Salines, Osmoles and Albumin

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ABSTRACT

In 2004, two large randomised multi-centre Australian clinical trials provided new information concerning optimal resuscitation for patients with traumatic brain injury (TBI). One examined hypertonic saline (HTS) and the other, albumin versus saline.

For the first time in a randomised trial, hypertonic saline was tested for pre-hospital resuscitation of hypotensive patients with traumatic brain injury, and for the first time a resuscitation fluid trial measured long term neurological function as the primary outcome. Despite many potential advantages which may have much greater relevance in the hospital setting, in the paramedic based Victorian trauma system, HTS did not improve neurological outcome compared to conventional pre-hospital fluid protocols. Nevertheless, HTS resuscitation was confirmed to be safe in TBI patients and may find application in future pre-hospital military settings where fluid weight is of primary importance.

The very large randomised SAFE trial found that there was no difference in 28 day survival between albumin and saline resuscitation for intensive care patients, and by providing very high quality data, this study has largely settled a generation old controversy. Intriguingly however, the SAFE study also reported that within a subgroup of 492 patients with TBI, 28 day survival was superior in patients receiving saline. This subgroup result was not considered definitive, but a post hoc examination of the TBI patients currently in progress by the SAFE investigators, is expected to provide further guidance for clinicians. In the meanwhile, and until more high quality data is available, many clinicians are likely to prefer crystalloid resuscitation for trauma patients, and especially for trauma patients with brain injury. (**Critical Care and Resuscitation 2005; 7: 177-180**)

Key words: Hypertonic saline, albumin, resuscitation, head injury, review

In 2004, the state of knowledge concerning optimal fluid resuscitation for patients with Traumatic Brain Injury was advanced by the publication of two large randomised multi-centre Australian trials. One examined hypertonic saline[1] and the other, albumin and saline.[2]

The background to the hypertonic saline trial was that patients with traumatic brain injury (TBI) were the major contributors to mortality in trauma patients generally and they also had poor neurological outcomes which had improved little either in Australia or internationally for many years. Many TBI patients also had pre-hospital hypotension which was known to worsen cerebral perfusion and secondary brain injury. It seemed likely that more efficient pre-hospital resuscitation might restore cerebral perfusion more quickly, decrease secondary brain injury and improve long term neurological function. Hypertonic saline both alone and combined with dextran, had been studied in previous randomised trials for pre-hospital resuscitation of trauma patients.[3-5] None had confirmed a hospital survival advantage, but most had reported encouraging trends.

Hypertonic saline expands intravascular volume by much larger amounts than the volumes infused, and so HTS had potential to restore cerebral perfusion more

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quickly than isotonic cystalloids. At the same time, HTS decreases cerebral edema by shifting water out of brain cells, so HTS was unlike other resuscitation fluids in that it may improve cerebral perfusion without aggravating cerebral edema. Furthermore, the safety profile of single dose 250 ml 7.5% HTS either combined or not with Dextran 70 to prolong duration of action, had been clearly established.[6]

Prior to 2004, HTS resuscitation had not been tested specifically in TBI patients, but improved hospital survival had been suggested by 2 post hoc subgroup analyses in TBI patients,[4,5] and by a cohort analysis of TBI patients from previous randomised trials of HTSDextran in trauma patients with and without TBI.[7] These papers encouraged design and funding of the first, double-blind, randomised controlled trial of pre-hospital hypertonic saline resuscitation specifically for TBI patients, and the first to measure long term functional neurological outcomes. Over 3 years in Victoria, Australia, Cooper *et al*.[1] randomised 229 patients to receive an identical bag of 250 mL of either 7.5% saline or Hartmann's solution in addition to standard resuscitation fluids. The patients had non-penetrating traumatic coma (blunt head injury and a Glasgow coma score of less than 9) and hypotension (systolic blood pressure < 100 mmHg) and patients with multi-system trauma were included. Randomisation was in blocks of four and was stratified by ambulance road car. Treatment allocation was concealed and pre-hospital personnel, hospital staff and outcome assessors were blinded. Paramedics infused the study fluid in addition to their usual protocols (including Hartmann's solution or Hemaccel®). Each patient's neurological outcome was measured 6 months after injury by an extended (8 grade) Glasgow Outcome Scale score obtained by a single trained assessor who used a standardised structured questionnaire.

The main results were that the two groups were equivalent at baseline with a median injury severity score of 38. Both groups received a median of 1250 mL of intravenous crystalloid and colloid resuscitation fluids in addition to their study fluids. Pre-hospital hypotension had been corrected equally in both groups on arrival at hospital. The patients receiving hypertonic saline had increased serum sodium at hospital admission which was maintained for the first 12 hours of hospital admission. They required a shorter duration of inotropic support ($P = 0.03$), and there was a trend to a lower intracranial pressure ($P = 0.08$) and more adequate cerebral perfusion pressure ($P = 0.06$). However, the median Glasgow Outcome Scale score at 6 months after injury, was unequivocally the same in both groups ($P = 0.45$) and the proportion of patients with favourable neurological outcomes at 6 months was also the same ($P = 0.96$). An encouraging trend towards increased survival at 6 months in those treated with hypertonic saline (55 versus 47%) ($P = 0.23$) was unfortunately balanced by an equivalent and discouraging trend to an increased number of survivors with severe disability.

This meticulous trial found that pre-hospital resuscitation with hypertonic saline did not improve functional neurological outcomes in severely injured multi-trauma patients with brain injury. The study had 80% power to identify a 20% (one grade) change in the extended Glasgow Outcome Scale score grade and found no advantage for hypertonic saline. Pre-hospital hypertonic saline resuscitation produced potential short-term benefits in relation to improved cerebral perfusion pressure and also to shorter duration of inotropic supports. However, the trial also pointed to a potential for harm, in a trend for an increased number of patients given hypertonic saline surviving with severe disability. Hypertonic saline did not improve functional outcomes and cannot therefore currently be recommended for pre-hospital resuscitation of patients with traumatic brain injury in an established metropolitan trauma system.

Hypertonic saline was previously known to be safe for trauma patients in general and in this study was found to be safe for hypotensive patients with TBI. Accordingly, the military continue to have great interest in hypertonic saline internationally for battlefield resuscitation where the actual weight of resuscitation fluids is of paramount importance. In 2005 this interest had fuelled very substantial NIH funding for a more than 3,000 patient randomised American trial of pre-hospital HTS and HTS-Dextran resuscitation for hypotensive TBI patients.

The second major trial (SAFE) of albumin versus saline[2] was conceived against a generation long controversy concerning the relative merits of colloids and crystalloids for resuscitation of critically ill patients. The controversy continued in part owing to the absence of large, high-quality, randomised controlled trials focused on appropriate patient-centred outcomes. This absence caused the rigour and relevance of meta-analyses summarising the existing trials[8-11] to be questioned. There was ambiguity about what importance to attach to studies examining the short-term effects of different fluid regimens on physiological variables and other surrogate outcomes, which might not correlate with major morbidity or mortality in the ICU setting.[12]

All of these issues were as relevant to trauma and brain injury patients as they were to other critically ill patients, and enabled exactly opposite views about optimal resuscitation fluids to be held by different clinicians. Advocates of crystalloid solutions for

resuscitation of critically ill patients noted that they were less expensive and carried a minimal risk of anaphylaxis or the transmission of infectious agents. Those favouring colloids countered that resuscitation with colloids required less volume, less resuscitation time and may be less likely to cause pulmonary and peripheral oedema. Both groups of enthusiasts had lacked large, randomised controlled trials to support their positions.

In 1998 and 1999 two meta-analyses from industry-independent research groups addressed the crystalloid versus colloid controversy.[8,9] Schierhout and Roberts concluded that colloid resuscitation was associated with a 4% (24 versus 20%) absolute increase in mortality when compared to crystalloid, with no evidence of differing effects in populations with different types of injury. Choi *et al*,[9] limited their meta-analysis to trials that compared isotonic crystalloids and colloids, reviewed 17 randomised controlled trials and found no difference in morbidity or mortality. Importantly however, in five trials including 302 trauma patients, crystalloid resuscitation was associated with decreased mortality (RR = 0.39 and 95% CI = 0.17–0.89).

In 1998 the Cochrane Injuries Group Albumin Reviewers also specifically challenged assumptions about the efficacy and safety of albumin.[10] Their meta-analysis of 30 randomised controlled trials concluded that, compared to crystalloid or no fluid, the administration of albumin-containing fluids to patients with hypovolaemia, hypoalbuminaemia and/or burns resulted in a 6% absolute increase in mortality (95% CI = 3–9%). This publication generated great interest, but did not separately consider patients with trauma or traumatic brain injury.

The SAFE Study investigators randomised 6997 patients to receive either normal saline or 4% albumin for all fluid resuscitation in the ICU and randomisation was stratified for presence or absence of trauma, in part owing to the earlier meta-analysis[9] which had found likely advantage for crystalloid resuscitation of trauma patients. Treating clinicians and patients were prevented from knowing which fluid was administered by the use of specially designed and manufactured masking cartons and administration sets. Almost all hypovolaemic patients were eligible with only patients admitted to the ICU following cardiac surgery, liver transplantation or burns excluded. The primary outcome was all-cause mortality within 28 days of randomisation and was also reported in six pre-defined subgroups including patients with and without trauma. The groups were well matched at base-line and vital status 28 days after randomisation was available for 6930 (99.0%) patients. The ratio of volume of study albumin to study saline administered over the first four days was 1:1.4. The two groups were resuscitated to similar clinical endpoints and as was anticipated, serum albumin concentration was higher in the albumin group throughout the study period.

Overall, the two groups had similar 28-day mortality; albumin 20.9% and saline 21.1% (RR 0.99, 95% CI, 0.91 – 1.09), and there was no difference in any of the secondary end-points. However for the 1186 trauma patients in SAFE, the relative risk of 28-day mortality for albumin versus saline was 1.36 compared with a relative risk for non-trauma patients of 0.96, (P = 0.04 for test for a common relative risk). The increased relative risk of death in patients with trauma was due to an excess of deaths in patients with trauma and brain injury (mortality: albumin 24.5%, saline 15.1%. RR 1.62, 95% CI 1.12–2.34; P = 0.009). For trauma patients overall, there were 81 (13.6%) deaths in the albumin group versus 59 (10.0%) in the saline group, (RR 1.36, 95% CI 0.99–1.86; P = 0.06).

The SAFE study findings in trauma patients and particularly in traumatic brain injury patients have sounded a strong note of caution to clinicians concerning albumin resuscitation, but the SAFE findings in these subgroups, are not of themselves definitive. There are several reasons for this. First, although trauma was a large (1196 patients) apriori stratified subgroup within the SAFE study, traumatic brain injury was not. It is therefore possible that baseline imbalance occurred within SAFE for severity of TBI -which favoured patients who had received crystalloids. Such an imbalance could conceivably also have accounted for the whole trauma patient subgroup finding favouring crystalloids. It is also possible that the somewhat atypical definition of TBI used in SAFE (history of trauma, Glasgow coma score < 14, and an abnormality consistent with TBI on CT head scan) may have in some way contributed to baseline imbalance. Finally, the primary SAFE study outcome of 28 day mortality was not optimal for TBI patients, in whom a longer term functional outcome score is desirable. These issues are currently being addressed by the SAFE study investigators in a formal evaluation of the TBI patient cohort from the SAFE study. This evaluation will include a long term (2 year) neurological outcome score for all the evaluable patients. Until this detailed post hoc analysis of TBI patients from SAFE is completed and published, many clinicians will likely chose to withhold albumin and other colloids during resuscitation of trauma patients - particularly when the primary SAFE study results clearly did not favour either solution.

These two large Australian trials have advanced the current state of knowledge concerning resuscitation for patients with traumatic brain injury. Hypertonic saline

has many potential advantages and will continue to be used as one component of treatment regimens for intensive care patients with intractable intracranial hypertension. However, hypertonic saline cannot now be recommended for pre-hospital resuscitation of hypotensive blunt TBI patients within a well established trauma system with relatively long transport times. The undesirable trend towards increased survivors with severe disability after hypertonic saline[1] will also sound a salutary note of caution until further high quality data are available. The SAFE study trauma subgroup analysis[2] suggested that albumin resuscitation may be harmful for patients with TBI, but the finding was not definitive. Although a pathophysiological mechanism for this startling finding is not immediately clear, clinicians will likely adjust their practice in favour of the potentially safer and cheaper alternative therapy for trauma patients whilst awaiting further reporting on the issue from the SAFE study investigators.

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