Perioperative intravenous iron to treat patients with fractured hip surgery: A systematic review and meta-analysis

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Abstract

Background: Treatment of preoperative anemia with intravenous iron is common within elective surgical care pathways. It is plausible that this treatment may improve care for people with hip fractures many of whom are anemic because of pre-existing conditions, fractures, and surgery.

Objective: To review the evidence for intravenous iron administration on outcomes after hip fracture.

Design: We followed a predefined protocol and conducted a systematic review and meta-analysis of the use of intravenous iron to treat anemia before and after emergency hip fracture surgery. The planned primary outcome was a difference in length of stay between those treated with intravenous iron and the control group. Other outcomes analyzed were 30-day mortality, requirement for blood transfusion, changes in quality of life, and hemoglobin concentration on discharge from the hospital.

Data Sources: EMBASE, MEDLINE, The Cochrane Library (CENTRAL, DARE) databases, Clinicaltrials.gov, and ISRCTN trial registries. Date of final search March 2022.

Eligibility Criteria: Adult patients undergoing urgent surgery for hip fracture. Studies considered patients who received intravenous iron and were compared with a control group.

Results: Four randomized controlled trials (RCT, 732 patients) and nine cohort studies (2986 patients) were included. The RCTs were at low risk of bias, and the nonrandomized studies were at moderate risk of bias. After metaanalysis of the RCTs there was no significant difference in the primary outcome, length of hospital stay, between the control group and patients receiving intravenous iron (mean difference: −0.59, 95% confidence interval [CI]: −1.20 to 0.03; I² = 30%, p = 0.23). Intravenous iron was not associated with a difference in 30-day mortality (n = 732, OR: 1.14, 95% CI: 0.62−2.1; I² = 0%, p = 0.50), nor with the requirement for transfusion (n = 732, OR: 0.85, 95% CI: 0.63−1.14; I² = 0%, p < 0.01) in the analyzed RCTs. Functional outcomes and quality of life were variably reported in three studies.

Conclusion: The evidence on the use of intravenous iron in patients with hip fracture is low quality and shows no difference in length of acute hospital stay and transfusion requirements in this population. Improved large, multicentre, high-quality studies with
1 | INTRODUCTION

Fragility hip fracture affects over 70,000 patients each year in the United Kingdom and over 250,000 annually in the United States. Anemia is a common finding in these patients. In a recent report, 44% were anemic on admission to hospital rising to 87% after surgery. Systematic reviews suggest that anemia in this population is associated with increased mortality and perioperative blood transfusion is common (approximately 30% of patients).

Patient blood management strategies (PBM) are currently recommended before surgery by NHS Blood and Transplant, The National Institute for Health and Care Excellence, and expert groups. PBM has been incorporated into the pathways of care for older patients undergoing elective orthopedic surgery, leading to a reduction in the requirement for perioperative blood transfusion. Intravenous iron preparations are now regularly used ahead of elective surgeries that are associated with significant blood loss. Commonly used preparations include ferric carboxymaltose up to 1000 mg or iron isomaltoside up to 20 mg/kg given intravenously as infusions over 15–30 min.

Observational studies link perioperative anemia with poor postoperative outcomes, increased mortality, and a reduction in quality of life following surgery for hip fracture and other types of surgery. Uncorrected anemia after hip fracture may impede functional recovery in this group of patients and may have a lasting effect on recovery and impact on quality of life. Other trials have assessed the use of interventions such as IV iron to minimize anemia and exposure to blood products in other surgical groups. The use of IV iron is not currently routinely employed after hip fracture in the United Kingdom. Potentially, the use of intravenous iron is an attractive option to improve outcomes for the hip fracture population, by avoiding exposure to blood products and improving the quality of recovery.

We undertook a systematic review to assess the evidence and effect of intravenous iron preparations on the duration of acute hospitalization, mortality, blood transfusion, quality of life, and discharge hemoglobin in patients presenting to surgery with hip fracture.

2 | METHOD

This systematic review was conducted in accordance with our predefined protocol registered prospectively on PROSPERO (CRD42020171197), and the preferred reporting items for systematic reviews and meta-analyses (PRISMA).

2.1 | Search strategy and study inclusion criteria

We searched EMBASE, MEDLINE, The Cochrane Library (CENTRAL, DARE) databases, Clinicaltrials.gov, and ISRCTN trial registries between January 2000 and January 2021. The search was repeated on 31st March 2022 to check for additional studies and one additional study met the inclusion criteria and was added to the meta-analysis. Studies eligible for inclusion were randomized or observational trials of adult patients (age over 18 years) undergoing emergency or urgent surgery for hip fracture and who received intravenous iron (any preparation) in the perioperative period. All study designs were considered if intravenous iron was compared with a control group of patients who did not receive this intervention and where one of the outcomes of interest was reported. Studies published in any language were considered. A full description of the strategy used is contained in Supporting Information S1.

Two review authors (R. C. F. Sinclair and M. J. A. Bowman) independently screened citations from the systematic search and extracted data. Discrepancies or disagreements were then adjudicated by a further author M. A. Gillies. Manual searching was also used to identify other reports, and all references in the selected full-text articles were reviewed to identify further possible studies for inclusion. We excluded studies where any of the outcomes of interest were not reported, where patients undergoing elective hip surgery were studied, and where there was no comparison group (who did not receive the intervention) reported.

The primary outcome for this review was the effect of intravenous iron after hip fracture surgery on the duration of acute hospitalization after emergency surgery (length of stay, measured in days). Secondary outcomes were mortality at 30 days/discharge and 90 days following surgery, change in the quality of life after emergency hip surgery, and postoperative red cell transfusion and hemoglobin concentration at acute hospital discharge.

2.2 | Data analysis

Statistical analysis and data presentation were performed using R (R Foundation, Vienna) and the meta-package. For randomized trials risk of bias was assessed using the Cochrane Collaboration tool for randomized controlled trials. The Newcastle Ottawa scale was used for observational studies. Funnel plots were used to detect publication bias for primary or secondary endpoints.

Statistical heterogeneity between studies was estimated using $X^2$ and $I^2$ tests. A p-value of 0.1 was used to denote the statistical significance of heterogeneity. For $I^2$ tests, cut-offs of 25%, 50%, and
75% were used to demonstrate the presence of low, moderate, and high between-trial heterogeneity. After performing the review, significant heterogeneity was detected in the studies because 8 of the 12 studies were observational studies as opposed to randomized studies. Therefore, a random-effects model (DerSimonian-Laird method) was used throughout this analysis. The planned use of a fixed-effects model was not employed. Outcomes were expressed as mean difference (MD) for continuous variables and odds ratio (OR) for dichotomous outcomes with 95% confidence intervals (CI).

Studies are presented separately as randomized and nonrandomized (observational) studies due to the heterogeneity and quality of the two types of studies.

A summary of the evidence was produced using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) methodology.22

2.3 Results

After study selection, according to our predefined protocol, 36 full-text manuscripts were reviewed and from these 13 studies, 3718 patients were suitable for inclusion in the review.23-35 (Figure 1) The studies excluded after full-text review are presented in Supporting Information S1. Of the included studies, four were randomized trials (732 patients)23,25,28,32 and nine were nonrandomized studies (2986 patients).24,26,27,29,31,33-35 Characteristics of individual studies are presented in Table 1. The first dose of IV iron was administered upon admission to the hospital in all but two studies. All studies compared the administration of intravenous iron to a control group or placebo. Three studies additionally compared the use of an erythropoiesis-stimulating agent (erythropoietin, EPO) in conjunction with intravenous iron against the control group.25,30,31

The four randomized trials were assessed as having a low risk of bias; however, the nine nonrandomized cohort studies were of variable quality with a range of Newcastle-Ottawa risk of bias scores between 4/8 and 6/8 (median score of 5/8) (Figure 2). Due to the risk of bias assessment, the RCTs and nonrandomized studies were analyzed separately and presented both separately and combined (the preponderance of nonrandomized studies returned by our search strategy was not known beforehand). No evidence of publication bias was detected (see Supporting Information S1). Nine of the 13 studies included were observational so we decided that using a

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses flowchart of study selection.
| Study                                      | Design              | N   | Duration of follow-up | Population | Intervention                                                                 | Timing of intervention                                      | Comparator                        | Reports duration of stay | Reports mortality | Reports quality of life | Reports transfusions | Reports discharge hemoglobin |
|-------------------------------------------|---------------------|-----|-----------------------|------------|------------------------------------------------------------------------------|-------------------------------------------------------------|-----------------------------------|------------------------|----------------------|------------------------|------------------------|------------------------|
| Bernabeu-Wittel 2016 (Spain)              | RCT multicentre     | 203 | 60 days postdischarge | Age >65 years | 1. FCM 1000 mg IV once Hb 90-120 g/L 2. FCM 1000 mg IV once plus EPO 40000 units SC once | Administered before surgery (first 48 h)                   | Placebo (usual care)  | Yes                   | Yes                   | Yes                    | Yes                    | Yes                    |
| Bleiza 2021 (Spain)                       | RCT                 | 253 | 12 months            | Age >70 years | Iron sucrose 200 mg IV, three doses                                           | Administered on Day 1, Day 3, Day 5                         | Placebo (saline)                | Yes                   | Yes                   | Yes                    | Yes                    | Yes                    |
| Blanco Rubio 2013 (Spain)                 | Retrospective, cohort | 120 | In hospital stay     | Age >65 years | Iron sucrose 200 mg IV, three doses                                           | Administered on day of admission                           | Historical cohort              | No                     | Yes                   | No                     | Yes                    | No                     |
| Clemmenson 2021 (Denmark)                 | Cohort              | 210 | 30-day mortality     | Acute hip fracture Hb <104 g/L on Day 3 | Iron isomaltoside 20 mg/kg single dose ± blood transfusion | Administered on Day 3 post-op if Hb < 104 g/L               | Historical cohort who did not receive IV iron, but still had blood transfusion | Yes                   | Yes                   | No                     | No                     | No                     |
| Cuence Espierrez 2004 (Spain)             | Cohort              | 127 | 30-day mortality     | Age >65 years | Iron sucrose 100 mg IV once                                                   | Administered on Day 1, Day 2, Day 3                         | Historical cohort              | Yes                   | Yes                   | No                     | Yes                    | No                     |
| Cuenga 2005 (Spain)                       | Cohort study, historical control group | 77  | 30-day mortality     | Age >65 years Hb <120 g/L                                                     | Iron sucrose 100 mg IV, up to three doses                   | First dose administered on admission, Dose 2 before surgery. A third dose was given between these timepoints, if the Hb < 120. | Historical cohort              | Yes                   | Yes                   | No                     | Yes                    | No                     |
| Study | Design | N  | Duration of follow-up | Population | Intervention | Timing of intervention | Comparator | Reports duration of stay | Reports mortality | Reports quality of life | Reports transfusions | Reports discharge hemoglobin |
|-------|--------|----|-----------------------|------------|--------------|------------------------|------------|------------------------|-----------------|---------------------|---------------------|---------------------------|
| Cuenca 2004 (Spain) | Cohort study, historical control group | 157 | 30-day mortality | Age >65 years | Iron sucrose 100 mg IV, up to three doses | First dose administered on admission, Dose 2 before surgery. A third dose was given between these timepoints, if the Hb < 120. | Historical cohort | Yes | Yes | No | Yes | No |
| Engel 2020 (USA) | Retrospective, case review | 239 | 30-day mortality and readmissions | Age >60 years, Proximal femoral fracture, Hb <110 g/L | Iron sucrose 300 mg IV once at discretion of treating team if Hb < 11 g/L | Administered when Hb < 110, either before or after surgery | Cohort during same time period who did not receive IV iron at discretion of treating team | Yes | Yes | No | Yes | No |
| Garcia-Erce 2005 (Spain) | Prospective intervention (non-randomized) | 124 | 30-day mortality | Age >65 years, Hb <130 g/L | Iron sucrose 100 mg IV 3 doses plus EPO 40000 units SC once | First dose administered on admission, then two further doses | Usual Care (No intervention) | Yes | Yes | No | Yes | No |
| Moppett 2019 (UK) | RCT | 80 | 30-day mortality | Age >70 years | Iron sucrose 200 mg IV 3 doses | Administered three doses on consecutive days starting within 24 h of admission | Control | Yes | Yes | No | Yes | No |
| Pareja Sierra 2019 (Spain) | Cohort, multiple arms, historical control | 298 | 6 months | Age >75 years | 1. Transfusion alone 2. Iron sucrose 200 mg IV, 2 doses plus EPO 30000 units SC once 3. Transfusion plus Iron sucrose 200 mg IV 2 doses plus EPO 30000 units SC once | Administered on day of admission and second dose 48 h later | Historical cohort | Yesa | Yesb | Yesb | Yes | No |

(Continues)
random-effects model for all analyses would be more appropriate due to the risk of heterogeneity.

2.4 | Primary outcome

The primary outcome was reported in 3300 patients, 732 in RCTs, and 2568 in nonrandomized studies. In the RCTs, the MD in duration of the length of stay was 0.59 days less in those who received IV iron when compared to placebo or usual care: MD: $-0.59$, 95% CI: $-1.20$, 0.03; $I^2 = 30\%$, $p = 0.23$ (Figure 3).

The sensitivity analysis for the nonrandomized studies returned a MD in length of stay of $-1.07$ days (95% CI: $-1.85$, $-0.28$; $I^2 = 88\%$, $p < 0.01$). The duration of hospital stay data (mean and SD data) from one cohort study$^{33}$ appears to represent an outlier study. A post-hoc sensitivity analysis without the inclusion of this study is presented in Supporting Information: Figure S3.

2.5 | Secondary outcomes

2.5.1 | Mortality

Four RCTs and eight nonrandomized studies, reported mortality at acute hospital discharge or 30 days,$^{23-30,32-35}$ including 732 and 2986 patients respectively. There was no difference between the groups in either the RCTs (OR: 1.14, 95% CI: 0.62, 2.1; $I^2 = 0\%$, $p = 0.50$), nonrandomized studies (OR: 0.58, 95% CI: 0.36, 0.93; $I^2 = 8\%$, $p = 0.37$) nor overall (OR: 0.73, 95% CI: 0.49, 1.10; $I^2 = 14\%$, $p = 0.31$). Two studies including 1887 patients reported mortality at 90 days.$^{28,33}$ There was no difference between groups (Figure 4, Supporting Information: Figures S4 and S5).

2.6 | Quality of life

Health-related quality of life was measured in three studies (two RCTs)$.^{25,28,31}$ One measured health-related quality of life using the Short Form 36 at baseline and 60 days after discharge from the hospital. Scores decreased from baseline to 60 days but they detected no difference in physical and mental component scores between the study groups.$^{25}$ Another reported functional outcomes at 3 and 6 months after hip fracture.$^{31}$ These were improved in the patients who received intravenous iron and erythropoietin; however, changes in the Barthel Index and Functional Ambulatory Category (FAC) scale between the groups did not reach statistical significance.$^{31}$ The most recent study, from 2021, reported a change in Barthel Index during the initial hospital stay before discharge home as its primary outcome.$^{28}$ There was no difference reported in the improvement in Barthel Index (over a median 10-day hospital stay) with the intravenous iron intervention compared to placebo.$^{28}$ The study was not powered to detect a difference in Barthel Index at 3 months.
**Figure 2** Risk of bias for (A) randomized trials (Cochrane risk of bias tool) and (B) nonrandomized studies (Newcastle Ottawa Scale).

**Figure 3** Sensitivity analysis for primary outcome, Length of Stay.
2.7 | Postoperative red cell transfusion

Twelve studies, including four RCTs (732 patients) and eight nonrandomized studies (2776 patients), reported red cell transfusion after surgery. In the RCTs, there was no difference in transfusions demonstrated: OR: 0.85, 95% CI: 0.63, 1.14; \( I^2 = 0 \% \), \( p < 0.01 \) (Figure 4). In the nonrandomized studies, fewer transfusions were administered to patients who had received IV iron: OR, 0.46; 95% CI, 0.31, 0.71; \( I^2 = 74\% \), \( p < 0.86 \).

2.8 | Discharge hemoglobin

Three studies, two RCTs (456 participants) and one nonrandomized study (1634 participants) reported discharge hemoglobin.
While a difference was demonstrated in discharge hemoglobin in the nonrandomized study, there was no difference in discharge hemoglobin between groups in the RCT (Supporting Information: Figure S6).

2.9 | GRADE quality of evidence

Grade assessment of bias for each outcome was analyzed and presented in Table 2. Complete quality assessment for each outcome within RCTs rates the evidence as very low (quality of life, discharge hemoglobin), low (transfusion), and medium quality evidence (LOS and mortality) (Supporting Information: Figure S1).

3 | DISCUSSION

The principal findings of this review were that perioperative treatment with IV iron in patients with hip fracture is not associated with a significant reduction in length of hospitalization, mortality, red cell transfusion, or discharge hemoglobin. We were unable to undertake a planned analysis on the effect of the intervention on health-related quality of life as this outcome was infrequently reported and used a variety of metrics. Cost-effectiveness and rates of infection were not examined in this study.

Another key finding from conducting this review was the paucity of work that has been published in this area: the published data comprised only four single-center randomized trials and nine observational studies. Although the risk of bias in the RCTs was low, the overall GRADE quality of data for the RCTs was of medium to very low quality. The nonrandomized studies identified were heterogeneous and a comparison of these varied cohort studies, which exhibited heterogeneous methodology and outcomes provides only low-quality evidence to complement the RCTs. There was marked variation between iron regimens and the use of adjuncts. The comparisons of changes in clinical practice with historic practice in an institution did not provide comparable controlled conditions to accurately evaluate new treatment regimens.

Our review presents up-to-date evidence in this field although similar reviews have previously been undertaken. This area of research has evolved since a narrative systematic review in 2010 reported a high incidence of perioperative anemia in a mixed orthopedic population; however, in this review, only two studies considered IV iron in hip fracture patients.

Another meta-analysis, in 2011, considered the effect of iron supplementation (oral or intravenous) versus no iron/placebo for treating anemia in a combined group of hip fracture and knee surgery patients. Meta-analysis reported an increase in hemoglobin associated with oral iron treatment (n = 855). In contrast to our review, which included only hip fracture patients, this study included combined emergency and/or elective orthopedic patients. Moreover, five of the six studies analyzed oral iron supplementation and only one used intravenous iron. The most recent systematic review included all forms of iron supplementation in the elderly undergoing hip fracture surgery and included six RCTs (n = 1201) in the meta-analysis. Four of these studies are included in our analysis; however, two further studies were excluded in our review due to methodological concerns and the use of oral iron. In this analysis, length of stay and red cell transfusion were reduced in the intervention group and mortality was not affected. The authors also concluded that infection was not increased with iron treatment.

As the treatment of anemia with intravenous iron is increasingly adopted into clinical practice, it is important that this therapy is supported by high-quality evidence. A recent large meta-analysis has questioned the benefits of PBM programs in patients presenting for major surgery and has not demonstrated an overall benefit to mortality. Further studies might be better focused on the effect that this intervention has on recovery and patient-reported outcomes rather than an absolute reduction in mortality. In another study, postoperative recovery after abdominal surgery was improved after IV iron despite there being no significant difference in the primary outcome of blood transfusion. Improvements in quality of life and other health-related quality of life measures may be a more valuable endpoint in people with hip fractures.

The strengths of this review include adherence to a registered predefined protocol, PRISMA guidance, and Cochrane recommendations. However, the limitations of the available evidence have resulted in weaknesses in the analysis. We were unable to analyze data pertaining to health-related quality of life, which was a prespecified outcome, due to inconsistency of reporting in the included studies. Searching returned a low number of randomized studies and a high number of nonrandomized cohort studies. We included analyses of separated and combined data to utilize as much patient data as possible, accepting that the nine cohort studies presented lower quality, heterogeneous evidence with a moderate risk of bias. Many of the cohort studies retrospectively compared changes in treatment plans (e.g., the introduction of intravenous iron to a clinical pathway) with groups of historical patients labeled as "usual care."

Other variations in study characteristics import weakness to the analysis. The variation between intravenous iron regimens and the definition of anemia should be considered (Table 1). Eleven studies reported the use of intravenous iron sucrose: one randomized study utilized ferric carboxymaltose. Iron sucrose dose ranged from 100 to 300 mg, given either once, twice, or three times perioperatively. In contemporary clinical practice, a more usual dose of intravenous iron administered in the preoperative period to elective patients is a higher, weight-based dose of either iron isomaltoside or ferric carboxymaltose in one or two infusions, respectively. Iron sucrose may be more representative of European clinical practice, as is the combination of intravenous iron with erythropoietin in three of the studies. The definition of anemia used was also variable (Table 1), and no studies confirmed iron deficiency. Last, one study with high weighting due to the number of patients included was a significant outlier within the primary outcome of the duration of
| Primary outcome: Length of hospitalization | Bernabeu | Wittell | Bielza | Moppett | Serrano | Trenas |
|------------------------------------------|----------|---------|--------|---------|---------|--------|
| Sequence generation                      | Low      | Low     | Low    | Low     | Low     | Low    |
| Allocation concealment                   | Low      | Low     | Low    | Low     | Low     | Low    |
| Blinding of assessor                    | Low      | Low     | Low    | Low     | Low     | Low    |
| Blinding of participants                | Low      | Low     | Low    | Low     | Low     | Low    |
| Blinding of personnel/clinicians        | Low      | Low     | Low    | Low     | Low     | Low    |
| Incomplete outcome data                 | Low      | Low     | Low    | Low     | Low     | Low    |
| Selective outcome reporting             | Low      | Low     | Low    | Low     | Low     | Low    |
| Other threats to validity               | Low      | Low     | Low    | Low     | Low     | Low    |
| GRADE risk of bias assessment for this outcome | Low risk of BIAS | Low risk of BIAS | Low risk of BIAS | Low risk of BIAS | High quality evidence |
| Overall GRADE risk of bias for this outcome | High quality evidence |

| Outcome: Mortality | Bernabeu | Wittell | Bielza | Moppett | Serrano | Trenas |
|--------------------|----------|---------|--------|---------|---------|--------|
| Sequence generation | Low      | Low     | Low    | Low     | Low     | Low    |
| Allocation concealment | Low     | Low     | Low    | Low     | Low     | Low    |
| Blinding of assessor | Low     | Low     | Low    | Low     | Low     | Low    |
| Blinding of participants | Low    | Low     | Low    | Low     | Low     | Low    |
| Blinding of personnel/clinicians | Low   | Low     | Low    | Low     | Low     | Low    |
| Incomplete outcome data | Low   | Low     | Low    | Low     | Low     | Low    |
| Selective outcome reporting | Low | Low     | Low    | Low     | Low     | Low    |
| Other threats to validity | Low | Low     | Low    | Low     | Low     | Low    |
| GRADE risk of bias assessment for this outcome | Low risk of BIAS | Low risk of BIAS | Low risk of BIAS | Low risk of BIAS | Low risk of BIAS |
| Overall GRADE risk of bias for this outcome | High quality evidence |

| Outcome: Transfusion | Bernabeu | Wittell | Bielza | Moppett | Serrano | Trenas |
|----------------------|----------|---------|--------|---------|---------|--------|
| Sequence generation | Low      | Low     | Low    | Low     | Low     | Low    |
| Allocation concealment | Low     | Low     | Low    | Low     | Low     | Low    |
| Blinding of assessor | Low      | Low     | Low    | Low     | Low     | Low    |
| Blinding of participants | Low    | Low     | Low    | Low     | Low     | Low    |
| Blinding of personnel/clinicians | Low   | Low     | Low    | Low     | Low     | Low    |
| Incomplete outcome data | Low   | Low     | Low    | Low     | Low     | Low    |
| Selective outcome reporting | Low | Low     | Low    | Low     | Low     | Low    |
| Other threats to validity | Low | Low     | Low    | Low     | Low     | Low    |
| GRADE risk of bias assessment for this outcome | Low risk of BIAS | Low risk of BIAS | Low risk of BIAS | Low risk of BIAS | Low risk of BIAS |
| Overall GRADE risk of bias for this outcome | High quality evidence |

Note: GRADE table of quality assessment for primary and secondary outcomes: (a) LOS, (b) 30-day mortality, (c) blood transfusion.

a Participants are not blinded to treatment but this unblinding is unlikely to affect the LOS.
b Clinicians are not blinded to treatment, this could affect LOS.
c Participants are not blinded to treatment but this unblinding is unlikely to affect mortality.
d Clinicians are not blinded to treatment but this unblinding is unlikely to affect mortality.
e Participants are not blinded to treatment but this unblinding is unlikely to affect transfusion.
f Clinicians are not blinded to treatment, this could affect blood transfusion.
hospital stay. Heterogeneity has resulted in all outcomes being downgraded for inconsistency during quality assessment using the GRADE classification.

In summary, the clinically relevant effect of IV iron in this population is unclear and medium- very low GRADE RCT evidence is published alongside a preponderance of cohort studies. Despite this, interest and use of intravenous iron in hip fracture patients is increasing. We therefore believe it is important to highlight the paucity of available evidence to allow clinicians to inform their clinical decisions. Better, large, high-quality studies employing contemporary optimized drug regimens and measuring outcomes important to patients and clinicians are needed to answer the questions raised in this review.

AUTHOR CONTRIBUTIONS

Conceptualization: Rhona C. F. Sinclair, Iain K. Moppett, and Michael A. Gillies. Methodology: Rhona C. F. Sinclair, Iain K. Moppett, and Michael A. Gillies. Formal analysis: Rhona C. F. Sinclair, Miranda J. A. Bowman, Iain K. Moppett, and Michael A. Gillies. Writing, original draft: Rhona C. F. Sinclair. Writing, review, and editing: Rhona C. F. Sinclair, Iain K. Moppett, and Michael A. Gillies. All authors have read and approved the final version of the manuscript. Rhona C. F. Sinclair had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. The author, Rhona C. F. Sinclair, affirms that this manuscript is an honest, accurate, and transparent account of the study undertaken. Discrepancies from the Moppett 2019 study. M. A. Gillies is a Chief Scientist’s Office Scotland NHS Research Scheme Clinician. M. J. A. Bowman has no competing interests.

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CONFLICT OF INTEREST

R. C. F. Sinclair has received an honorarium from Pharmacosmos UK. I. K. Moppett is Deputy Director of the Health Services Research Centre. I. K. Moppett is the colead of the Perioperative Specialist Interest Group of the Fragility Fracture Network and a member of the Quality Standards Group for NICE. I. K. Moppett has received research funding for studies into the perioperative management of hip fracture and his department has received consultancy funding from Astra Zeneca for work unrelated to hip fracture, blood transfusion, or intravenous iron. I. K. Moppett did not perform data extraction from the Moppett 2019 study. M. A. Gillies is a Chief Scientist’s Office Scotland NHS Research Scheme Clinician. M. J. A. Bowman has no competing interests.

TRANSPARENCY STATEMENT

We confirm that this manuscript represents an honest, accurate and transparent account of the study undertaken. Discrepancies from planned analysis have been explained within the methodology section.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

ETHICS STATEMENT

Ethical approval and patient consent were not required for systematic review. The review protocol was registered prospectively at Prospero. CRD42020171197. www.crd.york.ac.uk/PROSPERO.

REFERENCES

1. National Hip Fracture Database Report. 2019. https://www.nhfd.co.uk/files/2019ReportFiles/NHFD_2019_Annual_Report.pdf
2. Brauer CA, Coca-Parrilla M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. JAMA. 2009;302:1573-1579.
3. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology. 2010;113(2):482-495.
4. Potter LJ, Doleman B, Moppett IK. A systematic review of preoperative anaemia and blood transfusion in patients with fractured hips. Anaesthesia. 2015;70(4):483-500.
5. NICE. National Institute of Clinical Excellence Guideline [NG25] Blood Transfusion. www.nice.org.uk2015
6. nhsbt.nhs.uk
7. Munting KE, Klein AA. Optimisation of pre-operative anaemia in patients before elective major surgery—why, who, when and how? Anaesthesia. 74(S1), 2019:49-57.
8. Kotzé A, Harris A, Baker C, et al. British committee for standards in haematology guidelines on the identification and management of pre-operative anaemia. Br J Haematol. 2015;171:322-331.
9. Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet. 2011;378:1396-1407.
10. Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J Surg. 2015;102(11):1314-1324.
11. Foss NB, Jensen PS, Kehlet H. Risk factors for insufficient perioperative oral nutrition after hip fracture surgery within a multi-modal rehabilitation programme. Age Ageing. 2007;36(5):538-543.
12. Hagini T, Ochiai S, Sato E, et al. The relationship between anemia at admission and outcome in patients older than 60 years with hip fracture. J Orthop Traumatol. 2009;10(3):119-122.
13. Sim YE, Sim SD, Seng C, Howe TS, Koh SB, Abdullah HR. Preoperative anaemia, functional outcomes, and quality of life after hip fracture surgery. J Am Geriatr Soc. 2018;66(8):1524-1531.
14. Roman MA, Abbasciano RG, Pathak S, et al. Patient blood management interventions do not lead to important clinical benefits or cost-effectiveness for major surgery: a network meta-analysis. Br J Anaesth. 2021;126(1):149-156.
15. Richards T, Balkady RR, Clevenger B, et al. Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double-blind, controlled trial. Lancet. 2020;396(10259):1353-1361.
16. Sinclair R, Moppett I, Gillies M. Patient blood management and hip fracture. Anaesthesia. 2020;76:417-418.
17. Mohr D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-1012.
18. R Foundation for Statistical Computing. A Language and Environment for Statistical Computing, 2020.
19. Balduzzi S, Schwarzer D. How to Perform a Metaanalysis with {R}: A Practical Tutorial, 2019.
20. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

21. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiology. 2010;25(9):603-605.

22. Guyatt G, Oxman AD, Akl EA, et al. GRADE Guidelines: 1. Introduction- GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-394.

23. Moppeit IK, Rowlands M, Mannings AM, Marufu TC, Sahota O, Yeung J. The effect of intravenous iron on erythropoiesis in older people with hip fracture. Age Ageing. 2019;48(5):751-755.

24. Cuenca J, García-Erce JA, Martínez AA, Solano VM, Molina J, Muñoz M. Role of parenteral iron in the management of anemia in the elderly patient undergoing displaced subcapital hip fracture repair: preliminary data. Arch Orthop Trauma Surg. 2005;125(5):342-347.

25. Bemabeu-Wittel M, Romero M, Ollero-Batunre M, et al. Ferric carboxymaltose with or without erythropoietin in anemic patients with hip fracture: a randomized clinical trial. Transfusion. 2016;56(9):2199-2211.

26. Blanco Rubio N, Llorens Eizaguerru M, Seral G, Burillo Fuertes P, Ranera García M, Albareda Albareda J. Preoperative intravenous iron as a strategy for blood saving in surgery for hip fracture. Med Clin. 2013;141(9):371-375.

27. Cuenca Espiérrez J, García Erce JA, Martínez M, Solano VM, Modrego Aranda FJ. Safety and usefulness of parenteral iron in the management of anemia due to hip fracture in the elderly. Med Clin. 2004;123(8):281-285.

28. Bielza Galindo R, Llorente Gutiérrez J, Pérez G, et al. Intravenous iron, functional recovery and delirium in patients with hip fracture. FEDEREF study. Single-centre randomised, placebo-controlled, and double-blind clinical trial. Rev Esp Geriatr Gerontol. 2018;53(1):38-44.

29. Cuenca J, García-Erce JA, Muñoz M, Izuel M, Martínez AA, Herrera A. Patients with pertochohanetic hip fracture may benefit from preoperative intravenous iron therapy: a pilot study. Transfusion. 2004;44(10):1447-1452.

30. García-Erce JA, Cuenca J, Muñoz M, et al. Perioperative stimulation of erythropoiesis with intravenous iron and erythropoietin reduces transfusion requirements in patients with hip fracture. A prospective observational study. Vox Sang. 2005;88(4):235-243.

31. Pareja Sierra T, Bartolome Martín I, Rodríguez G, et al. Results of an anaemia treatment protocol complementary to blood transfusion in elderly patients with hip fracture. Rev Esp Geriatr Gerontol. 2019;54(5):272-279.

32. Serrano-Trenas JA, Ugalde PF, Cabello LM, Chofles LC, Lázaro PS, Benitez PC. Role of perioperative intravenous iron therapy in elderly hip fracture patients: a single-center randomized controlled trial. Transfusion. 2011;51(1):97-104.

33. Yoon B-H, Lee BS, Won H, Kim HK, Lee YK, Koo KH. Preoperative iron supplementation and restrictive transfusion strategy in hip fracture surgery. Clin Orthop Surg. 2019;11(3):265-269.

34. Clemmenson SJ, Kragholm KH, Melgaard D, et al. Association between intravenous iron therapy and short-term mortality risk in older patients undergoing hip fracture surgery: an observational study. J Orthop Surg Res. (2021);16:320.

35. Engel JL, Gabra JN, Kane P, et al. Intravenous iron may improve outcomes in elderly patients with operative hip fractures. Geriat Orthop Surg Rehabil. 2020;11. https://journals.sagepub.com/doi/abs/10.1177/2151459320911844

36. Yang Y, Li H, Li B, Wang Y, Jiang S, Jiang L. Efficacy and safety of iron supplementation for the elderly patients undergoing hip or knee surgery: a meta-analysis of randomized controlled trials. J Surg Res. 2011;171(2):e201-e207.

37. Chen R, Li L, Xiang Z, Li H, Hou XL. Association of iron supplementation with risk of transfusion, hospital length of stay, and mortality in geriatric patients undergoing hip fracture surgeries: a meta-analysis. Eur Geriat Med. 2020;12(1):5-15.

38. Izuel Rami M, García Erce JA, Gómez-Barrera M, Cuenca Espiérrez J, Abad Sazatornil R, Rabanaque Hernández MJ. Relationship between allogeonic blood transfusion, iron deficiency and nosocomial infection in patients with hip fracture. Med Clin. 2008;131(17):647-652.

39. Parker M. Iron supplementation for anaemia after hip fracture surgery: a randomised trial of 300 patients. J Bone Joint Surg Am. 2010;92(2):265-269.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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