Timing and volume of fluid administration for patients with bleeding (Review)

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[Intervention Review]

Timing and volume of fluid administration for patients with bleeding

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ABSTRACT

Background

Treatment of haemorrhagic shock involves maintaining blood pressure and tissue perfusion until bleeding is controlled. Different resuscitation strategies have been used to maintain the blood pressure in trauma patients until bleeding is controlled. However, while maintaining blood pressure may prevent shock, it may worsen bleeding.

Objectives

To assess the effects of early versus delayed, and larger versus smaller volume of fluid administration in trauma patients with bleeding.

Search strategy

We searched the CENTRAL (*The Cochrane Library* 2008, Issue 4), the Cochrane Injuries Group's Specialised Register (searched October 2008), MEDLINE (to October 2008), EMBASE (to October 2008), the National Research Register (in Current controlled trials.gov; searched October 2008) and the Science Citation Index (to October 2008). We checked reference lists of identified articles and contacted authors and experts in the field.

Selection criteria

Randomised trials of the timing and volume of intravenous fluid administration in trauma patients with bleeding. Trials in which different types of intravenous fluid were compared were excluded.

Data collection and analysis

Two authors independently extracted data and assessed trial quality.

Main results

We did not combine the results quantitatively because the interventions and patient populations were so diverse.

Early versus delayed fluid administration

Three trials reported mortality and two coagulation data.

In the first trial (n=598) relative risk (RR) for death with early fluid administration was 1.26 (95% confidence interval of 1.00−1.58). The weighted mean differences (WMD) for prothrombin time and partial thromboplastin time were 2.7 (95% CI 0.9−4.5) and 4.3 (95% CI 1.74−6.9) seconds respectively.

In the second trial (n=50) RR for death with early blood transfusion was 5.4 (95% CI 0.3−107.1). The WMD for partial thromboplastin time was 7.0 (95% CI 6.0−8.0) seconds. In the third trial (n=1309) RR for death with early fluid administration was 1.06 (95% CI 0.77−1.47).

Larger versus smaller volume of fluid administration

Three trials reported mortality and one coagulation data.

In the first trial (n=36) RR for death with a larger volume of fluid resuscitation was 0.80 (95% CI 0.28−22.29). Prothrombin time and partial thromboplastin time were 14.8 and 47.3 seconds in those who received a larger volume of fluid, as compared to 13.9 and 35.1 seconds in the comparison group.

In the second trial (n=110) RR for death with a high systolic blood pressure resuscitation target (100mmHg) maintained with a larger volume of fluid, as compared to low systolic blood pressure resuscitation target (70mmHg) maintained with a smaller volume of fluid was 1.00 (95% CI 0.26−3.81). In the third trial (n=25) there were no deaths.

Authors' conclusions

We found no evidence from randomised controlled trials for or against early or larger volume of intravenous fluid administration in uncontrolled haemorrhage. There is continuing uncertainty about the best fluid administration strategy in bleeding trauma patients. Further randomised controlled trials are needed to establish the most effective fluid resuscitation strategy.

PLAIN LANGUAGE SUMMARY

No evidence from trials to support or not to support the use of early or larger volume intravenous fluid in uncontrolled bleeding

About one third of injury deaths are due to shock from blood loss. Preventing shock in people with uncontrolled bleeding is, therefore, very important and is generally done by giving fluids intravenously. The aim is to maintain blood pressure and reduce tissue damage. The review of trials found that there is uncertainty about the best time to give fluid and what volume of fluid should be given. While increasing fluids will maintain blood pressure, it may also worsen bleeding by diluting clotting factors in the blood. More research is needed.

BACKGROUND

In 1990 approximately five million people died worldwide as a result of injury (Murray 1996). For people younger than 35 years, injury is now the leading cause of death. Nevertheless, the global epidemic of injury is only beginning. It is estimated that by 2020, deaths from injury will have increased from 5.1 million to 8.4 million (Murray 1997). About one third of injury deaths are due to haemorrhagic shock (Deakin 1994). Acute blood loss following injury leads to a reduction in tissue perfusion and tissue oxygen delivery that, if prolonged, causes lactic acidosis and organ failure. Treatment of haemorrhagic shock involves maintaining blood pressure and tissue perfusion until the bleeding is controlled. Over the past 50 years, a number of resuscitation strategies have been used to maintain the blood pressure in trauma patients until bleeding is controlled. The evidence for the effectiveness of these approaches has been the subject of a number of systematic reviews by the Cochrane Injuries Group and by others.

Pre-hospital use of medical anti-shock trousers

Medical anti-shock trousers (MAST) were first used in the Vietnam War to stabilise patients with haemorrhagic shock during transportation. After the war, MAST became widely used in the care of bleeding trauma patients. MAST increases blood pressure by compressing the blood vessels in the legs, thus increasing systemic vascular resistance, and by shunting blood from the lower body to the brain, heart and lungs. It was hoped that by increasing venous return to the heart, MAST would maintain blood flow to vital organs until definitive care was given. Nevertheless, a systematic review of randomised controlled trials of MAST use in pre-hospital trauma care provided no evidence that MAST increases survival, and a suggestion that it may increase the risk of death. The pooled relative risk of death with MAST was 1.13 (95% CI 0.97−1.32) (Dickinson 1999).

Paramedic ambulance crews

In high-income countries, an increasing number of ambulance crews include a paramedic trained in advance life support. Paramedics receive extra training in intubation, intravenous cannulation, and the administration of intravenous fluids. Only a small proportion of paramedic-attended trauma patients require intubation (1%), but a larger proportion (18%) receive intravenous fluids (Nicholl 1998). Because of the strong conviction amongst the public and medical profession that paramedic intervention is beneficial, it has been difficult to conduct randomised controlled trials comparing paramedic and non-paramedic trauma care. However, a review and meta-analysis of four cohort studies gave a significantly increased (p=0.03) risk of death in paramedic attended patients (RR=1.26) (Nicholl 1998). Because of the potential for confounding by injury severity, the validity of inferences from cohort studies must be questioned. Nevertheless, the results are consistent with the hypothesis that efforts by paramedics to raise the blood pressure of bleeding trauma patients may be counterproductive.

Colloid fluid resuscitation

Intravenous fluid administration, with colloid or crystalloid solutions, is the mainstay of the non-surgical management of bleeding trauma patients. Colloids are better than crystalloid solutions in expanding the circulation, because they are retained within the blood vessels to a greater extent. Crystalloid solutions rapidly leak out of the blood vessels into the interstitial spaces. After a colloid infusion, the increase in the circulating volume is about the same as the volume of colloid infused, whereas only about one quarter of the volume of a crystalloid infusion remains in the blood vessels (Weil 1999). Although colloids are effective in expanding the circulation there is no evidence that this improves outcome in critically ill patients (Alderson 2000).

The systematic reviews of medical anti-shock trousers, paramedic resuscitation and colloid administration call into question the benefits of raising the blood pressure in bleeding trauma patients. But by what mechanisms could fluid resuscitation adversely affect outcome? Stern, using a swine model of near-fatal haemorrhage, found that attempts to restore blood pressure with crystalloid resulted in increased haemorrhage volume and markedly higher mortality (Stern 1993). It was postulated that the increased pulse pressure from crystalloid resuscitation might cause the mechanical disruption of blood clots and worsen bleeding. It has also been proposed that fluid administration might also worsen bleeding by diluting clotting factors. In view of the concerns raised by the previous systematic reviews and by the results of animal models of haemorrhagic hypovolaemia, we have conducted a systematic review of the effect on mortality of early versus delayed fluid resuscitation, and of larger versus smaller fluid volumes.

OBJECTIVES

To examine the effect on mortality and coagulation times of two intravenous fluid administration strategies in the management of haemorrhagic hypovolaemia: early compared to delayed administration and larger compared to smaller volume of fluid administered.

METHODS

Criteria for considering studies for this review

Types of studies

All unconfounded randomised and quasi-randomised controlled trials of the timing or volume of intravenous fluid administration in haemorrhagic hypovolaemia.

Types of participants

Patients of all ages with haemorrhagic hypovolaemia of traumatic or non-traumatic origin. Because the physiological response to bleeding and to fluid resuscitation is likely to be similar among patients with internal bleeding (e.g. bleeding peptic ulcer) and those with external bleeding (e.g. penetrating trauma), both types of participants were included.

Types of interventions

Intravenous fluids including crystalloid solutions, colloids, plasma and blood. Trials in which the timing or volume of fluid administration is confounded by the type of intravenous fluid given – for example, a trial comparing the administration of 1000ml of colloid with 500ml blood – were excluded.

Types of outcome measures

Mortality from all causes at the end of the follow-up period scheduled for each trial. We sought mortality data in simple categorical form, and we did not extract data on time to death. If a report did not include the numbers of deaths in each group, we sought these data from the authors. We also sought data on prothrombin time and partial thromboplastin time during fluid administration.

Search methods for identification of studies

Searches were not restricted language, date or publication status.

Electronic searches

We searched:

- CENTRAL ((*The Cochrane Library* 2008, Issue 4),
- MEDLINE (1966 to October 2008),
- National Research Register (October 2008),
- EMBASE (1980 to October 2008),
- Web of Science; Science Citation Index (to October 2008),
- Cochrane Injuries Group Trials Register (searched October 2008),
- Current Controlled Trials (Searched October 2008).

The search strategy can be found in Appendix 1.

Searching other resources

We checked the reference lists of all included studies and contacted authors and experts in the field. The Science Citation Index was checked for eligible papers that cited two of the trials (Bickell 1994, Blair 1986) included in this review.

Data collection and analysis

Selection of studies

One reviewer (IK) examined the electronic search results for reports of possibly relevant trials and these reports were then retrieved in full. The first reviewer (IK) also contacted experts in the field for unpublished and ongoing trials. A second reviewer (FB) examined 10% of the electronic search results to check for agreement on eligibility criteria. Two reviewers (FB, IK) applied the selection criteria independently to the trial reports, resolving disagreements by discussion with a third (IR).

Data extraction and management

Two reviewers (IK, FB) independently extracted information on the following: method of allocation concealment, number of randomised patients, type of participants and the interventions, loss to follow-up and length of follow-up. The outcome data sought were numbers of deaths, prothrombin time and partial thromboplastin time. The reviewers were not blinded to the authors or journal when doing this. Results were compared and any differences resolved by discussion.
Where there was insufficient information in the published report we attempted to contact the authors for clarification.

Assessment of risk of bias in included studies

Since there is evidence that the quality of allocation concealment particularly affects the results of studies, two reviewers (IK, FB) scored this quality on the scale used by Higgins 2008 as shown below, assigning 'No' to poorest quality and 'Yes' to best quality:

- Yes = trials deemed to have taken adequate measures to conceal allocation (i.e. central randomisation; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment)
- Unclear = trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories
- No = trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth).

Where the method used to conceal allocation was not clearly reported, the author(s) were contacted, if possible, for clarification. We then compared the scores allocated and resolved differences by discussion.

Data synthesis

The following comparisons were made:

- early versus delayed intravenous fluids administration
- larger versus smaller volume of intravenous fluids administration.

The relative risk of death and 95% confidence interval (95% CI) was calculated, such that a relative risk of more than 1 indicated a higher risk of death in the first group named. The relative risk was chosen as it is more readily applied to the clinical situation. The weighted mean difference was calculated for coagulation times. Because of differences in the types of patients and in the nature of the trial interventions we did not pool the data in our analysis.

RESULTS

Description of studies

See: Characteristics of included studies.

Our original search strategy found 4,487 potentially eligible reports of which six unpublished trials met the inclusion criteria. A further 655 abstracts were retrieved from a search carried out in August 2007, and another search in October 2008 retrieved 261 abstracts. All search results were scanned by two individuals for potentially relevant studies. No new trials that met the inclusion criteria were indentified from these search results.

A. Early versus delayed intravenous fluids administration

Bickell 1994

This trial compared early versus delayed administration of Ringer's acetate solution, an isotonic crystalloid, in patients with penetrating torso injuries during the prehospital phase. Participants were adults over 16 years of age, with gunshot or stab wounds to the torso, and who had a systolic blood pressure of <90mmHg. Participants with head injury, a Revised Trauma Score of zero or minor injuries were excluded. During the trial, 22 patients (8%) in the delayed resuscitation group were inadvertently given fluid prior to surgery in violation of the protocol. Follow-up was until hospital discharge.

Blair 1986

This trial compared early versus delayed blood transfusion in patients with acute gastrointestinal haemorrhage during the first 24 hours after admission. Patients with oesophageal varices were excluded because of abnormal coagulation related to liver diseases. Follow-up was until hospital discharge.

Turner 2000

This trial compared early versus no/delayed fluid administration in trauma patients. Participants were all trauma patients with moderate to severe injuries, over the age of 16 years of age. Patients who were pregnant or without vital signs were excluded. Fluids given were crystalloids. Protocol compliance was poor with 31% of patients in the early fluid group receiving fluids and 80% of the delayed/no fluid group not given fluids. Follow-up was for six months.

B. Larger versus smaller volume of intravenous fluids administration

Dunham 1991

This trial compared fluid resuscitation using the rapid infusion system and conventional fluid administration method in trauma patients during the first 24 hours of admission. Participants were between 14 and 60 years of age and had a systolic blood pressure of <90mmHg. Patients with a Glasgow Coma Score of <5, cardiac arrest, quadriplegia and myocardial infarct on admission were excluded. Fluids given included red blood cells, platelets, fresh frozen plasma and crystalloids. Follow-up was until hospital discharge.

Dutton 2002

This trial compared the maintenance of target systolic blood pressures of 70 and 100mmHg respectively with fluid restriction (Plasma, Plasmalyte-A and red blood cells in the first 24 hours) in patients with blunt and penetrating trauma injuries. All participants suffered haemorrhagic shock with a systolic blood pressure (SBP) of <90mmHg. Patients with head or spinal cord injury were excluded. Length of follow-up period was until death or hospital discharge.

Fortune 1987

This trial compared the maintenance of haematocrit at 30% and 40% respectively with blood transfusion in patients following acute injuries and haemorrhage during the first 72 hours of admission. All participants had sustained Class III/IV haemorrhage with a systolic blood pressure of <90mmHg, heart rate > 100 beats per minute. Follow-up was for three days.

Risk of bias in included studies

A. Early versus delayed intravenous fluids administration

Bickell 1994

Randomisation was by alternate day allocation which allowed foreknowledge of treatment allocation. Data were analysed as randomised, on an intention-to-treat basis. Blinding of outcome assessment was not stated. There was no loss to follow-up.

Blair 1986

Contact with the author of this trial established the adequacy of the randomisation method used. Allocation was by opening sealed envelopes at the time of patient presentation. Blinding of outcome assessment was not stated. Data were analysed as randomised, on an intention-to-treat basis. There was no loss to follow-up.

Turner 2000

Paramedics rather than trauma patients were randomised, using computer-generated random numbers, stratified by base stations. The paramedics crossed over to alternate fluid protocol halfway through the trial and they were not blinded. Data were analysed as randomised, on an intention-to-treat basis. There was no blinding in outcome assessment.

B. Larger versus smaller volume of intravenous fluids administration

Dunham 1991

Method of randomisation and allocation concealment was unclear. Blinding of outcome assessment was not stated. Data on eight

patients who died during the first 12 hours were excluded from the analysis except for the outcome of death.

Dutton 2002

Randomisation was by selecting the next numbered envelope from a supply maintained in the Trauma Resuscitation Unit. The envelopes were made up in batches of 20 (10 to each group), thoroughly mixed, and then numbered for selection. Allocation was blinded to all Unit personnel prior to enrolment . Only the patients were blinded to the allocation in this trial after randomisation. Data were analysed as randomised, on an intention-to-treat basis. Blinding of outcome assessment was not stated. There was no loss to follow-up.

Fortune 1987

Contact with the co-author of this trial established the adequacy of the randomisation method used. Sequences of random allocations were generated by a statistician not involved with the study, in sets of sealed opaque envelopes, differentiated by sex and age groups. Both patients and physicians had no prior knowledge of which arm the patient would be assigned to. Blinding of outcome assessment was not stated. There was no loss to follow-up.

The characteristics of each trial are listed in Characteristics of included studies.

Effects of interventions

A. Early versus delayed fluid administration

One trial (Bickell 1994) reported mortality and coagulation time on a total of 598 hypotensive trauma patients with penetrating torso injuries. Mortality was 116/309 (38%) in the early and 86/289 (30%) in the delayed administration group. The relative risk for death with early fluid administration was 1.26 (95% CI 1.00−1.58). Prothrombin time and partial thromboplastin time were 14.1 and 31.8 seconds in the early, as compared to 11.4 and 27.5 seconds in the delayed administration group. The weighted mean difference (WMD) for prothrombin time and partial thromboplastin time was 2.7 (95% CI 0.90−4.5) and 4.3 seconds (95% CI 1.7−6.9) respectively.

One trial (Blair 1986) reported mortality and coagulation time on a total of 50 hypotensive patients with acute upper gastrointestinal haemorrhage. Mortality was 2/24 (8%) in the early as compared to 0/26 (0%) in the delayed transfused group. The relative risk for death with early blood transfusion was 5.4 (95% CI 0.3−107.1). Activated partial thromboplastin time was 48 in the early, as compared to 41 seconds in the delayed administration group. The WMD for partial thromboplastin time was 7.0 seconds (95% CI 6.0−8.0).

In one trial (Turner 2000) on a total of 1309 trauma patients, mortality was 73/699 (10.4%) in the early as compared to 60/610 (9.8%) in the delayed/no fluid administration group. The relative risk for death with early fluid administration was 1.06 (95% CI 0.77−1.47). There were no data on coagulation times.

B. Larger versus smaller volume of fluid administration

One trial (Dunham 1991) reported mortality and coagulation time on a total of 36 hypotensive trauma patients. Mortality was 5/20 (25%) in the group who received a larger volume of fluids administered conventionally, as compared to 5/16 (31%) in the group who received a smaller volume of fluids administered using the Rapid Infusion System. The relative risk for death is 0.80 (95% CI 0.28−2.29). Prothrombin time and partial thromboplastin time were 14.8 and 47.3 seconds in the group who received a larger volume of fluid as compared to 13.9 and 35.1 seconds in the comparison group.

In one trial (Dutton 2002) on a total of 110 hypotensive patients with blunt and penetrating injuries, mortality was 4/55 (7.3%) in the group administered a larger volume and 4/55 (7.3%) in the group administered a smaller volume (1000ml less than in the intervention group). The relative risk for death is 1.00 (95% CI 0.26−3.81). There were no data on coagulation times.

In one trial (Fortune 1987) on a total of 25 hypotensive patients with acute injury and haemorrhage, there were no data on mortality in both the groups administered with larger or smaller volume of blood. Contact with the co-author established that there were no deaths in either group. There were no data on coagulation times.

DISCUSSION

This review found insufficient evidence for or against the use of early or larger volume fluid resuscitation in the treatment of uncontrolled haemorrhage. While vigorous fluid resuscitation may be life-saving in some patients, results from clinical trials are inconclusive.

Every year, tens of thousands of patients receive intravenous fluids in the management of bleeding. The Advanced Trauma Life Support (ATLS) protocol of the American College of Surgeons recommends the liberal use of isotonic crystalloid to correct hypotension in bleeding trauma patients. Nevertheless, we could find no reliable evidence to support or not to support this recommendation. While we cannot exclude the possibility that we overlooked a large high-quality randomised controlled trial showing that early or larger volume fluid resuscitation is beneficial, we believe that this is unlikely. To identify eligible trials we screened over 4,000 potentially relevant reports, we searched the reference lists of included trials, and contacted authors and experts in the field.

Six published trials were reviewed. Due to their heterogeneity, in terms of types of patients and types of fluids used, we did not attempt to perform a meta-analysis of the studies.

Death was chosen as the primary end-point in this review for two reasons. First, death is a clinically relevant outcome that matters to patients. Second, death is not prone to measurement error and to reporting bias, as are pathophysiological end points. Mortality data were available for all six included trials, three on the effect of early fluid resuscitation (Bickell 1994; Blair 1986; Turner 2000) and three on the effect of larger volume fluid resuscitation (Dunham 1991, Dutton 2002, Fortune 1987).Three trials examined the effect of fluid administration on coagulation. Clotting times were significantly elevated in the immediate resuscitation groups (Bickell 1994, Blair 1986) and the group who received a larger volume (Dunham 1991). Method of randomisation was inadequate in two trials (Bickell 1994, Turner 2000) and unclear in another (Dunham 1991). Allocation concealment was inadequate in two trials (Bickell 1994; Turner 2000). Because inadequate randomisation and poorly concealed allocation can bias the results of randomised controlled trials, and because this bias can be large and can operate in either direction, the impact of early or larger volume fluid resuscitation on mortality remains difficult to estimate.

Interpretation of results also needs to be cautious due to the heterogeneous nature of traumatic injuries encountered in these trials. Haemorrhagic shock can be caused by a variety of underlying anatomic injuries. Some of these injuries, such as posterior pelvic fractures, may be more amenable to hypotensive management maintained by smaller volume of fluid, than liver injuries where haemostasis can be difficult to achieve (Dutton 2002).

The use of medical anti-shock trousers, early and larger volume fluid administration and colloid resuscitation are based on the idea that raising the blood pressure in bleeding trauma patients will maintain tissue perfusion and so prevent haemorrhagic shock and its consequences. However, while maintaining blood pressure may prevent shock, it may worsen bleeding. In view of the lack of evidence for or against the effectiveness of currently recommended resuscitation protocols and the potential for harm, the balance of risks and benefits of contemporary resuscitation practice warrants careful consideration. Further randomised controlled trials are required to identify the most effective strategies for the fluid management of bleeding trauma patients.

AUTHORS' CONCLUSIONS

Implications for practice

We found no evidence for or against the use of early or larger volume intravenous fluid administration in uncontrolled haemorrhage. There is uncertainty about the effectiveness of fluid resuscitation in patients with bleeding following trauma.

Implications for research

Large, well concealed, randomised controlled trials are urgently needed to establish the optimal fluid resuscitation strategy in haemorrhaging trauma patients, with a focus on specific types of injuries likely to benefit from the appropriate resuscitation strategy in terms of timing and volume of fluids given.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bickell 1994

Methods	Quasi-randomised controlled trial. (Allocation by alternation - odd and even numbered days of the month.)
Participants	598 trauma patients >16 years of age with penetrating injuries and hypotension. Mean age = 31 years. Exclusion: pregnancy, Revised Trauma Score = 0, minor injuries not requiring surgery.
Interventions	1) 870ml of Ringer's solution pre-hospital (n=309). 2) 92ml of Ringer's solution with IV cannulation pre-hospital (n=289).
Outcomes	• Haemodynamic variables, • amount of fluids given, • intraoperative blood loss, • post-op • complications, • process of care, • death.
Notes	Patients in both groups were treated with a standard paramedical protocol as appropriate until after IV cannulation. 22/289(8%) in delayed fluids group were inadvertently given fluids in violation of the protocol. Results were analysed as randomised on an intention-to-treat basis.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	

Blair 1986

Methods	Randomised controlled trial. (Allocation by opening sealed envelopes.)
Participants	50 patients with acute severe upper gastrointestinal haemorrhage. Mean age = 62 Exclusion: patients with oesophageal varices due to abnormal coagulation.
Interventions	1) >/= 2 units of blood in first 24 hr (n=24). 2) No blood transfusion during first 24 hr (n=26).

Blair 1986 (*Continued*)

Outcomes	• Coagulation times, • Haematocrit, • re-bleeding rate, • volume of blood given, • death.
Notes	5/26 patients in the no-blood group received blood in the first 24 hours when their Hgb < 8g/dl. Results were analysed as randomised on an intention-to-treat basis.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	

Dunham 1991

Methods	Randomised controlled trial. (Allocation unclear.)
Participants	36 trauma patients >14 <60 years of age with hypotension. Mean age = 35. Exclusion: Glasgow Coma Score <5, cardiac arrest, quadriplegia, myocardial infarct.
Interventions	1. 23,661ml of IV fluids (red blood cells, fresh frozen plasma, platelets and Plasmalyte-A)in first 24 hours via conventional fluid administration (CFA) (n=20). 2. 20,224 ml of IV fluids (red blood cells, fresh frozen plasma, platelets and Plasmalyte-A, given via the RIS (Rapid Infusion System). (n=16).
Outcomes	• Blood loss, • temperature, • Haematocrit, • coagulation times, • serum Lactate, • base excess, • ionised calcium, • costs, • death.
Notes	Data from 3/20 patients in CFA group and 5/16 patients in RIS group who died in the first 12 hours were excluded from subsequent analyses except for death.

Dutton 2002

Methods	Randomised controlled trial. (Allocation by drawing the next numbered envelope from a batch of 20, thoroughly mixed but sequentially numbered envelopes.)
Participants	110 trauma patients >16, <55 years of age with blunt and penetrating injuries and in shock. Mean age = 31 Exclusion: pregnancy, no pulse, head or spinal injury, known end-organ ischaemic disease.
Interventions	1. Bolus of fluids (plasma, Plasmalyte-A and packed red blood cells) to maintain systolic blood pressure of >100mmHg (n=55). 2. 1000ml less of fluids (plasma, Plasmalyte-A and packed red blood cells) to maintain a lower blood pressure of 70mmHg (n=55).
Outcomes	• Duration of bleeding, • average ISS, • death.
Notes	All patients maintained at a haematocrit of at least 25%. Results analysed as randomised on an intention-to-treat basis.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	

Fortune 1987

Methods	Randomised controlled trial. (Random allocations generated by a statistician blinded to the study, in sets of sealed opaque envelopes.)
Participants	25 patients with acute injury and haemorrhage, hypotensive, urine output < 20ml/hr. Mean age = 46. Exclusion: history of myocardial infarction in previous year as a higher haematocrit could be harmful.
Interventions	1. >/= 5 units of blood to maintain Haematocrit at 40% (n=13). 2. < 5 units of blood transfusion to maintain Haematocrit at 30% (n=12).
Outcomes	• Cardiopulmonary status, • death not reported, but later obtained from the author.
Notes	Study was designed to test the hypothesis that sufficient oxygen can be provided at lower haematocrit of 30%. Allocation concealment was later reported to be adequate when co-author was contacted.

Risk of bias

Item	Authors' judgement	Description

Fortune 1987 (*Continued*)

Allocation concealment?	Yes	

Turner 2000

Methods	Randomised controlled trial (of paramedics using computer-generated random numbers, stratified by base stations).
Participants	1309 trauma patients > 16 years of age. Exclusion: pregnancy, no vital signs.
Interventions	1. >/= 1 unit of fluids of Hartmann's solution and Haemacell pre-hospital (n=699) 2. Delayed/no fluids pre-hospital (n=610).
Outcomes	• Post-op complications, • process of care, • costs, • death.
Notes	Protocol compliance was poor with 31% of the fluid group receiving fluids and 80% of the no fluid group not given fluids.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	No	

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search strategy

Cochrane Inuries Group's Specialised Register (searched 22 October 2008)
(((fluid* or volume or plasma or blood) and (replace* or therap* or substitut* or restorat* or resuscitat*)) or ((fluid* or volume or plasma or blood) and (administrat* or challenge or perfusion or intravenous or shock))) and (timing or volume)
CENTRAL (*The Cochrane Library issue 4, 2008)*
#1 MeSH descriptor Fluid Therapy explode all trees
#2 MeSH descriptor Infusions, Intravenous explode all trees
#3 (fluid* or volume or plasma or blood) near3 (replace* or therap* or substitut* or restorat* or resuscitat*):ti or (fluid* or volume or plasma or blood) near3 (replace* or therap* or substitut* or restorat* or resuscitat*):ab
#4 (fluid* or volume or plasma or blood) near3 (administrat* or challenge or perfusion or intravenous or shock):ti or (fluid* or volume or plasma or blood) near3 (challenge or perfusion or intravenous or shock):ab
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Time Factors, this term only
#7 (timing or delayed or intermediate or early or selective or rapid or immediate*):ti
#8 rapid near3 infusion*
#9 (small* or large*) near3 volume
#10 MeSH descriptor Plasma Volume, this term only
#11 (#6 OR #7 OR #8 OR #9 OR #10)
#12 (#5 AND #11)
MEDLINE 1966 to October 2008
1. exp Fluid Therapy/
2. exp Infusions, Intravenous/
3. ((fluid* or volume or plasma or blood) adj3 (replace* or therap* or substitut* or restorat* or resuscitat*)).ab,ti.
4. ((fluid* or volume or plasma or blood) adj3 (administrat* or challenge or perfusion or intravenous or shock)).ti,ab.
5. 1 or 2 or 3 or 4
6. exp Time Factors/
7. exp Plasma Volume/
8. (timing or delayed or intermediate or early or selective or rapid or immediate*).ti.
9. (rapid adj3 infusion*).ab,ti.
10. ((small* or large*) adj3 volume).ab,ti.
11. 6 or 7 or 8 or 9 or 10
12. 5 and 11
13. randomi?ed.ab,ti.
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. placebo.ab.
17. clinical trials as topic.sh.
18. randomly.ab.
19. trial.ti.
20. or/13-19
21. humans.sh.
22. 20 and 21

23. 22 and 12

EMBASE 1980 to October 2008

1. exp Fluid Therapy/
2. exp Infusions, Intravenous/
3. ((fluid* or volume or plasma or blood) adj3 (replace* or therap* or substitut* or restorat* or resuscitat*)).ab,ti.
4. ((fluid* or volume or plasma or blood) adj3 (administrat* or challenge or perfusion or intravenous or shock)).ti,ab.
5. 1 or 2 or 3 or 4
6. (timing or delayed or intermediate or early or selective or rapid or immediate*).ti.
7. (rapid adj3 infusion*).ab,ti.
8. ((small* or large*) adj3 volume*).ab,ti.
9. *time factors/
10. *plasma volume/
11. 6 or 7 or 8 or 9 or 10
12. 5 and 11
13. exp Randomized Controlled Trial/
14. exp controlled clinical trial/
15. randomi?ed.ab.
16. placebo.ab.
17. exp Clinical Trial/
18. randomly.ab.
19. trial.ti.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp human/
22. 20 and 21
23. 22 and 12

PubMed (searched 22 Oct 2008; limit: last 90 days)

#1 Search "Fluid Therapy"[Mesh] OR "Infusions, Intravenous"[Mesh]

#2 Search (fluid* or volume or plasma or blood) AND (replace* or therap* or substitut* or restorat* or resuscitat*) Field: Title/Abstract

#3 Search (fluid* or volume or plasma or blood) AND (administrat* or challenge or perfusion or intravenous or shock) Field: Title/Abstract

#4 #1 or #2 or #3

#5 Search (small* or large*) AND volume Field: Title/Abstract

#6 Search rapid infusion* Field: Title/Abstract

#7 Search (timing or delayed or intermediate or early or selective or rapid or immediate*):ti Field: Title

#8 #5 or #6 or #7

#9 #4 and #8

#10 Search (randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh]) NOT ((models, animal[mh] OR Animals[mh] OR Animal Experimentation[mh] OR Disease Models, Animal[mh] OR Animals, Laboratory[mh]) NOT (Humans[mh]))

#11 #9 and #10

Web of Science; Science citation index: searched 22 Oct 2008

#1 Title=((fluid* or volume or plasma or blood) and (replace* or therap* or substitut* or restorat* or resuscitat*)) AND Title=(timing or volume) AND Topic=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial OR controlled clinical trial OR randomized controlled trials)

#2 Title=((fluid* or volume or plasma or blood) and (administrat* or challenge or perfusion or intravenous or shock)) AND Title=(timing or volume) AND Topic=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial OR controlled clinical trial OR randomized controlled trials)

#3 #1 or #2

WHAT'S NEW

Last assessed as up-to-date: 21 October 2008.

6 November 2008	New search has been performed	Search updated. No new trials were found for inclusion in the review.

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 1, 2001

20 August 2008	Amended	Converted to new review format.
12 April 2003	New search has been performed	Data have now become available from a trial (Dutton 2002) which was ongoing in 2000. These data did not affect the results or the overall conclusion of the review. Types of injuries may be an important consideration in the research design of future trials in fluids resuscitation.

CONTRIBUTIONS OF AUTHORS

IK screened citations, extracted data, contacted authors, entered data into RevMan and helped to write the review. IR developed the protocol, and helped to write the review. FB screened citations, extracted data, and commented on the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Institute of Child Health, University of London, UK.

External sources

- Global Programme on Evidence for Health Policy (GPE), World Health Organisation, Switzerland.

INDEX TERMS

Medical Subject Headings (MeSH)

Hemorrhage [*therapy]; Infusions, Intravenous; Plasma Substitutes [*administration & dosage]; Randomized Controlled Trials as Topic; Time Factors; Wounds and Injuries [blood; *complications]

MeSH check words

Humans