligible patients who required osmotherapy (see Table 1).

We studied 20 episodes of raised ICP in the 11 patients (10 allocated to each treatment group). All patients were optimally sedated with propofol and alfentanil infusions prior to the use of osmotherapy (Ramsay score 6). Patients required between one and five treatment episodes each on separate days. No patients were excluded for failing to respond to a second dose of osmotherapy. Baseline variables (ICP, serum sodium, serum osmolality, arterial pH, and pCO_2) were not different between the treatment groups (see Fig. 1a–f). As expected mean pH was significantly increased compared to baseline in the bicarbonate but not the saline group. There were no significant changes in arterial pCO_2, pH, sodium, chloride, or serum osmolality (see Fig. 1b–f)

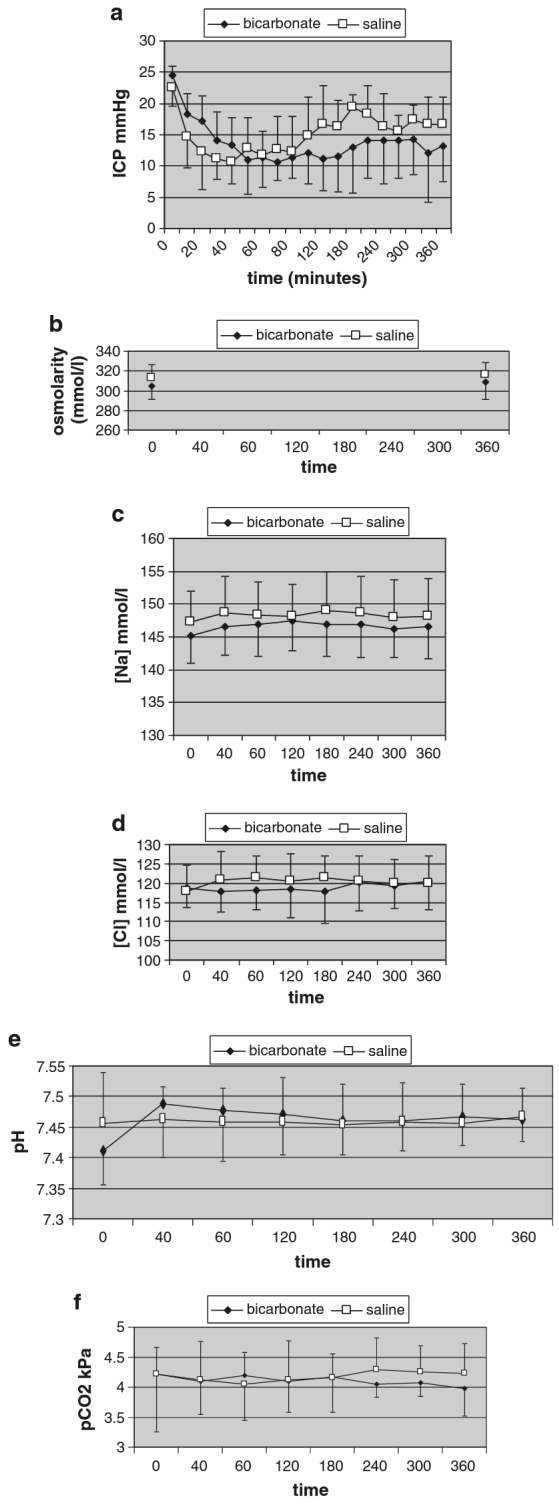
Intracranial pressure (ICP) fell below 20 mmHg after 30 min in all treatment episodes. Treatment was considered effective in all episodes although two patients treated with 5% saline required a second dose (as per protocol) within the 6 h study period.

Analysis of the data using a 2 way ANOVA with epsilon adjusted values of the *F*-statistic indicates that there was a statistically significant fall in ICP from baseline at all time points, $P < 0.001$. Overall there was no significant difference in ICP with time between those episodes treated with 5% sodium chloride or 8.4% sodium bicarbonate, $P = 0.504$ (see Fig. 1a). The delta ICP (mean (SD)) at 60 min was 12.1 (4.1) mmHg for bicarbonate and 10.1 (5.1) mmHg for hypertonic saline (difference not significant). However, after 150 min mean ICP was higher in the hypertonic saline group when compared to the bicarbonate group ($P < 0.05$, *t* test).

The overall hospital mortality was 27.3% which is consistent with that predicted for this patient population (severe traumatic brain injury +\− extracranial injury) in our unit.

Discussion

This prospective randomised controlled trial demonstrates that an equiosmolar dose of 8.4% sodium bicarbonate is as effective as 5% sodium chloride for the reduction of raised ICP after TBI. Although we identified a greater response in the bicarbonate group after 150 min, we would be cautious as to the interpretation of this in the light of the relatively small numbers in this study and concerns about the use of a t test for repeated measures.



◀ **Fig. 1** **a** Intracranial pressure against time, **b** osmolarity against time, **c**, serum sodium against time, **d** serum Chloride against time, **e** arterial pH against time, **f** arterial partial pressure of carbon dioxide against time

Several studies have examined the use of alternative hypertonic sodium solutions for control of raised ICP after TBI. Qureshi et al. [3, 4] demonstrated the effectiveness of hypertonic sodium chloride/acetate for reducing raised ICP in a number of studies. Ichai et al. [5] proved that a hypertonic sodium lactate solution was more effective than an equimosmolar dose of mannitol for ICP reduction with a trend to improved outcome. It has been recognized for over 90 years that hypertonic sodium bicarbonate causes a reduction in CSF pressure and brain bulk [6, 7], but to our knowledge we are the first group to have studied its effects on raised ICP in humans after severe TBI.

Hypertonic saline is thought to reduce ICP by a number of mechanisms including osmotic, hemodynamic and vasoregulatory. Sodium does not cross the blood brain barrier and exerts an osmotic effect on brain parenchyma causing dehydration of brain tissue. A study in neonatal dogs found that infusion of hypertonic sodium bicarbonate caused a significant reduction in brain water content [8]. The sodium dose was identical between our two treatments and we presume that sodium bicarbonate reduces ICP with a similar mechanism to sodium chloride.

A potential advantage of hypertonic sodium bicarbonate infusion is the avoidance of a hyperchloremic metabolic acidosis that is often the consequence of repeated dosing with hypertonic saline. The clinical significance of hyperchloremic metabolic acidosis is debated but hypertonic sodium bicarbonate may represent a useful alternative treatment for raised ICP in those patients with an established acidosis. A further study using repeated dosing would be required to assess the acid base changes of repeated doses.

The optimal dose or composition of hypertonic saline solution is not clear from available evidence. A dose of 100 ml of 5% sodium chloride is used in our unit. There is no reason to suggest that different concentrations of saline solution (e.g., 3% sodium chloride) would behave any differently when compared in an equimolar dose to sodium bicarbonate.

This study has several limitations. First, it was impossible to blind the treatments due to different volumes of infusion between treatments. The randomization sequence was concealed and therefore selection bias should have been minimized. The patients received doses of hypertonic saline or hypertonic saline in a random order, some having both. This may result in cross over effects between treatments. Only one study treatment was permitted per 24 h in order to reduce the likelihood of these cross over effects.

Table 1 Baseline characteristics

Patient number	Age	Unit outcome	Hospital outcome	GCS	Mechanism of injury	Extra cranial injuries	Ventriculostomy	Time to randomise (days)	Baseline creatinine (mmol/l)	Marshall score
1	23	Survived	Home	7	RTA	Nil	y	5	75	2
2	34	Survived	Rehabilitation	7	RTA	Splenic rupture	y	2	45	3
3	27	Died	Died	6	RTA	Pulmonary contusion	y	3	69	2
4	42	Survived	Rehabilitation	6	Fall	Nil	n	3	61	4
5	43	Survived	Home	8	Fall	Nil	n	4	70	2
6	61	Survived	Died	12	RTA	nil	n	7	101	4
7	33	Survived	Rehabilitation	7	Fall	Facial fractures	n	1	67	2
8	62	Survived	Rehabilitation	3	RTA	Pelvic fracture	n	2	65	4
9	18	Survived	Home	14	RTA	Nil	n	1	58	1
10	42	Died	Died	8	Fall	Nil	n	1	77	3
11	36	Survived	Rehabilitation	6	RTA	Nil	n	6	63	4

The study was not designed or powered to compare outcomes or to identify differential response to therapy between different injury subgroups.

Conclusion

Infusion of hypertonic sodium bicarbonate is as effective as hypertonic saline for the reduction of raised ICP after severe TBI. We would not advocate replacing hypertonic saline but hypertonic sodium bicarbonate could be used as an alternative to hypertonic saline in patients with established hyperchloremic metabolic acidosis. These results merit further study in large multi-center trials examining dose and effect on outcome.

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