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Hypertonic versus isotonic crystalloid for fluid resuscitation in critically ill patients (Unknown)

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[Intervention Unknown]

Hypertonic versus isotonic crystalloid for fluid resuscitation in critically ill patients

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ABSTRACT

Background

Hypertonic solutions are considered to have a greater ability to expand blood volume and thus elevate blood pressure and can be administered as a small volume infusion over a short time period. On the other hand, the use of hypertonic solutions for volume replacement may also have important disadvantages.

Objectives

To determine whether hypertonic crystalloid decreases mortality in patients with hypovolaemia with and without head injuries.

Search strategy

We searched MEDLINE, EMBASE, The Cochrane Controlled Trials Register and the Specialised register of the Injuries Group. We checked reference lists of all articles identified and searched the National Research Register.

Selection criteria

Randomised trials comparing hypertonic to isotonic crystalloid in patients with trauma, burns or undergoing surgery.

Data collection and analysis

Two authors independently extracted the data and assessed the quality of the trials.

Main results

Seventeen trials were identified with a total of 869 participants. Data on death were obtained in twelve of the studies. Only one trial reported data on disability. The pooled RR for death in trauma patients was 0.84 (95% CI 0.61-1.16), in patients with burns 1.49 (95% CI 0.56-3.95), and in patients undergoing surgery 0.62 (95% CI 0.08-4.57). In the one trial that gave data on disability using the Glasgow Outcome Scale the relative risk was 0.99 (95% CI 0.06-15.93).

Reviewers' conclusions

This review does not give us enough data to be able to say whether hypertonic crystalloid is better than isotonic crystalloid for the resuscitation of patients with trauma, burns, or those undergoing surgery. However, the confidence intervals are wide and do not exclude clinically significant differences. Further trials are needed comparing hypertonic to isotonic crystalloid. Trials need to be large enough to detect a clinically important difference.

PLAIN LANGUAGE SUMMARY

Synopsis

To be added

BACKGROUND

Fluid resuscitation is a mainstay of the medical management of haemorrhagic hypovolaemia. However, there is continuing uncertainty about the most appropriate fluid (Krausz 1995). Isotonic crystalloid solutions are often used to replace blood loss until a blood transfusion can be administered, but the wish to administer large volumes (ATLS guidelines suggest two litres of isotonic crystalloid), particularly in the pre-hospital phase when there may be problems with venous access, has stimulated the development of alternative approaches. One such approach is the use of hypertonic saline. Hypertonic solutions are considered to have a greater ability to expand blood volume and thus elevate blood pressure and can be administered as a small volume infusion over a short time period (Krausz 1995). Infusion of hypertonic saline is believed to act by causing an osmotic shift of fluid from the intracellular and interstitial spaces to the extracellular compartment. The resulting auto-transfusion of fluid increases blood pressure and circulating volume. The use of hypertonic solutions has the potential to provide rapid volume resuscitation but with less interstitial oedema than with isotonic saline solutions (Shackford 1983).

It has also been suggested that hypertonic solutions may be the fluid of choice in hypovolaemic patients with head injuries (Walsh 1991, Peterson 2000, Khanna 2000). Cerebral perfusion pressure depends on both ICP and mean arterial blood pressure ($CPP = \text{mean arterial blood pressure} - \text{mean ICP}$). Patients in hypovolaemic shock who have head injuries may require rapid blood pressure elevation to maintain cerebral perfusion pressure but excessive fluid and salt administration may result in brain swelling with an increase in intracranial pressure. Hypertonic solutions however, are believed to reduce intracranial pressure by establishing an osmotic gradient across the blood brain barrier that draws water from the brain tissue into the vascular space (Fisher 1992). Hypertonic solutions therefore have the potential to rapidly restore blood pressure but without increasing intracranial pressure. Hypertonic solutions are also thought to be beneficial in preventing the 'water logging' effect when there is interstitial lung injury, for example as occurs both in elective surgery and in trauma.

On the other hand, the use of hypertonic solutions for volume replacement may also have important disadvantages. In situations where haemorrhage is on-going hypertonic solutions may result in

continued bleeding from injured vessels. A potential problem in head injuries is that in patients with a disrupted blood brain barrier, excess sodium may leak into brain tissue drawing water with it, thus worsening cerebral oedema. At present there are no clinical ways to assess the integrity of the blood brain barrier. Furthermore, not only could the integrity of the blood brain barrier vary among patients with head injury, but it might also vary in different parts of the brain in a single patient. The possibility that hypertonic fluids may worsen outcome following head injury cannot therefore be dismissed (Krausz 1995, Shenkin 1976).

OBJECTIVES

To determine whether hypertonic crystalloid decreases mortality in patients with hypovolaemia with and without head injuries we conducted a systematic review of randomised controlled trials.

RESULTS

Death was reported either in the paper, or the information was obtained by contacting the researcher, in twelve of the studies. Data on death were not obtained for five trials (Gunn 1989, Jarvela 2001, McGough 1990, Younes 1988A, Younes 1988b). Only one trial (Vassar 1993 A) reported data on disability.

Due to the clinical heterogeneity of the different patient groups it was felt to be inappropriate to pool them, therefore only the results for the subgroups are given. The pooled relative risk for death in trauma patients was 0.84 (95% CI 0.61-1.16), for patients with burns 1.49 (95% CI 0.56-3.95) and for patients undergoing surgery 0.62 (95% CI 0.08-4.57). Only the Vassar 1993a trial gave data on disability using the Glasgow outcome scale. In that trial one person in each group had a poor outcome. The relative risk was 0.99 (95% CI 0.06-15.93).

DISCUSSION

This review does not give us enough data to be able to say if hypertonic crystalloid is better than isotonic crystalloid for the resuscitation of patients with trauma or burns, or those undergoing

surgery. However, the confidence intervals are wide and do not exclude clinically significant differences between hypertonic and isotonic crystalloid. A previous review (Alderson 1999) found there was a trend towards a favourable effect on mortality for colloids in hypertonic crystalloid compared to isotonic crystalloids, however, those results are compatible with the play of chance.

We chose not to pool the results of the burns, surgery and trauma patients as we felt these groups were too clinically heterogeneous. Bleeding and fluid management in patients undergoing elective surgery would tend to be more controlled and therefore different to that in trauma patients.

Most of the trials are small and quality was judged to be adequate in only five of them. There was variation in the type of participants, and length of follow up, and little standardisation in terms of fluid regimes. Also some of the trials were old. Although older trials will not necessarily be of poorer quality, it may be that treatment protocols have subsequently altered making these trials less relevant to current clinical practice. Indeed in the 1970s and 1980s there were few protocols on fluid resuscitation in the critically ill. Since the late 1980s there have been more clear guidelines and standardisation of fluid resuscitation regimes, although many areas of contention still exist.

Mortality was selected as the main outcome measure in this systematic review for several reasons. In the context of critical illness, death or survival is a clinically relevant outcome that is of immediate importance to patients, and data on death are reported in many of the studies. Furthermore, one might expect that mortality data would be less prone to measurement error or biased reporting than would data on pathophysiological outcomes. The use of a pathophysiological end point as a surrogate for an adverse outcome assumes a direct relationship between the two, an assumption that may sometimes be inappropriate. Finally, when trials collect data on a number of physiological end points, there is the potential for bias due to the selective publication of end points showing striking treatment effects.

Hypertonic solutions have been proposed as the fluid of choice in patients with head injuries (Walsh 1991), as they may maintain cerebral perfusion pressure without causing brain swelling with an increase in intracranial pressure. However, we found only one small trial (Simma 1998) among people with head injuries.

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REFERENCES

References to studies included in this review

Bortolani 1996 *{published data only}*

Bortolani A, Governa M, Barisoni D. Fluid replacement in burned patients. *Acta Chirurgiae Plasticae* 1996;**38**(4): 132-136.

Caldwell 1979 *{published data only}*

Caldwell FT, Bowser BH. Critical Evaluation of Hypertonic Solutions to Resuscitate Severely Burned Children. *Ann Surg* 1979;**18**(5):546-552.

Croft 1992 *{published data only}*

Croft D, Dion YM, Dumont M, Langlois D. Cardiac compliance and effects of hypertonic saline. *Canadian Association of General Surgeons* 1992;**35**(2):139-144.

Cross 1989 *{published data only}*

Cross JS, Gruber DP, Burchard KW, Singh AK, Moran JM, Gann DS. Hypertonic saline fluid therapy following surgery: a prospective study. *The Journal of Trauma* 1989;**29**(6):817-826.

Gunn 1989 *{published data only}*

Gunn ML, Hansbrough JF, Davis JW, Furst SR, Field TO. Prospective, randomized trial of hypertonic sodium lactate versus ringer's solution for burn shock resuscitation. *The Journal of Trauma* 1989;**29**(9):1261-1267.

Jarvela 2001 *{published data only}*

Jarvela K, Koskinen M, Kaukinen S, Koobi T. Effects of hypertonic saline (7.5%) on extracellular fluid volumes compared with normal saline (0.9%) and 6% hydroxyethyl starch after aortocoronary bypass graft surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 2001;**15**(2):210-215.

Jelenko 1978 *{published data only}*

Jelenko C, Wheeler ML, Calloway D, Divilio T, Bucklen KR, Holdredge TD. Shock and resuscitation II: volume repletion with minimal edema using the "HALFD" method. *JACEP* 1978;**7**(9):326-333.

McGough 1990 *{published data only}*

McGough EK, Kirby RR. Hypertonic saline for intraoperative fluid therapy. *Crit Care Med* 1990;**18**(4): 5193.

Shackford 1983 *{published data only}*

Shackford SR, Sise MJ, Fridlund PH, Rowley WR, Peters RM, Virgilio RW, Brimm JE. Hypertonic sodium lactate versus lactated ringers solution for intravenous fluid therapy in operations on the abdominal aorta. *Surgery* 1983;**94**(1): 41-51.

Shackford 1987 *{published data only}*

Shackford SR, Fortlage DA, Peters RM, Hollingsworth-Fridlund, Sise MJ. Serum osmolar and electrolyte changes associated with large infusions of hypertonic sodium lactate for intravascular volume expansion of patients undergoing

aortic reconstruction. *Surgery, Gynecology & Obstetrics* 1987;**164**:127-136.

Simma 1998 *[published data only]*

Simma B, Burga R, Falk M, Sacher P, Fanconi S. A prospective, randomized, and controlled study of fluid management in children with severe head injury: lactated ringer's solution versus hypertonic saline. *Critical Care Medicine* 1998;**26**(7):1265-1270.
Simma B, Burger R, Falk M, Sacher P, Torresani T, Fanconi S. The release of antidiuretic hormone is appropriate in response to hypovolemia and/or sodium administration in children with severe head injury: A trial of lactated ringer's solution versus hypertonic saline. *Anesthesia and Analgesia* 2001;**92**:641-5.

Vassar 1990 *[published data only]*

Vassar MJ, Perry CA, Holcroft JW. Analysis of potential risks associated with 7.5% sodium chloride resuscitation of traumatic shock. *Arch-Surg* 1990;**125**:1309-1315.

Vassar 1993 A *[published data only]*

Vassar MJ, Perry CA, Holcroft JW. Prehospital resuscitation of hypotensive trauma patients with 7.5% NaCl versus 7.5% NaCl with added dextran: a controlled trial. *The Journal of Trauma* 1993;**34**(5):622-633.

Vassar 1993 B *[published data only]*

Vassar MJ, Fischer RP, O'Brien PE, Bachulis BL, Chambers JA, Hoyt DB, Holcroft JW. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride. *Arch Surg* 1993;**128**:1003-1013.

Younes 1988A *[published data only]*

Younes RN, Aun F, Birolini D, Kawahara NT, Takeuti M, Casale L, Accioly C, Szajnbok I, Brito N. Initial treatment of hypovolemic patients with 7.5% solution of NaCl [O Tratamento inicial de pacientes hipovolemicos: Emprego da solucao hipertonica de NaCl a 7.5%]. *Rev. Hosp. Clin. Fac. Med. S. Paulo* 1988;**43**(3):138-141.

Younes 1988b *[published data only]*

Younes R, Bechara M, Langer B, Aun F, Birolini D, Kuznieck S, Guimaraes P. Hypertonic saline 7.5% in the prevention of hypotension in post abdominal aorta unclamping [Emprego da solucao hipertonica de NaCl a 7.5% na prevencao da hipotensao pos-desclameamento da aorta abdominal]. *Rev Ass Med Brasil* 1988;**34**(5):150-154.

Younes 1992 *[published data only]*

Younes RN, Aun F, Accioly CQ, Casale LPL, Szajnbok I, Birolini. Hypertonic solutions in the treatment of hypovolemic shock: A prospective, randomized study in patients admitted to the emergency room. *Surgery* 1992;**111**(4):380-385.

References to studies excluded from this review

Fisher 1992

Fisher B, Thomas D, Peterson B. Hypertonic saline lowers raised intracranial pressure in children after head trauma. *Journal of Neurosurgical Anesthesiology* 1992;**4**(1):4-10.

Holcroft 1987

Holcroft J, Vassar M, Turner J, Derlet R, Kramer G. 3% NaCl and 7.5% NaCl/Dextran 70 in the resuscitation of severely injured patients. *Ann Surg* 1987;**206**(3):279-287.

Shackford 1998

Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM, Clark DE. Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. *The Journal of Trauma* 1998;**44**(1):50-58.

References to ongoing studies

Cooper

Hypertonic Saline Resuscitation for Head Injured Patients. Ongoing study 1998.
Cooper DJ. Hypertonic Saline Resuscitation for Head Injured Patients. *Critical Care and Resuscitation* 1999;**1**:151-156.

Additional references

Alderson 1999

Alderson P, Schierhout G, Roberts I, Bunn F. Colloids versus crystalloids for fluid resuscitation in critically ill patients (Cochrane Review). In: *The Cochrane Library*, 2, 1999. Oxford: Update Software. 10.1002/14651858.CD000567

Berlin 1997

Berlin JA for the University of Pennsylvania Meta-analysis Blinding Study Group. Does blinding of readers affect the results of meta-analyses?. *Lancet* 1997;**350**:185-6.

Bickell 1994

Bickell WH, Wall MJ, Pepe PP, Martin RR, Ginger VF, Allen MK, Mattox KL. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *New Eng J Med* 1994;**331**:1105-1109.

Fisher 1992

Fisher B, Thomas D, Peterson B. Hypertonic saline lowers raised intracranial pressure in children after head trauma. *Journal of Neurosurgical Anesthesiology* 1992;**4**(1):4-10.

Jennett 1975

Jennett B, Bond M. Assessment of outcome after severe brain damage. A practical scale. *Lancet* 1975;**1**:480-484.

Khanna 2000

Khanna S, Davis D, Peterson B, Fisher B, Tung H, O'Quigley J, Deutsch R. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. *Crit Care Med* 2000;**28**(4):1144-51.

Krausz 1995

Krausz MM. Controversies in shock research: hypotonic resuscitation - pros and cons. *Shock* 1995;**3**:69-72.

Peterson 2000

Peterson B, Khanna S, Fisher B, Marshall L. Prolonged hypernatremia controls elevated intracranial pressure in head-injured pediatric patients. *Crit Care Med* 2000;**28**(4):1136-43.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical Evidence of Bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408-412.

Shackford 1983

Shackford SR, Sise MJ, Fridlund PH, Rowley WR, Peters RM, Virgilio RW, Brimm JE. Hypertonic sodium lactate versus lactated ringer's solution for intravenous fluid therapy in operations on the abdominal aorta. *Surgery* 1983;**94**:

41-51.

Shenkin 1976

Shenkin HA, Bezier HS, Bouzarth WF. Restricted fluid intake: rational management of the neurosurgical patient. *J Neurosurg* 1976;**45**:432-436.

Walsh 1991

Walsh JC, Zhuang J, Shackford SR. A comparison of hypertonic to isotonic fluid in the resuscitation of brain injury and hemorrhagic shock. *J Surg Res* 1991;**50**:284-292.

* *Indicates the major publication for the study*

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