Intravenous Fluid Therapy

Details of review team

Lead Reviewer:
Janine Dretzke
Systematic Reviewer
Department of Public Health & Epidemiology
University of Birmingham
Edgbaston
Birmingham
B15 2TT
Tel: 0121 4147850
Fax: 0121 4147878
Email: J.Dretzke@bham.ac.uk

Senior reviewer:
Amanda Burls
Senior Clinical Lecturer in Public Health and Epidemiology
Director of West Midlands Health Technology Assessment Collaboration
Department of Public Health and Epidemiology
University of Birmingham
Tel: 0121 4147508
Fax: 0121 4147878
Email: A.J.Burls@bham.ac.uk

Methodologist:
Josie Sandercock
Research Fellow (Medical Statistics)
Department of Public Health and Epidemiology
University of Birmingham
Tel: 0121 4142247
Fax: 0121 4147878
Email: J.Sandercock@bham.ac.uk

Statistician:
David Braunholtz
Senior Research Fellow
National Co-coordinating Centre for Research Methodology
Department of Public Health and Epidemiology
University of Birmingham
Tel: 0121 4147495
Fax: 0121 4147878
Email: D.A.Braunholtz@bham.ac.uk

Information Specialists:
Sue Bayliss
Information Specialist ARIF/WMHTAC
Department of Public Health and Epidemiology
University of Birmingham
Tel: 0121 4147914
Fax: 0121 4147878
Email: S.Bayliss@bham.ac.uk

Anne Fry-Smith
Information Specialist ARIF/WMHTAC
Department of Public Health and Epidemiology
University of Birmingham
Tel: 0121 4146769
Fax: 0121 4147878
Email: A.S.Fry-Smith@bham.ac.uk

Administrator:
Rebecca Mason
Department of Public Health and Epidemiology
University of Birmingham
Tel: 0121 4146852
Fax: 0121 4147878
Email: R.Mason@bham.ac.uk

Full title of research question

The effectiveness and cost-effectiveness of pre-hospital fluid administration versus no pre-hospital fluid administration in trauma patients.

Clarification of research question and scope

Traditionally, management of trauma patients suffering from haemorrhagic shock has included early, rapid pre-hospital intravenous fluid replacement on the basis that maintenance of blood pressure will ensure vital organ perfusion. More recently it has been suggested that this strategy may cause harm in some trauma patients, as fluid administration may worsen bleeding, dilute clotting factors and cause mechanical disruption of blood clots thus decreasing organ perfusion. In addition, pre-hospital fluid replacement may cause a delay in transferring the patient to hospital (unless it is performed en route), which may influence patient outcomes.

This systematic review will focus on the effectiveness of pre-hospital fluid administration versus no fluid administration, or early versus delayed pre-hospital fluid administration, in trauma patients. Both the effect of fluid per se and the delay of definitive treatment due to fluid replacement will be investigated. If possible, sub-group analysis will be carried out regarding patients, who receive fluids at the scene (compared to no pre-hospital fluids) or en route (compared to no pre-hospital fluids). A decision-analytical model will be developed to examine costs and benefits of different resuscitation strategies.

There are many additional issues surrounding pre-hospital fluid administration, including choice of fluid (e.g. crystalloid versus colloid), amount of fluid, type of infusion (rapid or controlled), type of trauma (e.g. blunt or penetrating) and trauma in children.

Report Methods

Inclusion and exclusion criteria for systematic review

Study design:
Randomised controlled trials.

Population:
Patients of any age with haemorrhagic hypovolaemia resulting from trauma.

Intervention:
Any type of pre-hospital fluid replacement.

Comparator:
No pre-hospital fluid replacement (definitive treatment, including fluid replacement, initiated in hospital)

Outcomes:
Short- and long-term morbidity, mortality; quality of life.

Search strategy

Systematic Review

An initial scoping search identified a recent well-conducted systematic review of randomised controlled trials in the Cochrane library (Kwan et al., 2001[1]), which was last updated on 25th September 2000. This review will form the starting point of the report, and the authors have agreed to make available any relevant files. We will rerun the Cochrane search strategy to identify any more recent relevant publications, and will also independently develop and run a search strategy in order to compare any potential differences in publications identified by the two search strategies. The following electronic databases will be searched: the Cochrane Controlled Trials Register (CCTR), MEDLINE, EMBASE and the Science Citation Index. In addition, citation lists of relevant publications will be checked, key journals will be hand searched and key web sites searched.

Unpublished data will be sought by contacting organisations and individual experts, including the Defence Medical Services (DMS), and by checking research registers of ongoing trials. Any data from the industry submission will be appraised and included as appropriate.

The inclusion and exclusion criteria will be applied independently by two reviewers to any additional identified citations, and any disagreement resolved by a third reviewer. Where a decision on inclusion or exclusion cannot be made on the basis of title or abstract, the full study will be retrieved

Additional Information to inform systematic review

Key observational studies relating to the main research question will be identified and critiqued. A systematic review of observational studies will not be undertaken as results of these studies are likely to be confounded and will not be used to contribute to the conclusions of the review.

Systematic reviews on related issues of interest, such as choice of fluid, amount of fluid, type of infusion or type of trauma, will be sought using the Aggressive Research Intelligence Facility (ARIF)[2] search strategy (see appendix 2).

We will attempt to clarify and summarize the existing evidence base surrounding these additional issues. A number of recent systematic reviews exist, which address many of these issues. [3-5] These, and any others identified, will be critically appraised by the review team and any gaps in the current evidence base will be highlighted. If current clinical evidence is equivocal, or if there are gaps in the clinical evidence base, studies using animal models may be sought for additional information.

Data extraction strategy

Data from existing systematic reviews will be used in its abstracted form. Where additional primary studies are identified, data will be extracted independently by two reviewers onto pre-piloted data extraction forms. Any discrepancies will be resolved through discussion or involvement of a third reviewer. Data will be extracted in terms of population characteristics, setting, intervention, comparator, outcomes, and size and direction of effect.

Quality assessment strategy

The quality of any additional relevant randomised controlled trials identified will be assessed using a checklist comprising the following quality criteria: method of randomisation stated, concealment of allocation, blinding, intention-to-treat analysis, loss to follow-up, comparability of baseline criteria, validity of outcome assessment tools and outcome measures used (see appendix 3).

Existing systematic reviews will be appraised using a checklist of quality criteria based on the Critical Appraisal Skills Programme (CASP)[6] checklist, which assesses the internal and external validity of the results of a review.

Methods of analysis/synthesis

The report will independently assess the findings from the Cochrane review and integrate these findings with any additional data identified. Data from all sources will be synthesized and interpreted by the review group. Data will be summarised into tables. Presentation of data in Forest plots will be considered in order to highlight the direction of effect and any statistical and clinical heterogeneity. Pooling of data will be performed if appropriate. Where possible, subgroup analysis will be performed in order to highlight potential differences in effectiveness for different sub-groups (e.g. different types of trauma or fluid) and to investigate the effects of fluid replacement per se and the effects of delaying treatment due to fluid replacement.

Methods for estimating qualify of life, costs and cost-effectiveness and/or cost/QALY
Economic data will be sought in included primary studies, and a search strategy will be developed to identify further studies containing economic data. The following electronic databases will be searched: MEDLINE, EMBASE, the NHS Economic Evaluation Database (NHS EED) and the Office of Health Economics Health Economic Evaluations Database (OHE HEED). Identified studies will be reviewed and relevant data reported.

Decision Analytic Model
A decision-analytic model will be developed to examine the costs and benefits of different resuscitation policies, based on the evidence obtained for this review. A cost-effectiveness analysis will be performed to estimate the cost per life year gained. As the impact of resuscitation is likely to be on short-term survival, with no impact on long-term health outcomes, information on the utility of different long-term health states for individuals surviving resuscitation episodes will be used to derive a cost-utility estimate.

Uncertainty in the model parameters and underlying assumptions will be explored in a probabilistic sensitivity analysis to quantify the uncertainty in the results obtained. If the uncertainty regarding the value of alternative resuscitation policies is large, further modelling will be undertaken to estimate the value for money of further research, and to make recommendations as to which areas of research are likely to be most influential in informing future policy.

Handling the company submission(s)

The industry dossier will be used as a source of data to identify studies that meet the inclusion criteria (randomised controlled studies) and for information on costs. Any industry models will be compared with the decision-analytic model outlined above. An analysis of any industry models will be undertaken, including the strengths, weaknesses and implications of different assumptions.

Project Management

a. **Timetable/milestones** - submission of:

Progress report: 16th April 2003

Assessment Report: 1st July 2003

b. **Competing Interests**
None.

APPENDICES

Appendix 1: Background

Injury is a leading cause of death for individuals under 40 years[7], and it is estimated that deaths from injury will increase from 5 million in 1990 to 8.4 million in 2020 worldwide.[8] Road traffic accidents cause a large proportion of these injuries, with around 40,000 serious injuries and 3400 deaths a year in the UK.[9] Around 700 children die every year as a result of accidents in England and Wales. Half of these die as a result of road traffic accidents, mainly from head injuries.[10]

Rapid blood loss caused by blunt or penetrating trauma can result in hypovolaemic shock. Shock is defined as cellular anaerobic metabolism, which means that cells are not receiving sufficient oxygen for survival. This is dependent on red blood cells being oxygenated in the lungs and delivery of red blood cells to the tissue cells.[11] Acute blood loss following injury can lead to a reduction in tissue perfusion, which, if prolonged, causes lactic acidosis and organ failure.[12]Classic signs of shock such as a small drop in systolic blood pressure, mild anxiety, skin coolness and tachycardia appear after blood loss of around 1000-1500ml.[10]

Resuscitation strategies used to raise blood pressure in bleeding patients until bleeding is controlled include the use of medical anti-shock trousers (MAST) and administration of intravenous fluids.[12] [13] The practice of early fluid administration is based on the idea that raising blood pressure will maintain tissue perfusion and therefore oxygen delivery. Fluid management of trauma victims traditionally consisted of early, rapid infusion of large quantities of fluid to maintain adequate systolic blood pressure until transfer to hospital.[14]

The basis for this approach lies with animal experiments performed in the 1950's and 60's, where researchers found that prolonged haemorrhagic hypotension resulted in a deficit of extracellular fluid, which was corrected only by the administration of isotonic crystalloid in volumes of 2-3 times the estimated blood loss.[13,15] This strategy has become established practice over the years, to the point where it has become a reflex response by attending medical personnel.[14] It is supported by the Advanced Trauma Life Support (ATLS) guidelines[16], which are taught to doctors throughout the world.

In recent years, however, doubts have been raised regarding the benefit of this strategy. Past animal studies have been criticised for not being representative of a trauma patients encountered in a pre-hospital setting. Animal studies using uncontrolled haemorrhage models conducted in the 80's and 90's found that the mortality rate increased if treatment with intravenous fluid was given before haemorrhage was controlled, whilst survival in the animals was increased by allowing blood pressure to remain low until bleeding was controlled (permissive hypotension). [13,15,17,18]

It has been suggested that fluid administration may worsen bleeding by diluting clotting factors, or may adversely affect the coagulation cascade in excess of dilutional effects.[12] The increased pulse pressure from crystalloid resuscitation may also cause the mechanical disruption of blood clots, a reverse of vasoconstriction resulting in increased bleeding and metabolic acidosis following reduced oxygen. [1,18] A further issue is whether the transfer time to hospital may affect patient outcomes, independent of any pre-hospital treatment given. Paramedic interventions result in an additional 12 minutes at the scene in the UK, so

attempting to replace fluid may delay the arrival to hospital, unless it is performed en route.[19]

Other relevant issues include which type of fluid to give (e.g. crystalloid or colloid, or type of colloid or crystalloid), the amount of fluids to give, whether fluid replacement may be more or les beneficial for different types of trauma and the role of fluid replacement in paediatric trauma.

Current guidelines

A number of organisations in the UK put forward a consensus view in 2001[20] on fluid resuscitation in pre-hospital trauma care with the aim of reconciling both current evidence and clinical experience. The organisations were the Royal College of Surgeons of Edinburgh, Faculty of Pre-hospital Care & Faculty of Accident & Emergency Medicine, The United Kingdom Military Defence Forces, Ambulance Service Association (ASA) with paramedics representatives, British Association for Immediate care (BASICS), London Helicopter Emergency Medical Service (HEMS) and researchers with an interest in pre-hospital care. Their conclusions were as follows:

- *Cannulation should take place en route where possible*
- *Only two attempt at cannulation should be made*
- *Transfer should not be delayed by attempt to obtain intravenous access*
- *Entrapped patients require cannulation at the scene*
- *Normal saline is recommended as a suitable fluid for administration to trauma patients*
- *Boluses of 250ml fluid may be titrated against the presence or absence of a radial pulse (caveats; penetrating torso injury, head injury, infants)*

The Joint Royal Colleges Ambulance Liaison Committee (JRCALC) guidelines[10] reflect this consensus view. They state that:
'current research shows little evidence to support the routine use of pre-hospital IV infusion in trauma patients. In cases of penetrating chest and abdominal injuries and aortic aneurysm dissection, an actual decrease in survival has been associated with pre-hospital fluid administration, by displacing fragile blood clots from bleeding vessels and causing re-bleeding. As a rule, IV infusions should be commenced en route to hospital, and only sufficient fluid given to maintain a systolic BP of 80-90 mmHg. 500 ml IV of crystalloid solution should be given, and the effects on the circulatory system assessed, before further fluids are given.' The guidelines also state that:
'it is vital to maintain blood pressure in cases of severe head trauma, as hypotension has been shown to reduce survival.'

Current service provision

Little has been identified in the literature on service provision in practice. Preliminary enquiries with the Ambulance Services Association (ASA) have identified that there is routinely collected data in the form of data sheets that are completed for each call out, although data is not co-ordinated nationally. Information on these forms refers to patient injuries and symptoms and any pre-hospital care given. The ASA will be contacted in order to determine whether data can be made accessible and in which form.

Appendix 2: ARIF search strategy for systematic reviews (September 2002)

1. **Cochrane Library**
- Cochrane Reviews
- Database of Abstracts of Reviews of Effectiveness (DARE)
- Cochrane Controlled Trials Register (CCTR)
- Health Technology Assessment (HTA) database

2. ARIF Database
An in-house database of reviews compiled from DARE and scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3. NHSCRD (WW Web access)
- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments (WW Web access)
- Office of Technology Assessment
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Co-ordinating Office for Health Technology Assessment
- New Zealand Health Technology Assessment
- Wessex DEC Reports
- Trent Institute for Health and Related Research reports
- NICE appraisals
- Agency for Healthcare Research and Quality (AHRQ)
- National Horizon Scanning Centre

5. Clinical Evidence

6. Bandolier (via the WWWeb)

7. National Research Register (via the WWWeb)
Includes Register of Reviews in Progress

8. InterTasc database

9. TRIP Database

10. Drug and Therapeutics Bulletin

11. Bibliographic databases
- Medline - systematic reviews (suggested strategy from CRD)
- Embase - systematic reviews (still being developed)
- Other specialist databases e.g. CINAHL, PsycLit

12. Contacts
- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (&MTRAC) and West Midlands Drug Information Service, Good Hope NHS Trust (url: www.ukmicentral.nhs.uk) for any enquiry involving drug products
- Scottish Intercollegiate Guidelines Network (SIGN). (Web page, newsletter and personal contact)
- Bristol Health Care Evaluation Unit.
- In special circumstances, Mailbase discussion lists e.g. Evidence Based Medicine

Appendix 3: Quality checklist for randomised controlled trials

	Yes	No	CT	Comment
Randomisation Was trial described as random? Was randomisation method stated? If randomisation method described, was it adequate?				
Concealment Was there a statement regarding concealment? Was method of concealment described? If method of concealment described, was it adequate?				
Blinding Was the trial described as blind? Was there statement regarding blinding of outcome assessors?				
Loss to follow-up/ITT Was loss to follow-up stated for both groups? Was there a statement regarding intention to treat analysis? Was this confirmed by the data/results presented?				
Comparability of treatment groups Were intervention and control group characteristics comparable at entry? Were intervention and control groups treated identically apart from the intervention? Were intervention and control groups followed-up for the same length of time?				

CT=can't tell

Other issues of interest to be recorded:

- were the outcome measures and outcome assessment tools appropriate?
- were power calculations performed?

1 Kwan I, Bunn F, Roberts I, WHO Pre-Hospital Trauma Care Steering Committee. Timing and volume of fluid administration for patients with bleeding following trauma. [Review] [16 refs]. *Cochrane Database of Systematic Reviews* 2001; **1**:CD002245.

2 Aggressive Research Intelligence Facility (ARIF) Access date: 5 Dec. 2002, URL: www.bham.ac.uk/arif/

3 Alderson P, Schierhout G, Roberts I, Bunn F. Colloids versus crystalloids for fluid resuscitation in critically ill patients. [Review] [70 refs]. *Cochrane Database of Systematic Reviews* 2000;(2):CD000567.

4 Alderson P, Bunn F, Lefebvre C, Li WP, Li L, Roberts I, *et al*. Human albumin solution for resuscitation and volume expansion in critically ill patients. [see comments.] [update of Cochrane Database Syst Rev. 2000;(2):CD001208 ; 10796756.]. [Review] [62 refs]. *Cochrane Database of Systematic Reviews* 2002;(1):CD001208.

5 Bunn F, Roberts I, Tasker R, Akpa E. Hypertonic versus isotonic crystalloid for fluid resuscitation in critically ill patients. [update in Cochrane Database Syst Rev. 2002;(1):CD002045 ; 11869619.]. [Review] [31 refs]. *Cochrane Database of Systematic Reviews* 2000;(4):CD002045.

6 Critical Appraisal Skills Programme, Institute for Health Sciences, Oxford. 2002.
Ref Type: Internet Communication

7 Kwan I, Bunn F, Roberts I, Wentz R. The development of a register of randomized controlled trials in prehospital trauma care. *Prehospital Emergency Care* 2002; **6**(1):27-30.

8 Murray,CJL, Lopez,AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* **349**[1498], 1504.1997

9 Coats,TJ, Davies,G. Prehospital care for road traffic casualties. *British Medical Journal* **324**[1135], 1138.2002

10 Joint Royal Colleges Ambulance Liaison CommitteePre-Hospital Guidelines 2002. Ed. University of Warwick, JRCALC and QinetiQ 2002 2002

11 Prehospital Trauma Life Support Committee of the National Association of Emergency Medical Technicians in Cooperation with The Committee on Trauma of the American College of Surgeons. Basic and Advanced Prehospital Trauma Life Support. 3th ed. Mosby, Inc., 1994.

12 Roberts I, Evans P, Bunn F, Kwan I, Crowhurst E. Is the normalisation of blood pressure in bleeding trauma patients harmful? [see comments.]. [Review] [34 refs]. *Lancet* 2001; **357**(9253):385-387.

13 Stern SA. Low-volume fluid resuscitation for presumed hemorrhagic shock: helpful or harmful?. [Review] [74 refs]. *Current Opinion in Critical Care* 2001; **7**(6):422-430.

14 Hyde,JAJ, Graham,TR. Pre-hospital fluid resuscitation for thoracic trauma. *Pre-hospital Immediate Care* **3**, 99-101.1999

15 Pepe PE, Mosesso VN, Jr., Falk JL. Prehospital fluid resuscitation of the patient with major trauma. [Review] [81 refs]. *Prehospital Emergency Care* 2002; **6**(1):81-91.

16 American College of Surgeons Committee on Trauma. Advanced Trauma Life Support® for Doctors. Student Course Manual.Ed. American College of Surgeons Chicago 1997

17 Roberts I, Kwan I, Evans P, Haig S. Does animal experimentation inform human healthcare? Observations from a systematic review of international animal experiments on fluid resuscitation. [see comments.]. [Review] [25 refs]. *British Medical Journal* 2002; **324**(7335):474-476.

18 Nolan J. Fluid resuscitation for the trauma patient. [Review] [101 refs]. *Resuscitation* 2001; **48**(1):57-69.

19 Nicholl,J, Hughes,S, Dixon,S, Turner,J, Yates,D. The costs and benefits of paramedic skills in pre-hospital trauma care. *Health Technology Assessment* **2**[17].1998

20 Fluid Resuscitation in Pre-Hospital Trauma Care: a consensus view. [Review] [46 refs]. *Journal of the Royal Army Medical Corps* 2001; **147**(2):147-152.