



Rocos, B., Whitehouse, M. R., & Kelly, M. B. (2017). Resuscitation in hip fractures: A systematic review. *BMJ Open*, 7(4), Article e015906. <https://doi.org/10.1136/bmjopen-2017-015906>

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BMJ Open Resuscitation in hip fractures: a systematic review

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To cite: Rocos B, Whitehouse MR, Kelly MB. Resuscitation in hip fractures: a systematic review. *BMJ Open* 2017;7:e015906. doi:10.1136/bmjopen-2017-015906

► Prepublication history and additional material are available. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-015906>).

Received 13 January 2017
Revised 27 February 2017
Accepted 28 February 2017

ABSTRACT

OBJECTIVES

To evaluate the evidence for the resuscitation of patients with hip fracture in the preoperative or perioperative phase of their treatment and its impact on mortality.

Design We searched MEDLINE, EMBASE, CENTRAL and PROSPERO databases using a systematic search strategy for randomised trials and observational studies investigating the fluid resuscitation of any patient with hip fracture. No language limits were applied to the search, which was complemented by manually screening the reference lists of appropriate studies.

Outcome measures Mortality at 1 week, 30 days and 1 year following surgery.

Results Two hundred and ninety-eight citations were identified, and 12 full manuscripts were reviewed; no studies satisfied the inclusion criteria. The background literature showed that the mortality for these patients at 30 days is approximately 8.5% and that bone cement implantation syndrome is insufficient to explain this. The literature was explored to define the need for an interventional investigation into the preoperative resuscitation of patients with hip fracture.

Conclusions Patients with hip fracture show similar physiological disturbance to major trauma patients. Nineteen per cent of patients presenting with hip fracture are hypoperfused and 50% show preoperative anaemia suggesting that under resuscitation is a common problem that has not been investigated. A properly conducted interventional trial could improve the outcome of these vulnerable patients.

INTRODUCTION

The scale of the problem

Across England, 65 000 people suffer a hip fracture every year, with a cost to the National Health Service of approximately £2 billion.¹ While some of these fractures occur in younger patients, the majority occur in elderly adults, with a mean age at presentation of 80 years. A best practice tariff for fragility hip fractures was introduced in 2010 with the aim of encouraging prompt surgery and appropriate involvement of geriatric medicine specialists.² Despite the improvements in the care of patients with hip fractures since then, the diagnosis is still considered by some to be a preterminal event with a 30-day mortality of 8% (equating to over 5000 deaths per

Strengths and limitations of this study

- This review addresses a significant public health disease with a very poor prognosis.
- Thorough literature search revealed no relevant articles.
- Current practice has no evidence base and requires a clinical trial to inform it.
- A small improvement in mortality would lead to a large real number of patients surviving.

year) and a 1-year mortality of approximately 20%.^{3 4}

The care pathway of these patients is complicated. Patients are typically frail and generally have multiple comorbidities, polypharmacy and are often living dependently at the time of injury.³⁻⁸ Forty per cent shows cognitive impairment and 20% will present with an acute delirium. Despite these data suggesting that a hip fracture is a potentially devastating event with multiple factors influencing overall outcome and survival, this population continues to be managed as if the hip fracture was an isolated, skeletal injury.

In contrast, patients who sustain major trauma or multiple fractures, where multiple pathologies influence outcomes, are routinely managed in a secondary and tertiary trauma network with multidisciplinary input and aggressive resuscitation strategies. In recent years, this has led to an improvement in their outcomes and a marked reduction in mortality.⁹

It has been established that hip fracture in elderly adult patients causes a similar physiological insult as major trauma does in younger patients and so should be considered equivalent to major trauma.^{10 11} For young patients who sustain major trauma, the primary early cause of death is shock, which modern protocols tackle with early aggressive fluid resuscitation.¹² Furthermore, as a result of military practices, modern civilian trauma protocols dictate that patients who need intravenous resuscitation on the assumption of shock in major trauma are



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resuscitated with blood rather than crystalloid or colloid fluids prior to the receipt of laboratory or point of care testing results.^{13–17}

A hip fracture, in an elderly, vulnerable patient, constitutes a major traumatic event. While definitive evidence is absent, it is strongly suggested that from the work in patients who have sustained major traumatic injuries that patients who are under resuscitated have worse outcomes and that resuscitation is most effective when it is performed with blood rather than crystalloid or colloid fluids.^{13–15 18 19} It then follows that early and appropriate resuscitation in the elderly hip fracture population, tempered by attention to their fragile cardiovascular system, has the potential to improve survivorship and perhaps overall outcome.

We have conducted a literature review to identify relevant evidence supporting the use of blood resuscitation in adult patients aged 65 years and over who have presented within 24 hours of sustaining a fracture of the proximal femur when compared with crystalloid or colloid resuscitation. Furthermore, we describe our experience and results of performing a pilot study investigating this intervention, a patient's perspective of the clinical problem and present strategies used in initiating and maintaining the investigation.

METHODS

The first step in conducting the investigation was a review of relevant existing evidence. To conduct a comprehensive study of the evidence, we performed a systematic review with narrative review of the literature. Our review was conducted in accordance with preferred reporting for systematic reviews and meta-analyses (PRISMA) guidelines.²⁰

No protocol was registered for the review because of its small size. We then identified a precise population, intervention, comparator, outcome (PICO) question. In this review, we stipulated the question as: in patients aged ≥65 years presenting with fracture of the proximal femur who are resuscitated with blood products compared with crystalloid, colloid or other intravenous fluid prior or during surgery, are 30-day mortality and morbidity rates reduced?

Using the OVID portal (Wolters Kluwer, Alphen aan den Rijn, The Netherlands), the MEDLINE (1950–present), EMBASE (1980–2015 week 16), PROSPERO (no date limits) and CENTRAL (no date limits) databases were searched for articles using a systematic search strategy. The search defined the population as those with hip fracture and mapped this to Medical Subject Headings (MeSH) terms and defined the intervention as fluid administration and/or resuscitation with this and synonyms mapped to MeSH (online supplementary appendix 1). No language limits were placed on the searches. We complemented the search by manually scanning reference lists of identified articles for relevant publications.

The titles of articles identified by the search strategy were then screened by a single author (BR) to verify inclusion into the review. The abstracts of titles that showed potential for inclusion were then reviewed by a single author (BR). For those papers where the abstract was insufficient to confidently either include or exclude from the review, the full manuscript was sourced (figure 1). Any ambiguity for inclusion was resolved through discussion between all authors. Data were to be collected through a custom designed data collection tool by a single author (BR). Bias was to be assessed through the same tool, and its influence included within the narrative analysis. The assessment of bias was based on the criteria laid out by the Critical Appraisal Skills Programme.^{21 22}

Outcomes analysed were to include unadjusted 30-day mortality and length of stay as a surrogate for function and morbidity. Summary measures anticipated to be used were ORs. Any assessment of health economics would also be analysed. Subgroup analysis of the very elderly patients (aged ≥80 years) would be performed in the event that these data were available.

RESULTS

Despite widespread focus on the care in this population in the developed world, a systematic search of the literature shows that preoperative resuscitation in the frail elderly patient with hip fracture has been overlooked. The search did not yield any articles that investigated fluid resuscitation or the use of blood as a fluid for resuscitation prior to surgery in adults aged ≥65 years presenting with hip fracture, and none assessed the impact of modifying preoperative fluid resuscitation on mortality or functional outcomes in this population. References to fluid resuscitation focused on anaesthetic techniques and the monitoring of fluid administration. Most articles do not identify preoperative resuscitation in these patients as an opportunity to modify outcomes. The existing literature focuses on blood transfusion (as opposed to blood resuscitation) as a treatment for established anaemia or investigates techniques and strategies for controlling the postoperative administration of intravenous fluid.

Inadequate resuscitation is easily missed in this patient group and would be rapidly and safely treated in any other age group with the same relative traumatic insult; however, standard practice in hip fracture care is to maintain the existing fluid status of patients using intravenous saline.^{12 23–26} While the literature does not specifically investigate resuscitation in hip fracture, it does offer some supporting evidence for early blood product resuscitation in this vulnerable group.

The blood loss associated with a hip fracture has been quantified. Kumar *et al* showed that the average haemoglobin concentration fell by 2.23 g/dL in subtrochanteric fractures, 1.1 g/dL in intertrochanteric fractures and 0.7 g/dL in intracapsular fractures following admission but before surgery. Foss *et al* suggested that this only worsens with treatment due to blood loss during

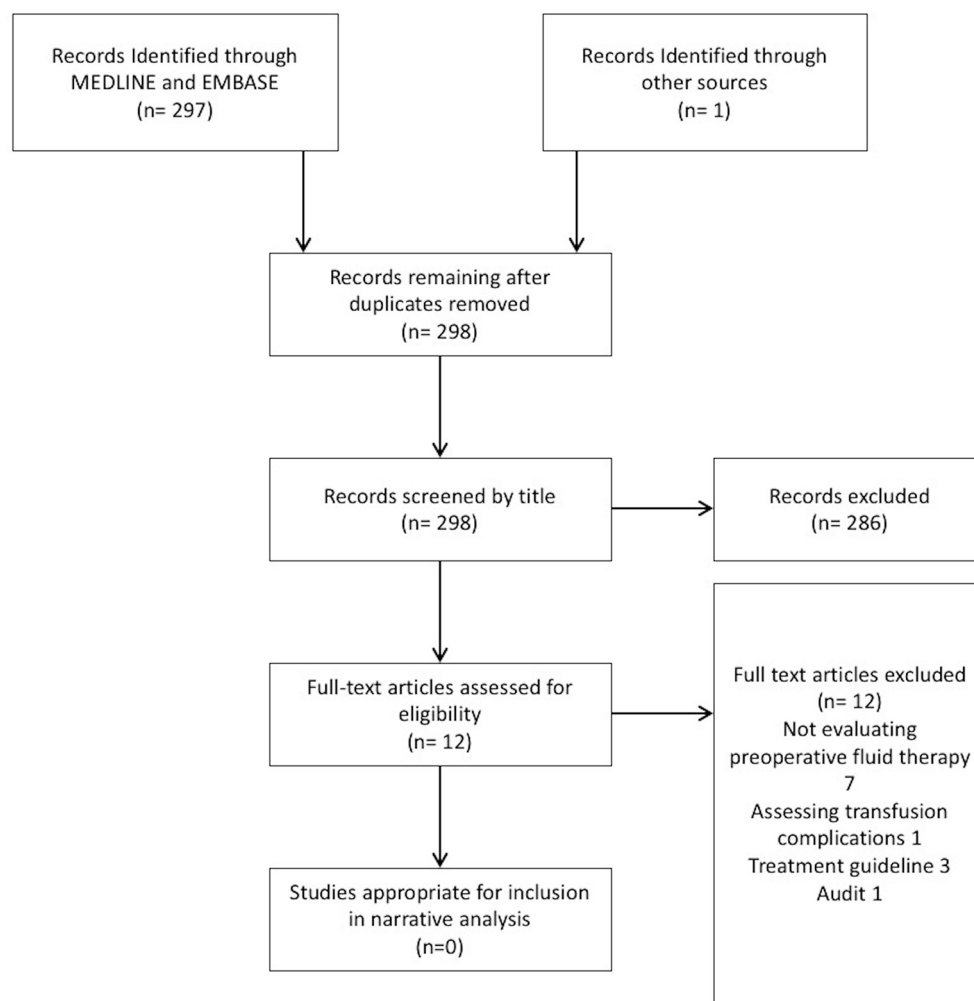


Figure 1 The preferred reporting for systematic reviews and meta-analyses (PRISMA) diagram representing the systematic literature search.

hip fracture surgery ranging from 547 to 1473 mL.^{27 28} Irrison *et al* showed that the haemoglobin concentration follows a linear decline in the first 3 days postoperatively, suggesting that measuring haemoglobin concentration 24 hours will not detect incomplete postoperative resuscitation.²⁹

Inadequate resuscitation leads to a relative hypovolaemia that is likely to have two fundamental consequences: hypoperfusion (shock) and reduced oxygen carrying capacity, which exacerbates the effects of the hypoperfusion. Overt shock in hip fracture is uncommon in the absence of other injuries. Occult shock (ie, shock not evident on examination or non-invasive investigation) is defined by a serum lactate higher than 2.5 mmol/L. It is associated with a significant increase in the risk of death, is more common than overt shock and is under diagnosed.^{23 30–35} Uzoigwe *et al* showed that there is a 1.2-fold increase in the odds of death per 1 mmol/L increase in serum lactate in elderly hip fracture patients, a trend also observed by other authors.^{31 36} Salottolo *et al* showed that in elderly trauma patients, a lactate of ≥ 2.5 mmol/L led to a 2.62-fold increase in the odds of mortality and that failure to recognise occult hypoperfusion led to an

increase in mortality in elderly patients from 12% to 35%.^{11 23} Venkatesan *et al* investigated the association between the recorded lactate level and mortality in the hip fracture population and found that 19% of hip fracture patients showed a lactate of >3.0 mmol/L and that these patients showed a mortality 4.5 times greater than those with a lactate of <3.0 mmol/L when covariates of interest were adjusted for (6% vs 28%).³⁰

The effect of inadequate resuscitation is exacerbated by the reduced ability of the circulation to deliver oxygen to the end organs with a low serum haemoglobin concentration. Some evidence exists to support this position in the context of anaemia. Anaemia is common among the elderly, affecting 17% of all patients aged over 65 years, rising to 50% in patients presenting with hip fracture, in turn leading to compromised patient outcomes and an increased risk of mortality.^{5 6 37 38} The scale of this increased mortality is best described by a meta-analysis of 10 studies investigating patients with hip fracture produced by Potter *et al* in 2015, showing that preoperative anaemia is associated with an increase in the relative risk of mortality of 1.64 (95% CI 1.47 to 1.82) at all time points beyond 30 days.³⁹ Similar effects are seen in elderly

patients in other surgical cohorts with anaemia causing an increase in mortality of between 6% and 182% using a variety of study designs.^{40–45}

Adequate resuscitation has a role in reducing the risk bone cement implantation syndrome (BCIS), a condition of ill-defined aetiology associated with an increase in very early postoperative mortality.⁴⁶ This syndrome may occur when the cement that is used to fix in place the femoral stem of patients treated for displaced intracapsular hip fractures is inserted. There is no agreed definition of BCIS; however, it is characterised by hypoxia, hypotension, cardiac arrhythmias, increased pulmonary vascular resistance and cardiac arrest in response to cement or prosthesis implantation at arthroplasty.⁴⁷ It is generally accepted that the pathophysiological process involved is as a result of embolism caused by high intramedullary pressures during cementation.⁴⁷ The risk of BCIS is thought to be reduced by two strategies. One is to alter the surgical field to reduce the risk of embolisation by the use of pulsatile lavage, a suction catheter as well as a retrograde cementation technique.⁴⁸ The second is to ensure adequate fluid resuscitation and maintenance of an adequate blood pressure at the time of cement insertion, failure to do this is associated with excess early death.^{46 47} The effect of goal-directed intraoperative fluid administration is as yet unclear. Sinclair *et al* showed in a 40-patient prospective randomised trial that goal-directed restoration of optimal stroke volume reduced length of stay and improved postoperative recovery.⁴⁹ This conclusion was challenged by Price *et al* in a 2004 Cochrane Review, which concluded that there was no evidence for using goal-directed intraoperative fluid therapy over a traditional approach.³⁵ More recently, this conclusion has been confirmed by Moppett *et al* and Bartha *et al*⁵¹ who both showed in a larger trial that goal-directed fluid therapy does not confer any appreciable benefit.⁵⁰

BCIS does not explain the excess mortality rate in patients with hip fracture. In a large study of over 25 000 patients using the Australian Orthopaedic Association National Joint Replacement Registry, Costain *et al* were able to show that cemented hemiarthroplasty showed equivalent mortality to uncemented prostheses (where BCIS cannot occur) at 7 days and 1 month following surgery, and a reduced mortality at 1 year.⁵² Other mechanisms must have a role in influencing the high mortality observed in these patients.

Preoperative resuscitation using crystalloid, colloid fluids or blood products has the potential to treat hypovolaemia, anaemia and BCIS.^{29 39 53–56} Crystalloids and colloid fluids do not remain in the circulation for long and fail to address the reduced oxygen carrying capacity.^{13 14 16 17} Despite the fall in 2,3-diphosphoglycerate (2,3-DPG) concentration in stored blood, the sustained improvement in haemodynamics through the timely administration of blood should lead to improved end organ perfusion.^{53 57 58} If a survival advantage exists, then administering appropriate fluid resuscitation preoperatively may prevent deterioration before appropriate

treatment can be commenced and prevent irreversible decline in function and the associated increased risk of mortality. The 2015 Cochrane Review by Brunskill *et al*⁵⁹ concluded that further research was needed into blood product resuscitation in the preoperative phase of hip fracture care to include frail, unstable and cognitively impaired patients in an effort to improve mortality and functional outcomes. This conclusion is supported by Parker *et al*⁵⁵, the FOCUS trial and Potter *et al*³⁹, each of which concludes that a trial investigating preoperative blood product resuscitation in patients with hip fracture should take place to investigate potential improvements in the outcomes for these vulnerable patients.⁵⁶

Understandably, it would be reasonable to expect the medical community to be reluctant to administer blood products to patients outside the traditional indications because of the risk of complications and side effects. However, the published refutes these hypotheses and shows that blood administration in elderly adult patients shows no increase in the risk of transfusion-related illness. The Transfusion Requirements in Frail Elderly (TRIFE) study showed no increase in transfusion-related complications in patients with hip fracture when compared with a control group.⁶⁰ This is confirmed by the TITRe2 trial, the FOCUS trial and by Parker and colleagues who carried out a study in the elderly hip fracture cohort and showed no increase in complications with a protocol-driven transfusion strategy rather than a clinically guided (more restrictive) strategy.^{55 56 61 62} Potter *et al* noted that trials to date, which have shown an increase in morbidity due to transfusion, are influenced by uncontrolled confounding factors,³⁹ and Jansen and colleagues describe how the immunological dysfunction attributed to blood administration applies only in massive transfusion.¹³

While the literature is unable to inform the use of blood product in the preoperative resuscitation of elderly adults presenting with hip fracture, it is able to provide an informed foundation on which subsequent investigations can be built. There is a case for interventional trial looking at the effect of preoperative blood product resuscitation in patients with hip fracture with the aim of reducing mortality and improving functional outcomes in answer to their pathophysiology following injury. Equally, there remains sufficient equipoise in using blood products for resuscitation in major trauma for an investigation specific to this patient group to be justified. The use of blood products in this age group is safe and is unlikely to lead to subsequent disease, and the scale of the clinical and socioeconomic burden of this condition is such that an interventional trial with the aims of reducing mortality and morbidity is a reasonable proposal.

CONCLUSION

The literature contains no evidence of any study that has investigated the effects of preoperative resuscitation in older adult patients presenting with hip fracture, despite

the high early mortality associated with this injury. Elderly patients are vulnerable to inadequate resuscitation, and from the evidence describing the status of patients with hip fracture and resuscitation in major trauma, we hypothesise that there are advantages to the early appropriate resuscitation of patients with hip fracture. In the absence of any literature or evidence that this is likely to have a deleterious effect, there is sufficient equipoise for the conduct of a randomised controlled trial to establish whether standard care pathways or preoperative resuscitation with blood products in elderly patients with a hip fracture is superior.

Contributors BR and MBK conceived the article. BR conducted the literature search. BR, MRW and MBK all contributed to the production of the manuscript and approved submission.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No unpublished data is available following this study.

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BMJ Open 2017 7:

doi: 10.1136/bmjopen-2017-015906

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