Perioperative fluid volume optimization following proximal femoral fracture

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ABSTRACT

Background

Proximal Femoral Fracture (PFF) or ‘hip fracture’ is a frequent injury, and adverse outcomes are common. Several factors suggest the importance of developing techniques to optimize intravascular fluid volume. These may include protocols that enhance the efficacy of clinicians’ assessments, invasive techniques such as oesophageal Doppler or central venous pressure monitoring, or advanced non-invasive techniques such as plethysmographic pulse volume determination.

Objectives

To determine the optimal method of fluid volume optimization for adult patients undergoing surgical repair of PFF. Comparisons of fluid types, of blood transfusion strategies or of pharmacological interventions are not considered in this review.

Search strategy

We searched CENTRAL (The Cochrane Library, issue 4, 2003), MEDLINE (1985 to 2003), EMBASE (1985 to 2003), and bibliographies of retrieved articles. Relevant journals and conference proceedings were handsearched.

Selection criteria

Randomized controlled studies comparing a fluid optimization intervention with normal practice or with another fluid optimization intervention, in patients following PFF undergoing surgery of any type under anaesthesia of any type.

Data collection and analysis

Searches and exclusion of clearly irrelevant articles were performed by one reviewer. Two reviewers examined independently the remaining studies, extracting study quality and results data. A wide range of short- and long-term outcome data were sought. Studies were excluded if they did not meet selection criteria or if results were likely to be biased. Due to inconsistent data reporting, combination of data was not generally possible.

Main results
Searches identified four trials, of which two studies, randomizing a total of 130 patients, were of adequate quality and addressed the review question. Both studies were of invasive advanced haemodynamic monitoring, either oesophageal Doppler ultrasonography or central venous pressure monitoring, during the intraoperative period only. In both, invasive monitoring led to significant increases in fluid volumes infused and reductions in length of hospital stay. The pooled Peto odds ratio for in-hospital fatality was 1.44 (95% confidence interval 0.45-4.62). Neither study followed patients beyond hospital discharge or assessed functional outcomes. No serious complications were directly attributable to the interventions. There were no studies of protocol-guided fluid optimization or of advanced non-invasive techniques.

Authors’ conclusions

Invasive methods of fluid optimization during surgery may shorten hospital stay, but their effects on other important, patient-centred, longer-term outcomes are uncertain. Adverse effects on fatality cannot be excluded. Other fluid optimization techniques have not been evaluated. The lack of randomized studies of adequate quality addressing this important question is disappointing. More research is needed.

PLAIN LANGUAGE SUMMARY

Techniques, for detecting when patients undergoing surgery for hip fracture need more fluid, may reduce hospital stay, but more research is needed.

Hip fracture is common, and the outcome may be poor. Many patients need more fluid, but clinicians find it difficult to tell how much is needed. Protocols (formal guidance) or advanced monitoring techniques (such as central venous pressure monitoring) may help guide fluid therapy. This review of trials found no evidence about the value of protocols. Some small trials suggest that advanced monitoring techniques shorten the duration of hospital care and have few adverse effects, but more research is needed.
BACKGROUND

Proximal Femoral Fracture (PFF) is a common and important injury. Patients are among the most elderly and frail to undergo urgent surgery of any kind. One year fatality after hip fracture may exceed 25%, over 10% of surviving (previously independent-living) patients need permanent institutional care and only 40% of those able to walk without aid prior to fracture do so one year later (Keene 1993). The term PFF encompasses fractures of the femoral head, the femoral neck, the trochanters and the inter- and sub-trochanteric regions, but excludes fractures of the acetabulum and of the femoral shaft below the subtrochanteric region. Proximal femoral fractures may be known collectively as “hip fracture” or “neck of femur fracture”, although these terms are imprecise, ambiguous and should be avoided.

The majority of fractures occur in older women. Median age is around 80 years, and women outnumber men by around four to one (Parker 1993). Worldwide predictions are dramatic: by 2050, the population over 60 years increases over three-fold (from 606 millions to 2,000 millions), and nonagenarians eight-fold (from seven millions to 61 millions) (United Nations 2000). The greatest relative increases occur in developing nations. Furthermore, age-specific PFF rates may be increasing (Evans 1997). Combining these trends, PFF incidence in developed nations is expected to triple or quadruple by mid-century (Kannus 1999; Sanders 1999). Relative increases in developing nations are likely to exceed this.

Most PFFs are treated surgically, and of all older people undergoing surgery, patients with PFF are well represented, dominating the subsets undergoing urgent surgery and the very old. The surgery itself is usually straightforward; medical factors determine outcome. Amongst older people undergoing surgery, pre- and postoperative medical problems are common (Seymour 1989; Vaz 1989); respiratory, cardiac and cognitive problems predominate. The 1996 Report of the United Kingdom National Confidential Enquiry into Perioperative Deaths (Callum 1999) focuses on extremes of age, including the very old. It notes that around 50% of all deaths in the very old follow PFF; anaesthetists reported preoperative medical problems in 95% of all older surgical patients who died.

Fluid resuscitation for hypovolaemia is a key component of the management of all critically ill patients, and many factors suggest the importance of developing appropriate techniques to optimize intravascular fluid volume in patients following PFF. Modest degrees of hypovolaemia are difficult to recognize on clinical grounds alone, and there may be clinical reluctance to prescribe fluid due to concern that this may precipitate heart failure. The high prevalence of chronic heart failure, chronic renal failure and vascular disease (coronary, cerebral and other) in patients with PFF suggests that there may be enhanced sensitivity to the effects of suboptimal intravascular volume. Additionally, chronic volume depletion is common in older people, secondary to diuretic use and reduced fluid intake. This may be exacerbated at the time of fracture by haemorrhage and at times by a significant period of immobility and starvation prior to admission. Occult hypovolaemia may lead to poor tissue perfusion, and thus to covert suboptimal organ function or overt organ failure. Many organs are susceptible to the effects of hypo-perfusion, especially skin, gut and kidney. There is therefore a wide spectrum of putative benefits of improved tissue perfusion, in the short and long term. Longer-term benefits may include reduced pressure sore incidence, decreased postoperative malaise, more effective rehabilitation, earlier mobilization and discharge, reductions in the incidence of delirium and longer-term postoperative cognitive dysfunction, and a reduction in the need for long-term institutional care.

Fluid overload can be just as harmful to tissue oxygenation as hypovolaemia. Pulmonary oedema is a common sequela of iatrogenic fluid overload; it can occur in patients with or without relevant comorbid conditions, clinical warning signs are sometimes absent, and cardiorespiratory arrest may be the mode of first clinical presentation (Arieff 1999). There are many reasons for administration of large quantities of fluid pre-, intra- and postoperatively, including hypotension following induction of anaesthesia, expansion of the fluid “third space” following surgery, blood loss and fever with increased insensible loss, but determining the optimal volume of fluid to be administered is not straightforward. Virtually all protocols for postoperative fluid management recommend frequent monitoring of fluid volume status, utilizing readily available clinical parameters including blood pressure, heart rate, urine output, lung crepitations, body weight, and net fluid balance. However, each of these parameters has disadvantages when used to guide fluid infusion. For example, they may be difficult to assess accurately (chest crepitations; body weight), insensitive to moderate changes in volume state (blood pressure) or convey potentially misleading information (for example tachycardia as a response to either hypovolaemia and left ventricular failure).

In some cases, clinicians therefore elect to attempt to assess circulatory status more objectively. In high-risk patients undergoing major surgery, fluid and/or inotrope therapy guided by pulmonary artery catheter may improve outcome (Shoemaker 1988; Berlauk 1991; Boyd 1993). These and other techniques have been less well evaluated and are less commonly applied to patients following PFF, despite their acknowledged vulnerability. The 1996 Report of the United Kingdom National Confidential Enquiry into Perioperative Deaths (NCEPOD 1996) noted that only 3% of the 422 patients who died following PFF had been monitored invasively during surgery (central venous or arterial pressure monitoring) and only 6% were managed in a high dependency area post-operatively. The widespread adoption of such monitoring technologies in patients with PFF would have significant resource implications. This, in addition to the possibility of significant effects on outcome (beneficial or adverse), supports the need for the rigorous evaluation of methods to optimize intravascular fluid volume.

The choice of resuscitation fluid - of colloid versus crystalloid,
and then of a specific colloid or crystalloid - has been considered in other Cochrane Reviews (Alderson 2003; Bunn 2003) and is not considered in detail here. Colloids are used and recommended widely, but there is evidence that they do not reduce fatality in critically ill patients following trauma, burns or major surgery (Alderson 2003), and there is no evidence that one colloid solution is more effective or safe than any other (Bunn 2003). These two Cochrane Reviews identified 100 studies that met their inclusion criteria, and although several studies included patients undergoing elective total hip replacement, no study included patients following PFF. The extension of these conclusions to patients following PFF is therefore uncertain.

**OBJECTIVES**

To determine the optimal method of fluid volume optimization for adult patients undergoing surgical repair of hip fracture.

Comparisons of fluid types (e.g. crystalloid versus colloid) or of blood transfusion strategies or of other pharmacological interventions (e.g. inotropes) are not considered in this review.

The following null hypotheses were tested:

- There is no difference in outcome between 'usual care' and advanced haemodynamic monitoring (all techniques; see criteria for considering studies for this review)
- There is no difference in outcome between 'usual care' and central venous pressure monitoring
- There is no difference in outcome between 'usual care' and oesophageal Doppler ultrasonography monitoring
- We had also intended to test the following null hypothesis, but no evidence from randomized trials was available:
  - There is no difference in outcome between 'usual care' and systematized (protocol-guided) fluid optimization by clinicians

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We included only randomized controlled trials. Quasi-randomized trials (e.g. alternation) and trials in which treatment allocation was inadequately concealed were considered for inclusion. Unpublished studies and studies published only in abstract form were included if adequate method and results data could be obtained.

**Types of participants**

We included studies on adults with PFF who underwent surgical treatment of any type under regional or general anaesthesia.

**Types of interventions**

Interventions could include

1. systematized (protocol-guided) fluid optimization by clinicians, utilizing clinical signs and/or universally available parameters such as blood pressure, heart rate or urine output.
2. advanced haemodynamic monitoring
   i) invasive techniques of determination of fluid status (e.g. Swan-Ganz catheter, central venous catheter, transoesophageal Doppler)
   ii) non-invasive techniques of determination of fluid status (e.g. plethysmographic pulse volume determination, impedance plethysmography)

**Types of outcome measures**

Outcome following PFF is multi-dimensional (Fairbank 1999), encompassing

1. fatality
2. complications
3. return of function and wellbeing

The outcomes included in this review have been selected on the basis of those that are most likely to help decision-making. Our preferred outcomes of interest, with preferred timings of assessment, were as follows.

a) Case fatality (in-hospital and at 30 days, 120 days, 6 months and 1 year)
b) Return of patient to pre-fracture category of accommodation (at hospital discharge and at 30 days, 120 days, 6 months and 1 year)
c) Independence in basic Activities of Daily Living (ADL; e.g. washing, dressing; at 120 days)
d) Return to pre-fracture mobility (at 120 days)

In addition, data was sought from the following categories.

a) Peri-operative cardiopulmonary parameters
   - Hypotension
   - Cardiac output
   - Pre- and postoperative blood gases
   - Changes in catecholamines and other stress response mediators

b) Complication specific to the trial intervention
   e.g. pneumothorax, haemothorax, upper limb venous thrombosis, line sepsis, local haematoma

c) Complications during the in-patient stay not specific to the trial intervention
   - Pneumonia
   - Congestive cardiac failure
   - Respiratory failure
• Myocardial infarction
• Renal failure
• Cerebrovascular accident
• Delirium
• Venous thrombo-embolism
• Pulmonary embolism
• Pressure sores
• Wound infection or breakdown
• Postoperative nausea and vomiting

d) Rehabilitation
• Independence in Instrumental Activities of Daily Living (IADL; e.g. shopping, cooking; at 120 days)
• Walking speed, stair climbing time, leg extensor power (fractured limb)
• Return of patient to pre-fracture social integration (at 120 days)
• Attainment of patient-specified outcome goals
• Time to mobilization
• Time to be declared fit for discharge
• Total time in hospital
e) Readmission
Rate of emergency readmission (for any reason) within 30 days of discharge
f) Cognitive state
• Incidence of delirium during inpatient stay
• Severity and prevalence of postoperative cognitive dysfunction (at one week and three months)

Search methods for identification of studies
Due to developments in many aspects of peri-operative care, it was not considered that studies of fluid optimization published prior to 1985 would be applicable to the modern clinical setting. Therefore only studies published after this date were considered. We therefore identified relevant randomized trials published in any language by:
1. searching CENTRAL (The Cochrane Library, issue 4, 2003)
2. searching MEDLINE in October 2003, for the period 1985 to 2003, using the following search strategy:
#1 - "Clinical Protocols" all subheadings
#2 - "Water-Electrolyte-Balance" all subheadings
#3 - "Fluid-Therapy" all subheadings
#4 - "Infusions-Intravenous" all subheadings
#5 - "Catheterization-Central-Venous" all subheadings
#6 - "Catheterization-Swan-Ganz" all subheadings
#7 - "Axillary-Vein" all subheadings
#8 - "Echocardiography" all subheadings
#9 - "Echocardiography-Transesophageal" all subheadings
#10 - "Pulmonary-Wedge-Pressure" all subheadings
#11 - "Critical-Care"
#12 - "Cardiac-Output"
#13 - Monitoring-Physiologic"
#14 - "Hemodynamics"
#15 - #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
or #11 or #12 or #13 or #14
#16 - "Femoral fractures" all subheadings
#17 - "Hip-Fractures"
#18 - "Femoral-Neck-Fractures"
#19 - #16 or #17 or #18
#20 - #15 and #19
3. searching EMBASE in October 2003 (1985 to 2003) with a similar strategy
4. hand-searching relevant journals not previously hand-searched by Cochrane Review Groups and therefore not included in the Controlled Trials Register. These journals were:
• Trauma. Year 2000 - October 2003.
5. searching the reference lists of trials and review articles

Data collection and analysis
Methods of the review
One reviewer scanned the title and abstract of articles that had been identified, identifying those that may possibly meet the inclusion criteria. The full published report of these was obtained. Articles in all languages were considered. One reviewer examined the full published reports of all potential primary studies, extracting data regarding inclusion criteria. Studies possibly fulfilling the inclusion criteria were retained for further consideration.
Two reviewers examined independently the remaining studies, extracting study quality and results data. A data extraction form was used to facilitate extraction and review of inclusion criteria (study type, participants, interventions and outcomes), quality criteria and results. When necessary data were missing from a published report, the author was contacted if possible. Data entry was performed by one reviewer.
Studies were excluded if
a) they did not meet the study criteria, or
b) validity was considered sufficiently poor that the results were likely to be biased.
Details of excluded studies are reported in the Characteristics of Excluded Studies Table. Differences were resolved by discussion between two reviewers, and if necessary by the input of a third.

**Assessment of study quality**

The quality of method of each trial meeting the inclusion criteria was assessed using a ten-point instrument, a modification of that used by Parker (Parker 2003). The dominant criterion is allocation concealment (having a maximum score of 3; see below), with nine further criteria yielding an optimal quality score of 12. Quality data was extracted independently by two reviewers, and differences resolved by discussion. The scoring system was an aid to study assessment: there was no single, rigid threshold above or below which all studies were included or excluded. As well as the aggregate quality score, each quality criterion has been reported for each study. Studies that, in the judgement of all reviewers, were seriously compromised by weaknesses in design, conduct or analysis were excluded. Where information about a specific quality criterion could not be obtained, the lowest quality grade was allocated.

a) Concealment of allocation.
Trials with clear concealment of allocation (e.g. numbered opaque sealed envelopes drawn consecutively) score 3. Trials where there was a possibility of assignment disclosure score 2. Trials in which allocation concealment was not stated or unclear score 1. Those using quasi-randomization (e.g. even or odd date of birth) score 0.

b) Inclusion and exclusion criteria.
Score 1 if adequately defined. Otherwise score 0.
c) Comparability of groups at baseline.
Were the treatment and control groups adequately described at entry (at least four criteria - e.g. age, sex, mobility, residence, fracture type, ASA grade, cognition)?
Score 1 if adequately described. Otherwise score 0.
d) Treatment protocol
Were care protocols described reproductibly, for both control and intervention groups?
Score 1 if yes; 0 if no.
e) Were the care programmes identical, other than trial interventions?
Score 1 if yes; 0 if no.
f) Were the outcome measures defined clearly?
Score 1 if yes; 0 if no.
g) Were outcome assessors blind to treatment group?
Score 1 if yes; 0 if no.
h) Timing of outcome measures.
Were both short and long-term (three months or greater) outcome measures sought for all patients?
Score 1 if yes; 0 if no.
i) Intention-to-treat analysis.
Were outcomes of patients who withdrew or were excluded after allocation described and included in an intention-to-treat analysis? This applies particularly to patients allocated to intervention groups where the desired intervention (e.g. central venous catheter placement) was not achieved because of technical difficulties.
Score 1 if yes; 0 if no.
j) Loss to follow-up.
Was this reported, and if so, were less than 5% of patients "lost"? Score 1 if yes; 0 if no.
For each study, where possible, odds ratios and 95% confidence limits were calculated for dichotomous outcomes, and mean differences and 95% confidence limits for continuous outcomes. Where possible and appropriate, results of comparable groups of trials were pooled using both fixed and random effects models, and heterogeneity between comparable trials was tested using a standard chi-squared test.

**RESULTS**

**Description of studies**

See: Characteristics of included studies; Characteristics of excluded studies.
Four studies (Schultz 1985; Sinclair 1997; Gan 1999; Venn 2002) were identified by the comprehensive search strategy described above. All were studies of invasive advanced haemodynamic monitoring. There were no studies of either a) systematized (protocol-guided) fluid optimization by clinicians, or b) non-invasive advanced haemodynamic monitoring.
One study (Gan 1999) was identified in abstract form by hand-searching. The paper describes a randomized controlled trial of intraoperative fluid optimization by oesophageal Doppler, with significantly improved recovery in the intervention group. However, contact with the authors and reference to the final published paper (Gan 2002) confirmed that none of the included patients underwent surgery for PFF, and the study was excluded.
Three studies (Schultz 1985; Sinclair 1997; Venn 2002) met the inclusion criteria and had been published as full papers. One study (Schultz 1985) has been excluded from analysis due to several significant concerns regarding validity of results. These are summarized in the Characteristics of Excluded Studies Table, and include:
(a) overall methodological score (4/12) was significantly less than that of other studies (although this may reflect comprehensiveness of reporting rather than study quality itself)
(b) allocation concealment was unclear
(c) significant differences in the characteristics of control and intervention groups suggest allocation bias. For example age; control group mean 67 years, standard deviation 11 years, n=35; intervention group mean 78 years, standard deviation 11 years, n=35 (P<0.0005; two sample t test)
Perioperative fluid volume optimization following proximal femoral fracture (Review)

(d) lack of completeness of description of interventions
(e) inapplicability of aspects of management to modern clinical practice (e.g. 17 of 70 patients waited seven days or more for surgery)
(f) lack of availability of further information from the authors

Individual trial details of the two included studies are given in the Characteristics of Included Studies table. The two studies involved a total of 130 patients. They were performed at a similar historical time, in similar clinical environments, and had broadly similar catchment populations. Both studies included only patients undergoing general anaesthesia, as in each case one of the intended interventions (oesophageal Doppler monitoring) precluded regional anaesthesia. Inclusion criteria and patient characteristics were broadly similar; the relative youth and lower American Society of Anesthesiologists (ASA) grade of patients in the study of Sinclair 1997 is explained by a more inclusive age criterion and the use of two exclusion criteria (fracture associated with previous surgery; fracture occurring during hospitalization) that apply more frequently to patients that are older and more frail.

Neither study provides further information describing the prevalence and types of comorbidity that may affect fluid replacement (heart or renal failure, hypertension or ischaemic heart disease). In neither study were inotropes administered. Notably, both the included studies applied interventions that were solely intraoperative. In both cases, fluid infusions were managed conventionally during the more extended pre- and postoperative periods. This is considered more fully in the Discussion section.

Risk of bias in included studies

The methodological quality scores for the two included studies, as assessed by the scoring system described earlier, are stated below:

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These good scores confirm the belief of the reviewers that the included studies were well designed and comprehensively reported and that the results are likely to be of high validity. However, both studies report limited outcome data: neither study continued follow-up beyond hospital discharge (as little as four days in some patients), reported the proportion of patients returning directly to home from hospital, or assessed ability to perform ADL at discharge. These are clear weaknesses in the evaluation of interventions in this patient group.

Effects of interventions

The outcome data reported in the two included trials include:

- Case fatality
- Hospital stays
- Complication specific to the trial intervention
- Complications during the in-patient stay not specific to the trial intervention
- Perioperative cardiopulmonary parameters

In view of the striking methodological similarity of the two included trials, analysis of combined data would be valid. However, continuous outcomes are not reported consistently between studies. Combination of data is possible for only dichotomous outcomes reported in both studies; the sole example of such an outcome is fatality. In order to summarize continuous data consistently within studies, to combine them and to perform further analysis, we requested that individual patient data be made available. This has been obtained from Venn 2002, but is not available from the study of Sinclair 1997.

Preferred outcome measures

a) Case fatality (in-hospital; 30 days; 120 days; six months and one year)

Included studies reported only in-hospital fatality. Sinclair 1997 reported non-significant reductions in fatality in the Doppler-optimized group. Venn 2002 reported non-significant increases in fatality in both Doppler- and CVP-optimized groups. Combining data, these differences were not significant (Peto Odds Ratios: usual care vs. all techniques of advanced haemodynamic monitoring = 1.44 (95% CI 0.45 - 4.62); usual care vs. oesophageal Doppler monitoring = 0.98 (95% CI 0.23-4.09)). Test for heterogeneity: P>0.3.

b) Return of patient to pre-fracture category of accommodation (at hospital discharge; 30 days; 120 days; six months and one year)

Not reported by either study.

c) Independence in basic Activities of Daily Living (ADL; e.g. washing, dressing; 120 days)

Not reported by either study.

d) Return to pre-fracture mobility (120 days)

Not reported by either study.

Secondary outcome measures

a) Perioperative cardiopulmonary parameters

Both studies report some measures of intraoperative fluid and cardiovascular status. In general, favourable changes are observed. For example, Venn 2002 reports significant increase in central venous pressure in the CVP group. A significant reduction in episodes of severe intraoperative hypotension was observed in the combined CVP and Doppler groups. Sinclair 1997 report significant improvements in stroke volume and cardiac output in the Doppler group.

Although these results are interesting and reassuring, the clinically important question remains whether favourable physiological changes translate into the worthwhile patient-centred outcomes discussed earlier.

Neither study reports effect on blood gases, catecholamines or other stress response mediators. Neither study reports changes in heart rate or urine output.

b) Complication specific to the trial intervention

c) Complications during the in-patient stay not specific to the trial intervention


Venn 2002. There were non-significant reductions in postoperative morbidity in each intervention group (CVP and Doppler).

d) Rehabilitation

- Hospital stays

Significant reductions in certain measures of length of stay were noted in each study. Reflecting the typical separation of hospital facilities in the United Kingdom into ‘acute’ and ‘rehabilitation’ facilities, both studies report acute and total lengths of stay separately. Additionally, both studies report the time taken for patients to be declared ‘medically fit for discharge’, reflecting the fact that discharge may be delayed by factors independent of changes in patients’ condition since fracture such as the time taken to reintroduce previous care arrangements.


Acute hospital stay: 18 days (10-20) versus 10 days (9-15). P<0.05 (Mann-Whitney U test).

Days before medically fit for discharge: 15 days (10-32) vs. nine days (8-10). P<0.05 (Mann-Whitney U test).

Total duration of hospital stay: 20 days (10-32) versus 11 days (8-15). P<0.05 (Mann-Whitney U test).

Venn 2002. Group A (conventional) versus Group B (CVP) vs. Group C (Doppler) (mean; 95% C.I. (after taking reciprocal values and back-transforming)).

Acute hospital stay: 16.7 days (13.2-22.2) versus 11.1 days (8.3-17.5) vs. 12.5 days (11.1-16.7). P=0.17 (ANOVA).

Days before medically fit for discharge: 13.9 days (11.9-16.9) vs. 10.0 days (8.1-12.0) vs. 7.7 days (5.9-12.3). P=0.035 (ANOVA).

Total duration of hospital stay: 17.5 days (13.9-24.4) vs. 13.3 days (10.3-19.2) vs. 13.5 (10.9-17.5). P=0.27 (ANOVA).

Rehabilitation data from the two included trials cannot be combined in the form in which they were reported.

Neither study reported outcomes for the following:

- Independence in Instrumental Activities of Daily Living (IADL; e.g. shopping, cooking)
- Walking speed; stair climbing time; leg extensor power (fractured limb)
- Return of patient to pre-fracture social integration
- Attainment of patient-specified outcome goals
- Time to mobilization

e) Readmission

Rates of emergency re-admission are not reported in either included study.

f) Cognitive state

Neither study reported short- or long-term cognitive outcomes.

DISCUSSION

This review sought to identify high quality evidence that fluid optimization technologies of any type improve important outcomes following PFF. Despite the inclusiveness of the applied criteria for "types of intervention", only two studies of adequate quality were identified. These were small studies, randomizing a total of 130 patients (81 to intervention groups; 49 to control). Each applied only invasive techniques during only the intraoperative period. It is notable that no trials were identified of systematized (protocol-guided) fluid optimization.

In view of the importance of longer term and multi-dimensional outcome evaluation in this patient group, follow-up in both studies was too short and too narrowly focused on acute pathophysiology. As Hannan (Hannan 2001) observes, mortality and functional status outcome measures appear to vary independently between hospitals, perhaps reflecting the importance to each outcome of differing aspects of the process of care. Clinicians are vulnerable when seeking to extend short-term results to longer term patient-centred outcomes such as return to previous level of mobility, return to previous level of accommodation and independence in activities of daily living. Extrapolation to the longer term would prove false if

a) short-term benefits (physiology, length of stay) were sought and observed but were not followed by long-term benefits ('false positive')

b) short-term benefits were sought but not observed, yet important longer-term benefits occurred ('false negative').

Previous studies of preoperative optimization in other patient groups (Berlauk 1991; Boyd 1993) have shown substantial benefit of invasive monitoring in high-risk (non-orthopaedic) surgical patients. However, patients with PFF are a heterogeneous group: some present low anaesthetic risk and have a high probability of good outcome. Caution must therefore be exercised in deriving putative effect sizes in patients with PFF from these earlier optimization studies. Multiple factors contribute to outcome following PFF, and these and other factors may modulate the effect of fluid optimization techniques. Future studies should consider prospective identification of subgroups for analysis. The number of patients currently randomized is insufficient to address primary outcomes adequately, much less the secondary issue of which subgroups of patients benefit. For example, many patients undergoing surgery following PFF are anesthetized by methods other than general anaesthesia. The optimal volumes and types of fluid administered are likely to differ according to the type of anaesthesia,
and the efficacy of monitoring methods may also differ accordingly.

Improved fluid management may enhance perfusion of many organs, with associated reduction in morbidity - for example perfusion of brain (reduced delirium) and skin (improved wound healing and reduced pressure sores). It is interesting that Venn 2002 observed non-significant reductions in a broad spectrum of adverse outcomes (for example chest, wound and urinary infection), not solely for those outcomes such as heart failure or renal impairment that are more directly and immediately attributable to suboptimal fluid volume status.

Factors that may affect the type and amount of fluid replacement are multiple, and include many easily quantified and non-invasively determined clinical parameters (for example blood pressure, urine output, heart rate) as well as others that are less easily quantified (for example tissue turgor, peripheral perfusion, jugular venous pressure). Fluid optimization techniques often incorporate these as at least a part of the optimization strategy, although studies should attempt, as far as possible, to standardize both the frequency and breadth of clinical parameters monitored, as well as the response of clinicians to perceived fluid imbalance.

Resource implications

Typically, in the United Kingdom, perioperative monitoring of patients with PFF is limited to clinical (nursing and/or physician) assessments, complemented in the intraoperative and immediate postoperative period by non-invasive (oscillometric) blood pressure determination, continuous ECG and continuous oximetry. Invasive fluid optimization techniques are used rarely, and their application to all or a substantial proportion of patients following PFF would have resource implications - equipment cost, personnel time and skill. However, fluid optimization techniques, although costly in themselves, may improve health and social outcomes to such a degree that they are substantially cost-negative, ameliorating the consequences of the forecast dramatic increase in PFF incidence. Guest 1997 reports a cost-effectiveness analysis of preoperative optimization of high-risk (non-orthopaedic) patients, demonstrating likely reductions in cost of hospital care.

International context

Care must be taken in extrapolating the results of the included studies - performed in large University hospitals in the developed World - to other contexts. Efficacy and cost-effectiveness is likely to vary depending on patient and service characteristics. As well as obvious differences between developed and developing nations, differences in practice between developed nations are likely to be significant. For example, compared to the United Kingdom, “usual practice” in the United States involves more frequent invasive monitoring, lengths of hospital stay following PFF are shorter and fewer patients are discharged to their own home, a majority being discharged to skilled nursing facilities (Gan 1997).

Authors’ conclusions

Implications for practice

The included studies demonstrate that the universal application of invasive fluid monitoring technologies to patients following PFF is clinically feasible and that it probably provides short-term benefits, particularly to lengths of hospital stay. Changes in in-hospital mortality are non-significant. The possibility of harm cannot be excluded.

Any new technology, particularly one with considerable manpower and revenue implications, should be evaluated extensively before its introduction can be recommended. Much larger studies of efficacy and cost-effectiveness in diverse settings must be performed before fluid optimization techniques may be recommended for routine care following PFF. Until such evidence has been gathered, clinicians considering such interventions should where possible encourage enrolment of patients into randomized controlled trials.

It is hoped that later revisions of this review will identify further research into this important area, and that identified studies will be of sufficient quality to merit inclusion, and of sufficient size to permit firm conclusions about the efficacy and cost-effectiveness of the intervention(s) in specific clinical contexts. The availability of additional evidence may enable later revisions to stratify optimization methods, according to the weight and direction of evidence, as either (1) useful (2) probably useful (3) possibly useful (4) not useful, or harmful.

Implications for research

There is sufficient evidence of clinical feasibility and of possible benefit to justify further studies of fluid optimization. Further studies should extend the evidence base beyond the two included trials, not simply replicate their methods. Given the high morbidity, mortality, health and social service costs of this patient group, and the rapidly escalating worldwide incidence, the need for further high quality research should be considered urgent.

Size of Study

The number of patients currently randomized is insufficient to address primary outcomes adequately, much less the secondary issue of which subgroups of patients benefit. Excluding the possibility of harm, particularly excess early mortality, would require very much larger studies. For example, a study with 80% power to detect a 50% increase in in-hospital mortality (from 10% to 15%) would require randomization of 1000 patients ($\alpha = 0.05$). It is possible that future studies of fluid optimization following PFF...
may reveal a trade-off between increased short-term mortality and improved rehabilitation outcomes (e.g. reduced length of stay).

**Intervention types**

It is notable that no trials were identified of systematized (protocol-guided) fluid optimization by clinicians. It remains possible that the key component of invasive fluid optimization techniques is the administration of a volume of fluid in excess of that routinely administered, rather than the individual tailoring of fluid infusion that advanced monitoring permits. Systematized (protocol-guided) interventions may deliver important benefits, and they may be relatively undemanding of resources or technical skill. For example, the simplest ‘pragmatic’ studies may involve only the infusion of a fixed volume of fluid in excess of ‘normal care’. These methods warrant development and evaluation.

Both the included studies applied interventions that were solely intraoperative. Anaesthesia is a period of especial challenge for patients - fluid losses are rapid, and their effects are compounded by acute pharmacological as well as physiological challenge (such as patient cooling). However, the issue of fluid optimization and its potential benefit (or harm) extends beyond the period of anaesthesia to include the pre- and post-operative period. Each of these periods of potential benefit may be of several days duration: preoperatively extended by medical issues or logistical delays, and postoperatively extended by medical complications. Future trials should consider extending the optimization period where techniques permit, as well as considering the influence of type of anaesthesia (general versus regional).

**Reporting**

More complete and consistent reporting of data would have strengthened the power of this review. Where outcome variables are continuous, authors should state the assumptions used (e.g. approximation to a normal distribution) and provide standard deviations and standard errors. It is important that some outcome measures are common to different trials to allow comparison and aggregation of results where appropriate. The primary outcome measures described in this review, based on the work of Fairbank (Fairbank 1999) are suggested.

**Cost-effectiveness analysis**

Trials should include design features that enhance the power and validity of cost-effectiveness analyses. The guidance of the United Kingdom National Institute of Clinical Excellence is helpful (Sculpher 2001; NICE 2001).

**Acknowledgements**

Thanks to Mr Keith Willett and Professor Grimley Evans for helpful discussions and comments.

**References**

**References to studies included in this review**

**Sinclair 1997** (published data only)


**Venn 2002** (published data only)


**References to studies excluded from this review**

**Gan 1999** (published data only)


**Schultz 1985** (published data only)


**Additional references**

**Alderson 2003**


**Arieff 1999**


**Berlauk 1991**

Perioperative fluid volume optimization following proximal femoral fracture (Review)

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Boyd 1993

Bunn 2003

Callum 1999

Evans 1997

Fairbank 1999

Gan 1997

Gan 2002

Guest 1997

Hannan 2001

Kannus 1999

Keene 1993

NCEPOD 1996

NICE 2001

Parker 1993

Parker 2003

Sanders 1999

Sculpher 2001

Seymour 1989

Shoemaker 1988

United Nations 2000

Vaz 1989

* Indicates the major publication for the study
### Characteristics of included studies

#### Sinclair 1997

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized by sealed envelope technique. Methodological quality score 11/12.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Teaching hospital; London, United Kingdom. 40 patients undergoing repair of PFF under general anaesthesia. Exclusions: age &lt; 55 years, fracture secondary to neoplasm, fractures occurring during hospitalization for acute illness, fracture through the site of a previous surgical correction or associated with instability of a previous prosthesis, planned regional anaesthesia (this would preclude the planned intervention). Age: mean 75 years, range 69-82 years. ASA grade: median 2, interquartile range 2-3. Goldman cardiac risk index: median 9. Number lost to follow-up: nil. Surgery type: dynamic hip screw (+/- plate) 18; AO cannulated screw 7; arthroplasty 15.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Group A: Conventional intraoperative fluid replacement. Group B: as group A plus repeated colloid fluid challenges monitored by oesophageal Doppler ultrasonography to maintain maximal cardiac stroke volume.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Length of follow-up: total hospital stay only. Inpatient fatality. Acute hospital bed stay. Days before deemed medically fit for discharge. Total hospital stay. Change in intra-anaesthetic physiological parameters including: stroke volume corrected flow time cardiac output</td>
</tr>
<tr>
<td>Notes</td>
<td>Volume of colloid administered and &quot;total fluid administered per minute operating time&quot; were significantly greater for the intervention group (B). Volume of crystalloid administered were not significantly different between groups.</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>
Methods
Randomized by sealed envelope technique.
Methodological quality score 11/12.

Participants
Teaching hospital; London, United Kingdom.
90 patients undergoing repair of PFF under general anaesthesia.
Exclusions: age < 65 years, fracture secondary to neoplasm, oesophageal pathology, patients with central venous cannula in situ, planned regional anaesthesia (this would preclude one of the planned interventions).
Age: mean 84 years (SD 8 years).
ASA grade: median 3, interquartile range 3-4.
Orthopaedic POSSUM score: median 38, interquartile range 34-41.
Number lost to follow-up: nil.
Fully mobile prior to fracture: 57%.

Interventions
Group A: Conventional intraoperative fluid management.
Group B: conventional fluid management plus additional intraoperative fluid challenges guided by central venous pressure.
Group C: conventional fluid management plus fluid challenges guided by oesophageal Doppler measurements.

Outcomes
Length of follow-up: total hospital stay only.
Time to medical fitness to discharge.
Total hospital stay.
Postoperative morbidity.
Hospital fatality.
Incidence of severe intraoperative hypotension.
Intraoperative central venous pressure (groups A and B only).
Change in intra-anaesthetic physiological parameters including stroke volume corrected flow time cardiac output central venous pressure.

Notes
Volume of colloid administered and "total intraoperative fluids minus blood loss" were greater for the intervention groups (B and C).
Intervention and control groups (A, B and C) received similar volumes of crystalloid.

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>
### Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reasons for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan 1999</td>
<td>No participants underwent repair of PFF.</td>
</tr>
<tr>
<td>Schultz 1985</td>
<td>Overall methodological quality score 4/12. Allocation concealment unclear. Significant differences in characteristics of control and intervention groups suggesting allocation bias, for example age: Control - mean 67 years, standard deviation 11 years, n=35 Intervention - mean 78 years, standard deviation 11 years, n=35 P&lt; 0.0005; two sample t test Lack of completeness of description of interventions. Inapplicability of aspects of management to modern clinical practice (e.g. 17 of 70 patients waited seven days or more for surgery).</td>
</tr>
</tbody>
</table>
## DATA AND ANALYSES

### Comparison 1. "Usual care" versus advanced haemodynamic monitoring (all techniques)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital fatality</td>
<td>2</td>
<td>130</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>1.44 [0.45, 4.62]</td>
</tr>
</tbody>
</table>

### Comparison 2. "Usual care" versus central venous pressure monitoring

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital fatality</td>
<td>1</td>
<td>60</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>2.89 [0.66, 12.64]</td>
</tr>
</tbody>
</table>

### Comparison 3. "Usual care" versus oesophageal Doppler ultrasonography monitoring

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital fatality</td>
<td>2</td>
<td>99</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.98 [0.23, 4.09]</td>
</tr>
</tbody>
</table>

## WHAT’S NEW

Last assessed as up-to-date: 9 November 2003.

16 January 2008 | Amended  | Converted to new review format.

## HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 1, 2002
CONTRIBUTIONS OF AUTHORS

JDP and JWS identified the need for the review.
All authors developed the protocol.
JDP performed the initial searches.
JDP and RMV extracted study data and applied inclusion criteria.
JDP and JWS performed statistical analyses.
All authors reviewed and refined the final manuscript.

DECLARATIONS OF INTEREST

Richard Venn is a co-author of one of the included studies.

SOURCES OF SUPPORT

Internal sources

• Oxford Radcliffe Hospitals NHS Trust, UK.

External sources

• No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)
Femoral Fractures [therapy]; Fluid Therapy [*methods]; Hip Fractures [complications; *surgery]; Hypovolemia [complications; *therapy]; Length of Stay; Randomized Controlled Trials as Topic

MeSH check words

Humans