

Hypertonic Saline Resuscitation for Head Injured Patients

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ABSTRACT

Objective: To discuss the reasons why 250 ml 7.5% hypertonic saline was chosen as a pre-hospital resuscitation fluid for head injured patients in a multicentred, prospective, randomised controlled trial investigating its long term effects on central nervous system outcome.

Data sources: Recent published peer-review articles on the incidence and mechanisms of traumatic head injury and clinical use of hypertonic saline in pre-hospital resuscitation of trauma.

Summary of review: Head injury is commonly associated with major trauma and if hypotension also exists the morbidity and mortality due to cerebral injury are high. Hypertonic saline has been used in clinical practice to treat cerebral oedema and resuscitate burns patients following experimental evidence that it reduces tissue oedema, improves blood flow to damaged organs and may reduce the incidence of multiple organ dysfunction, when compared with resuscitation using isotonic solutions. In pre-hospital trauma patients, initial resuscitation using hypertonic saline rather than conventional isotonic solutions has the potential advantage of requiring a small volume of fluid that is easily stored and administered, and may improve cerebral circulation and reduce the long term neurological effects that are determined by pre-hospital hypovolaemia and hypotension.

To answer the question whether hypertonic saline will improve the outcome in trauma patients with hypotension and head injury, a multicentred, randomised controlled trial comparing 250 ml of 7.5% hypertonic saline (320 mmol) with 250 ml of Hartmann's solution (32 mmol) in pre-hospital resuscitation of trauma patients with a Glasgow coma score < 9 and systolic blood pressure < 100 mmHg, began in 1998 and is anticipated to be completed by 2001.

Conclusions: Pre-hospital resuscitation of head injured and hypotensive trauma patients using hypertonic saline, has the potential to reduce long term cerebral injury and reduce social and financial costs to the community. (**Critical Care and Resuscitation 1999; 1: 157-161**)

Key words: hypertonic saline, trauma, brain injury, resuscitation, hypotension, cerebral oedema, randomised clinical trial

Head injury is common in patients with major trauma, occurring in 50% of 400 major trauma patients admitted to the Alfred Hospital Trauma Centre in 1998. It has been estimated that 10,000 people are disabled annually in Australia as a result of head injury and 1500 are markedly disabled.¹ Despite best management, these patients have a high mortality with only 50-65% survival reported from Europe and United States of America,^{2,3} although survival may be better in Australia where there are less penetrating injuries, with 69% survival being

reported in a recent New South Wales study.⁴

However, in Victoria, 79% of road trauma patients who die after the arrival of an ambulance have head injury, and in 58% of cases the head is the major site of trauma.⁵ Patients who survive have a high morbidity with up to 14% of cases being either severely disabled or vegetative. Head injury also imposes a high financial cost to the community. In Victoria each severe head injury survivor is estimated to cost approximately \$500,000 - \$750,000.⁶ Thus any intervention which

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might conceivably improve the outcome has the potential to produce major social benefits as well as cost savings to the community.

SECONDARY BRAIN INJURY

Hypotension

Secondary brain injury (occurring after the primary insult) is potentially reversible. There are many factors which contribute to its formation, but hypotension is a key factor as it predicts a poor outcome, yet is amenable to modification.⁷ Recent studies have consistently identified hypotension as the predominant cause of secondary brain injury during both pre-hospital and intensive care periods of management.

Post injury hypotension causes ischaemic brain injury and in one review was observed in 90% of head injury fatalities.⁷ In one North American review of patients with traumatic coma, hypotension was associated with an increased morbidity and a doubling of mortality (up to 75%).⁷ Increased mortality has been reported following both pre-hospital hypotension⁸ and hypotension at hospital arrival.³ Similarly, in the New South Wales study, patients with traumatic brain injury and coma, pre-hospital hypotension predicted a 42% mortality compared with a 27% mortality when the blood pressure was normal.⁴

The injured brain is sensitive to ischaemia, and therefore hypotension due to hypovolaemia is considered the most important extra cerebral factor affecting outcome after traumatic brain injury (TBI). In the United States Traumatic Coma Data Bank, mortality from TBI was doubled in the presence of haemorrhagic shock.⁷ In the New South Wales study, hypotension was one of three independent factors that predicted poor neurological recovery.

Although conclusive evidence that correcting pre-hospital hypotension improves outcome is lacking, reversal of causes of secondary brain injury in the field has been associated with a 42% decrease in the frequency of poor outcomes (e.g. death, vegetative survival, or severe disability) at 3 month follow up.⁷ Consequently the rapid treatment of hypovolaemia and hypotension at the site of the accident before reaching hospital is now considered to be a key factor in improving the outcome of trauma patients. In support of this concept, trauma management systems which include advanced prehospital care and treatment of hypotension, have been associated with a decrease in deaths attributable to head injury.^{7,9}

Cerebral oedema

In patients with head injury, cerebral oedema also contributes to secondary brain injury by increasing intracranial pressure, and was also associated with

higher mortality in the New South Wales study.⁴

Several studies in head injured patients managed in intensive care with intracranial pressure monitoring, have supported the view that control of intracranial pressure improves outcome.⁵ It is not known whether minimisation of pre-hospital cerebral oedema might also improve outcome, but the hypothesis would seem to be reasonable.

By contrast, mildly hypotonic conventional resuscitation fluids like Hartmann's solution might increase brain oedema when used to correct hypotension during traumatic haemorrhage.

TREATMENT

Resuscitation

Presently in Victoria, hypotensive trauma patients are resuscitated using either intravenous Hartmann's solution and/or 3.5% gelatin solution (Hemaccel®). Both solutions have practical advantages as they are stable under varying conditions, but the volumes that can be realistically administered through a peripheral vein are often inadequate to restore blood pressure and cerebral perfusion to optimal levels in patients who have head injury.

It is also uncertain whether synthetic colloids (which may be able to restore the intravascular volume faster) or crystalloids (being cheaper and having less adverse reactions) are preferable in trauma patients. Two major recent meta-analyses have heightened the debate but also added to the uncertainty by arriving at very different conclusions.^{10,11} The Victorian Metropolitan Ambulance Service has decided not to change their protocols until clear evidence one way or the other is available.

Cerebral perfusion pressure

In intensive care units, interventions to maintain cerebral perfusion pressure above predetermined targets are widely accepted during the first days after TBI, although maintaining these target values after this time is controversial.

Unfortunately however, significant secondary brain injury with significant associated morbidity may already have occurred at the road side and during transport to hospital – well before an arterial line, central line or ICP monitor can be inserted and effective blood pressure and cerebral perfusion pressure restoration commenced.

Hypertonic saline

Intravenous hypertonic saline (HTS) has for many years been one of the measures used by some Intensivists to counter raised intracranial pressure.¹² It increases cerebral perfusion and decreases brain

swelling more effectively than conventional resuscitation fluids.¹³

Hypertonic solutions extract fluid from cells and expand intravascular volume by considerably more than the volume infused. For example, the combination of 7.5% HTS and dextran expands the blood volume by 3-4 times the infused volume.¹³ Hypertonic saline 7.5% expands intra-vascular volume about 10 times more than the equivalent volume of 0.9% saline. Restoration of intravascular volume and myocardial preload is therefore likely to be much faster and more complete with HTS than with conventional fluids.

Furthermore, because pre-hospital conditions may make infusion targets difficult to achieve, the relatively small volumes of HTS required (e.g. 250 ml) may make effective resuscitation more achievable at the accident site and during transport. In animal models and in both phase II and III studies of patients with traumatic hypotension, HTS increased blood pressure more effectively than conventional fluids.¹³

It also counteracted the cellular oedema of shock, by shifting fluid from the intracellular to the extracellular compartment, and decreased intracranial pressure in both animals and TBI patients.^{12,13} In this respect HTS behaves like 20% mannitol which is often used in patients with acute cerebral oedema to reduce brain swelling. However, unlike HTS, mannitol induces a diuresis which is relatively contraindicated in patients with both TBI and hypovolaemia as it may worsen intravascular volume depletion and decrease cerebral perfusion.

Potential advantages

During the early resuscitation of patients with TBI, HTS rapidly restores intravascular volume, increases blood pressure, and decreases intracranial pressure. Cerebral perfusion pressure, cerebral blood flow and cerebral function of survivors may be improved.

Hypertonic saline has other advantages for pre-hospital resuscitation, compared with conventional resuscitation fluids. For example:

- the established pre-hospital infusion volume of 7.5% HTS is 250ml. This volume is easy to transport, and may be infused rapidly by peripheral intravenous catheters, to provide equivalent efficacy of up to 10 times the volume of other fluids.¹³
- despite rapid infusion rates, HTS has an established safety record. No adverse reactions have been reported in human studies using the recommended dose (i.e. 4 ml/kg of 7.5% HTS in 250 ml). In 1993 it was reported that more than 600 patients had received HTS in clinical trials from one institution with no significant adverse reactions reported.¹⁴ Despite frequent usage in patients with penetrating

trauma, no suggestion of increased bleeding has been reported.¹³

- HTS is cheap, and (being an uncomplicated salt solution) is not patentable. Paradoxically this feature may also be the reason why it is difficult to generate company support for clinical trials in the United States of America, and perhaps why a pharmaceutical industry initiated cessation of clinical trials occurred before efficacy in patients with hypotension could be determined (Chesnut R, personal communication 1998).
- In addition to improved cerebral circulation, HTS improved regional blood flow to renal and mesenteric vascular beds and decreased injury to lungs and liver during hypovolaemic shock, complicated by experimental sepsis.¹⁵ These benefits may result from HTS decreasing endothelial oedema and improving capillary blood flow more effectively than alternative solutions.¹⁶ It is conceivable that HTS might also improve cardiac diastolic dysfunction which may be worsened by myocardial oedema and may be a determinant of patient survival during severe hypovolaemic shock.¹⁷
- Finally HTS may have anti-inflammatory properties and may decrease white blood cell adherence to capillary endothelium in all important microcirculatory beds.¹⁸ It may therefore reduce the incidence of multiple organ dysfunction syndrome.

Potential disadvantages

Potential adverse effects of HTS have been carefully assessed and excluded, with one group concluding that "Extensive toxicological evaluations and lack of reports of adverse effects in the human trials indicate that the proposed therapeutic dose of 4ml/kg of 7.5% HTS should present little risk".¹³ The dose 4 ml/kg was chosen to avoid peripheral vascular irritation, excessive hypernatraemia, and potential neurological sequelae, none of which have been reported in multi-centre clinical studies including large numbers of trauma patients.

Animal studies report an increase in serum sodium concentration of 12 mmol/L after 4 ml/kg of 7.5% HTS,¹³ with the maximum tolerated dose 4-5 times the therapeutic dose. Recent safety studies using 5 times the proposed therapeutic dose have demonstrated no significant adverse effects.¹⁹

In clinical studies in trauma patients, after 250 ml of 7.5% HTS, the mean serum sodium concentration was 151 mmol/L, and the highest serum sodium concentration was 155 mmol/L.²⁰ This concentration is commonly targeted in critically ill patients with raised intracranial pressure. Venous thrombosis or tissue necrosis from extravasation from intravenous drips have

not been reported and in the concentration of 7.5% does not damage peripheral veins.¹³ The high sodium load in elderly patients with impaired cardiac function might worsen congestive cardiac failure, however this has not yet been reported.

The effect of HTS on coagulation has also been questioned. In the experimental animal with uncontrolled haemorrhage, bleeding was exacerbated during resuscitation when HTS was used.²¹ However, clinical studies, including large numbers of patients with penetrating trauma, do not support this concern, as increased bleeding has not been found in patients receiving HTS.^{14,20} Convulsions and hyperchloraemic acidosis are possible side effects with HTS, but neither have been reported in trauma patients. Hyperchloraemic acidosis may occur with HTS but lactic acidosis is simultaneously reduced due to an improvement in resuscitation.

Three multicentre, prospective, randomised clinical trials of HTS for pre-hospital resuscitation involving more than 50 patients have been reported.^{14,20,22} Each study enrolled patients with hypotension rather than focussing on the patients with head injury or decreased Glasgow coma score (i.e. those who may be most likely to benefit). None of the studies were designed to determine post hospital neurological function in the survivors. Vassar *et al.*,²⁰ reported 166 patients from a helicopter retrieval service and found a small increase in survival from 59% to 64% with HTS and Dextran 70 compared with Ringers Lactate (i.e. Hartmann's solution). Two years later the same group¹⁴ reported 233 patients from a planned 600 patient study from 6 trauma systems but divided into 4 study arms. Survival increased from 49% to 60% with HTS (but did not reach significance) although it was significantly better than that predicted by injury severity scores. Post hoc analysis of the patients entering the trial with a Glasgow coma score (GCS) < 9 revealed a significant improvement in mortality in those receiving HTS (i.e. 12% to 34%).

Mattox *et al.*,²² reported 359 patients from 3 American states. Safety was established but there were no significant survival differences reported (e.g. 80% vs 83%). In 1997 Wade *et al.*,²³ extracted 222 patients with TBI from earlier preclinical studies of HTS in a meta-analysis. Survival increased from 26.9% with placebo to 37.9% ($P < 0.05$) with HTS and dextran.

One may conclude from these studies that HTS is safe and likely to improve outcome in trauma patients with hypotension and head injury. However, the hypothesis remains unproven. In 1995, Chesnut stated that "A prospective, multi-centre, randomised controlled trial is needed to establish the utility of hypertonic saline resuscitation in decreasing mortality and morbidity in

severe head injury patients"⁷. Currently, HTS is not used as a routine pre-hospital resuscitation solution.

HYPERTONIC SALINE STUDY

In December 1998 a multi-centre, randomised, pre-hospital clinical study designed to answer the question 'does hypertonic saline resuscitation improve long-term neurologic outcome in severe head injury patients' commenced in metropolitan Melbourne. The study objectives were to prospectively define pre-hospital adult patients most likely to benefit from HTS as those with traumatic coma (GCS < 9) and hypotension (systolic blood pressure < 100 mmHg) and to compare standard pre-hospital treatment protocols with standard treatment plus a single rapid intravenous dose of 250 ml 7.5% hypertonic saline (containing 320 mmol of sodium). Patients were enrolled by ambulance officers as soon as they satisfied entry criteria, and received the study solution before they reached hospital.

The study is controlled using an identically appearing 250 ml bag of Hartmann's solution (containing 32 mmol of sodium), prospectively randomised and grouped by ambulance base to equalise numbers in each group at each of the receiving hospitals. All study participants are blinded except the statistician, who is not involved in patient management but holds the randomisation codes. All 11 hospitals in metropolitan Melbourne which receive trauma patients are participating, but in practice (and reflecting prevailing triage practices), 60 % of the patients are managed at the Alfred Hospital Trauma Centre. Unlike all previous studies of this type, neurological outcome scores will be measured on all patients up to 6 months after hospital discharge. The primary end point will be the 3 month post injury Glasgow outcome score.

Pre-study sample size calculations indicated that a one grade (i.e. 20%) change in Glasgow outcome score could be identified with 220 patients, including 110 patients in each arm of the study. Estimates based on existing data bases, coupled with a 6 month pilot study indicated that there would be about 100 eligible patients per year in metropolitan Melbourne. A 3 year study enrolling, at a conservative estimate, seventy patients per year was then planned. Enrolments in the first three study months are consistent with this target. Sample size analyses indicate that the study is unlikely to confirm a difference in patient mortality (at least 400 patients would be needed to realistically reach this conclusion). However the patients final neurological outcome grade may be the more important factor, being directly related to cost, impact on community, and on capacity to return to work. Cost implications will be quantified by accessing the Victorian Transport Accident Commission database for road trauma patients.

The study is projected to run until end 2001. It received 'start up' funding first from the Australian and New Zealand Intensive Care Society, then from the Neurosurgical Research Foundation and from the Alfred Hospital.

Published evidence available to date is consistent with the study hypothesis: 'In trauma patients with coma and hypotension, early pre-hospital administration of hypertonic saline will improve long term neuro-logical outcome compared with otherwise identically managed patients treated with standard trauma management protocols.' Regardless of whether this hypothesis is upheld or not, the study will provide detailed outcome and cost data for severely injured, poor prognosis trauma patients who are managed in Intensive Care Units and comprise a large fraction of patients who eventually die.

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