World J Surg (2019) 43:1677–1691
https://doi.org/10.1007/s00268-019-04971-7

SCIENTIFIC REVIEW

The Effect of Perioperative Iron Therapy in Acute Major Non-cardiac Surgery on Allogenic Blood Transfusion and Postoperative Haemoglobin Levels: A Systematic Review and Meta-analysis

Anders Schack[1] · Adam A. Berkfors[1] · Sarah Ekeloef[1] · Ismail Gögenur[1] · Jakob Burcharth[1]

Published online: 1 March 2019

Abstract

Background Perioperative anaemia in relation to surgery is associated with adverse clinical outcomes. In an elective surgical setting, it is possible to optimize patients prior to surgery, often by iron supplementation with correction of anaemia. Possibilities for optimization prior to and during acute surgical procedures are limited. This review investigates whether iron treatment initiated perioperatively improves outcomes in patients undergoing major acute non-cardiac surgery.

Method This systematic review was performed using PubMed, EMBASE (Ovid) and Scopus to identify current evidence on iron supplementation in acute surgery. Primary outcomes were allogenic blood transfusion (ABT) rate and changes in haemoglobin. Secondary outcomes were postoperative mortality, length of stay (LOS), and postoperative complications. Iron was administered at latest within 24 h after end of surgery.

Results Of the 5413 studies screened, four randomized controlled trials and nine observational cohort studies were included. Ten studies included patients with hip fractures. A meta-analysis of seven studies showed a risk reduction of transfusion (OR = 0.35 CI 95% (0.20–0.63), $p = 0.0004$, $I^2 = 66\%$). No influence on plasma haemoglobin was found. Postoperative mortality was reduced in the iron therapy group in a meta-analysis of four observational studies (OR 0.50 (CI 95% 0.26–0.96) $p = 0.04$). No effect was found on LOS, but a reduction in postoperative infection was seen in four studies.

Conclusions This review examined perioperative iron therapy in acute major non-cardiac surgery. IV iron showed a lower 30-day mortality, a reduction in postoperative infections and a reduction in ABT largely due to the observational studies. The review primarily consisted of small observational studies and does not have the power to formally recommend this practice.

Introduction

Perioperative anaemia in relation to major surgery is associated with adverse outcomes in terms of increased risk of 30-day mortality, increased postoperative length of stay (LOS), as well as a higher complication rate [1, 2]. To counteract perioperative anaemia, allogenic blood transfusion (ABT) is often used; however, this practice may lead to adverse outcomes and has been found to be a significant contributor to the increased morbidity in acute surgical patients [3, 4].

In an elective surgical setting, it is possible to correct anaemia prior to surgery by oral [5–7], intravenous (IV) iron therapy [8–11], or with erythropoietic agents. This is not possible in acute surgery. In itself, acute major surgery is related to worse outcomes than elective surgery due to

✉ Anders Schack
aesc@regionsjaelland.dk

[1] Center for Surgical Science (CSS), Department of Surgery, Zealand University Hospital & University of Copenhagen, Lykkebaekvej 1, 4600 Koege, Denmark

the underlying disease and the often already existing systemic inflammation [12]. Among patients undergoing acute major non-cardiac surgery, there are an increased risk of haemorrhage and requirement of blood transfusion [3, 13]—both have been suggested among the leading causative factors for the inferior clinical outcomes related to acute surgery [3, 4, 14].

IV iron in immediate relation to elective surgical procedures has been shown to reduce the need for blood transfusion [15–19]. IV iron therapy thus has the potential to benefit patients, but the evidence is not uniform, and the contrary has also been reported [20–23]. The purpose of this review was to investigate whether iron treatment, initiated perioperatively, improves clinical outcomes in terms of need for ABT, changes in haemoglobin, length of stay (LOS), postoperative infections and mortality in patients undergoing acute major non-cardiac surgery.

Methods

Protocol and registration

The hypothesis for the study was that perioperative iron therapy reduces the need for postoperative ABT, reduces the postoperative fall in haemoglobin, decreases the risk of mortality, and lowers LOS in patients undergoing major acute non-cardiac surgery.

The protocol for this systematic review was registered at PROSPERO (registration number: CRD42018087385). Preferred reporting items for systematic reviews and meta-analyses statement (PRISMA) [24] and checklist were followed for reporting of this systematic review.

Eligibility criteria

The population of interest concerned patients undergoing major acute non-cardiac surgery. We included studies, where the interventions consisted of oral or intravenous iron with the primary administration being done between indications of surgery until 24 h after ended surgery. We included studies with iron therapy interventions of any dose, frequency, and duration, oral or IV, and with adjuncts. Studies that compared oral or IV iron to no intervention, placebo, an active comparator, or to each other were included.

Primary outcomes of interest were peri- and postoperative blood transfusion, and clinical efficacy of therapy, measured by changes of the haemoglobin levels. The latter was chosen as it is relevant in clinical decision-making, especially when deciding to give a transfusion. Secondary outcomes were mortality, LOS, and adverse reactions to therapy incl. infections.

We reported on all original studies, i.e. randomized clinical trials (RCTs), prospective cohort studies, and observational studies, written in Danish, English, French, or Spanish.

Studies concerning elective surgery were excluded. Cardiac surgery (due to extracorporeal circulation) or surgery performed on children (under the age of 18) was also omitted. We excluded studies with less than ten patients or without a control group.

Studies containing both elective and acute patients were only included, if data from the acute population alone were stated and thus only data from acute surgery were included.

We excluded experimental studies (i.e. studies involving animals or conveyed in a laboratory), abstracts, conference publications or proceedings, letters, and duplicate publications.

Information sources and search

A systematic search strategy was developed. The databases PubMed, EMBASE (Ovid) and Scopus were searched from inception until 11 November 2017 using combinations of relevant keywords and Medical Subject Heading terms. Searches were run without filters, limits, and publication date or language restrictions. The complete search strategy can be found in Appendix 1. Furthermore, a manual screening of reference lists of identified studies and systematic reviews was performed.

Study selection

Two reviewers performed screening and selection of relevant studies individually and in duplicate. Titles and abstracts of studies identified were screened using the above-mentioned criteria. Disagreements were discussed and consulted with a third part. The relevant citations were retrieved in full text and, respectively, screened and read, thereby assessing studies for eligibility. Authors of potentially relevant studies were contacted by email when important information with respect to study design was missing.

Data collection process and data items

Data were retrieved from all eligible studies with respect to predefined variables. All variables not reported as the appropriate format were converted to suitable format. No assumptions were made, if data were not readily available from tables or text. Authors of potentially relevant studies were contacted by email if important variables were missing.

Risk of bias assessment

Risk of bias was assessed at study level, using the Cochrane risk of bias tool for RCTs [25] and Newcastle–Ottawa Scale [26].

Synthesis of results

We performed a narrative synthesis of all eligible studies, describing the study origin and methodological characteristics (study design, blinding, study arms, dosage regimen). Clinical variables, patient characteristics (type of surgery, etc.) and a summary of the study findings for each of the outcomes of interest were described. All outcomes were narratively summarized, and quantitative meta-syntheses of each outcome or exposure were done if possible (more than three studies included per outcome). *Revman version 5.1 software, Cochrane Collaboration, 2011,* was used for meta-analysis. For typing in data, the generic inverse variance method was used. The random-effects model was chosen on all outcome variables not assumed to be identically defined or collected between the studies. Meta-analysis was performed using adjusted multivariate data whenever possible (risk ratio, hazard ratio, or odds ratio). When only univariate data were provided, it was incorporated in the quantitative analyses if data were presented in a manner so that a 2 × 2 table could be created.

Results of meta-analysis was not reported, when heterogeneity was considerable (I-squared $> 75\%$) or if data on the outcome were deemed insufficient (size and number of trials).

In outcome variables with heterogeneity (I-squared $> 0\%$), both the random-effects model and the fixed-effects model were tested to identify a potential small-study effect, by assessing the influence of the chosen method on the estimated effect estimate. In case of a suspected small-study effect, a random-effects model was chosen. If data were found available from the included studies, data were analysed individually with regard to the management of therapy, i.e. whether iron was administered alone or as part of a patient blood management (PBM) protocol.

Results

Our search yielded 5413 studies, which were screened against title and abstract. Hereof 481 studies were full-text-screened and 468 excluded due to the reasons depicted in Fig. 1. A total of 13 studies, four RCTs [27–30] and nine observational studies [18, 31–38], were identified as eligible for inclusion in the review. Of these, ten studies concern orthopaedic surgery, one study in abdominal surgery, one study in gynaecological surgery, and one study with a cohort of mixed surgical patients, totalling 3044 patients. One study consisted of both elective and acute patients, but data were presented individually for the two groups [18].

Among included studies, a great level of heterogeneity was found towards study design, population, intervention, outcomes, and methodological quality, as seen in Table 1. Appendices 2 and 3 show the bias assessments of individual studies. The overall findings of the included studies are shown in Table 2.

Primary outcome analysis

Total number of blood units transfused peri- and postoperatively

Eight studies reported on the transfusion rates, hereof two RCTs [29] and six observational studies [31–36]. Transfusion policies differed between the studies, as seen in Table 2. Seven studies were eligible for meta-analysis based on outcome coherence. One study was excluded from the meta-analysis as the study population, partly consisted of patients from already included studies [18]. One study was excluded from the meta-analysis as it consisted of three study arms [32].

The eligible studies included 812 primarily hip fracture patients and all investigated IV iron. One study conveyed an extended protocol, i.e. PBM [34]. Two RCTs [29, 30] were included, hereof one which investigated IV iron against PBM and controls. A meta-analysis of the eligible studies showed a reduced risk of receiving an ABT in the intervention groups, OR = 0.35 CI 95% (0.20–0.63), $p = 0.0004$, $I^2 = 66\%$ (Fig. 2a). The funnel plot (Fig. 2b) shows a slight asymmetry, but depicts only five studies, and interpretation should be done with caution.

In one RCT, a non-significant reduction in ABT rate was seen in a population of 176 hip fracture patients treated with IV iron within 24 h of admission (33.3% in the treated patients vs. 41.3% in controls (p value not reported, NS)) [29]. Another RCT also failed to show a significant difference in a mixed surgical population [30].

A sensitivity analysis of the five observational studies showed a favourable effect of iron therapy OR = 0.29 CI 95% (0.15–0.56), $p = 0.0003$, whereas an according analysis of the two RCTs showed no significant effect with OR = 0.69 CI 95% (0.39–1.22), $p = 0.2$.

The pooled retrospective observational study [18] included 1361 orthopaedic patients, with 1000 patients receiving IV iron (a subpopulation also EPO) and 361 controls. A significant reduction ($p < 0.01$) from 48.8 to 32.4% of patients transfused in the treated group was seen.

The last observational study had three study arms [32], where a total of 131 patients in two groups received iron,

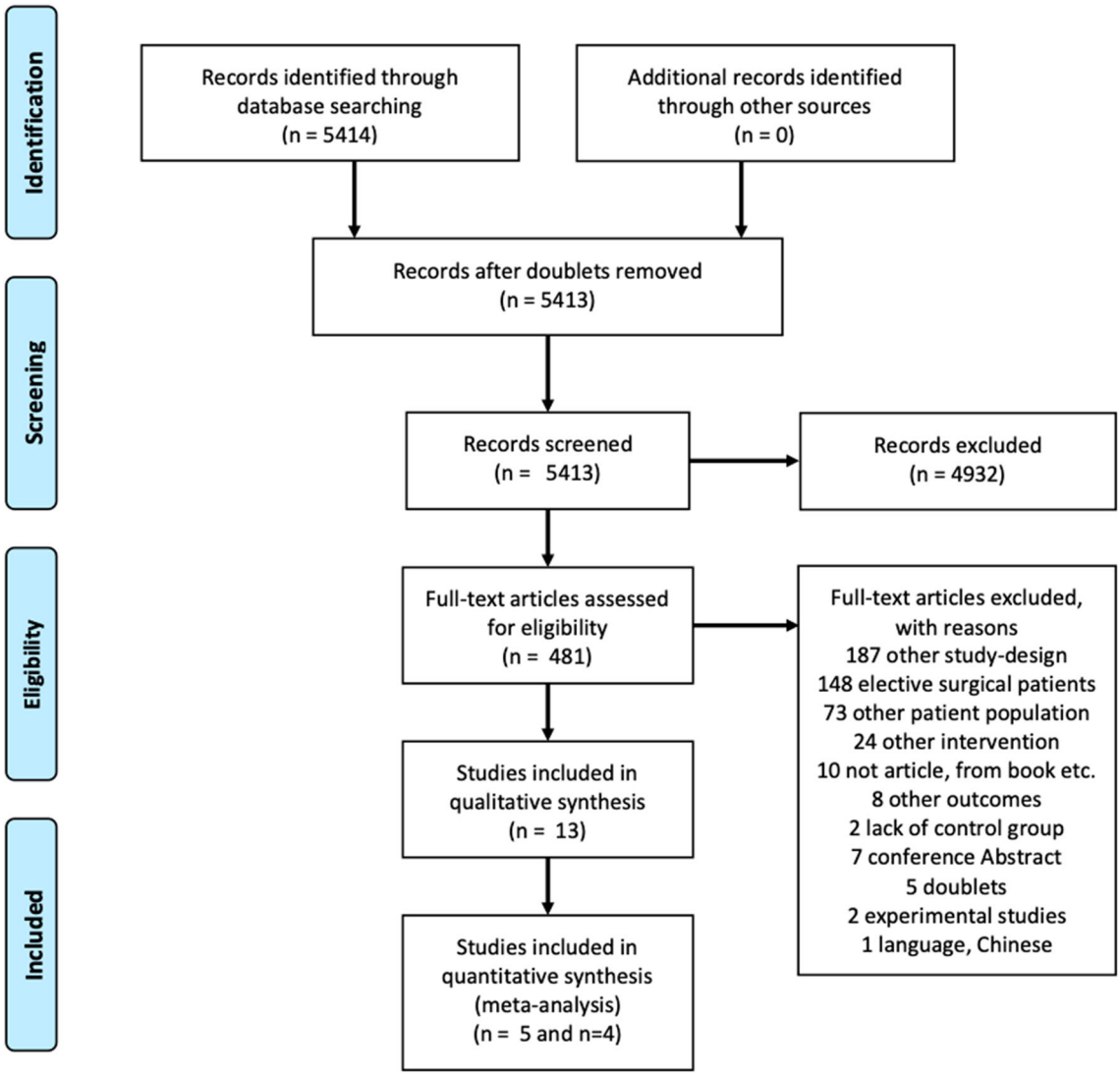

Fig. 1 Study selection

compared to 102 control patients. We found no effect of iron therapy on the risk of ABT with an OR 1.03, CI 95% (0.66–1.60), when comparing patients receiving iron to controls.

Clinical efficacy of perioperative iron therapy (measured by difference in plasma haemoglobin levels between groups)

Twelve studies reported on plasma haemoglobin [18, 27, 28, 30–38] and one on haematocrit (hct) [29]. The timing of measurement of haemoglobin was mixed throughout the studies, ranging from preoperatively to 6 weeks after surgery, as seen in Table 2.

None of the studies were found eligible for a meta-analysis, due to heterogeneity in reporting and in the study design. A visual presentation of the changes in haemoglobin over time is depicted in Fig. 3a–d. Results on haemoglobin changes are somewhat diverse with respect to effect of iron administration with no consistency among all studies. No short-term effect of IV iron seemed to be present in the included studies.

In two RCTs, oral iron was administered for 28 days after surgery in a population of 152 patients with a hip fracture [27, 28]. A positive benefit of oral iron was seen in this patient cohort with a haemoglobin increase in the intervention group exceeding control population by 2.8 g/L after six weeks ($p = 0.07$) [28] and 7.5 g/L after 4 weeks ($p = 0.04$) [27]. Two additional prospective studies were investigating the effect of intravenous iron but found no significant difference [29, 30].

Table 1 Identified studies

Study	Design	Type of surgery	Time of intervention	Comparison	N	Dosage regimen	Additional treatment	Mean age (years) (interquartile range)	Quality
Prasad et al. [27]	RCT, single-blinded	Fermur neck fracture	POD 0-2	G1: Oral iron	32	Ferrous sulphate, P.O. 200 mg 3 times a day for 28 days		82 (8.3)	Good
				G2: No intervention	34			82 (6.9)	
Parker [28]	RCT	Hip fracture	POD 0-5	G1: Oral iron	120	Ferrous sulphate, P.O. 200 mg 3 times a day for 28 days		81 (60–96)	Fair
				G2: No intervention	123			83 (61–104)	
Karkouti et al. [30]	RCT, double-blinded	Mixed surgical	POD1	G1: IV iron	11	Iron sucrose, IV, 200 mg from POD1-3		62 (11)	Good
				G2: PBM	10	Iron sucrose, IV, 200 mg from POD1-3	EPO 300 U/kg POD1 -2, 600 U/kg POD3	56 (15)	
				G3: no intervention	10			62 (5)	
Serrano-Trenas et al. [29]	RCT	Hip fracture	Upon admission	G1: IV iron	86	Iron sucrose, IV, 200 mg 1–3, 48 h intervals presurgery		83.5(7.11)	Good
				G2: No intervention	90			82.5 (6.37)	
Panarese et al. [38]	Retrospective observational	Major abdominal surgery	Preoperatively	G1: PBM	55	Iron orally	EPO, folate	61.7 (33–84)	***
				G2: No intervention	55			74.1 (48–90)	
Blanco-Rubio et al. [31]	Retrospective observational case–control	Hip fracture	Upon admission	G1: IV iron	57	Iron sucrose, IV, 200 mg, 3 times		85.95 (6.8)	*****
				G2: No intervention	63			82.25 (9.6)	
Izuel-Rami et al. [32]	Retrospective observational	Osteoporotic hip fracture	Upon admission	G1: IV iron	68	Iron sucrose, IV, 100 mg	Oral iron	81.8(7.2)	*****
				G2: PBM	63	Iron sucrose, IV, 200 mg/48 h. Folic acid, Vit c EPO 40000 IU if hb < 13 g/dL		82.8 (7.7)	
				G3: No intervention	196			81.1 (7.6)	
Muñoz et al. [18]	Retrospective pooled observational	Lower limp surgery for hip fractures	Preoperatively	G1: IV iron	1000	Iron sucrose, IV, 1–200 mg, up to 3 times	40.000 IU EPO to some	83 (8)	*******
				G2: No intervention	361			83 (7)	

Table 1 continued

Study	Design	Type of surgery	Time of intervention	Comparison	N	Dosage regimen	Additional treatment	Mean age (years) (interquartile range)	Quality
Cuenca Espierrez et al. [33]	Pseudo-experimental historic cohort	Hip fracture	Upon admission	G1: IV iron	23	Iron sucrose 100 mg iv		84.5 (4.9)	******
				G2: No intervention	104			82.7 (9.3)	
Cuenca et al. [34]	Prospective cohort compared to historic control	Hip fracture (DSHF)	Upon admission	G1: IV iron	20	Iron sucrose 100 mg iv x2-3		81 (6.2)	****
				G2: No intervention	57			81.7(7.9)	
Cuenca et al. [35]	Prospective cohort compared to historic control	Hip fracture (PHF)	Upon admission	G1: IV iron	55	Iron sucrose 100 mg iv x2-3		86 (7)	****
				G2: No intervention	102			83(9)	
Garcla-Erce et al. [36]	Prospective observational study	Hip fracture patients	Upon admission	G1: PBM	83	Iron sucrose 100 mg iv x3	40000 IU rHuEPO if hb < 130 g/L	81 (8)	********
				G2: No intervention	41			84 (7)	
Armand-Ugón et al. [37]	Prospective cohort	Postpartum anaemia after caesarean section	POD1	G1: Oral iron	14	Iron sucrose 200 mg POD1-3		25 (6)	*****
				G2: IV iron	14			26 (7)	

RCT randomized controlled trial; *POD* postoperative day; *PHF* pertrochanteric hip fracture; *DSHF* displaced subcapital hip fracture; *PBM* patient blood management protocol; *hb* haemoglobin; *rHuEPO* recombinant human erythropoietin; *Vit C* vitamin C; *P.O.* peroral; *IV* intravenous

Table 2 Findings

Study	Comparison	N	ABT, % (n)	Mortality (30 d)	Reported Hb	Transfusion policy	Treatment-related events	Postsurgical infection	LOS, days, mean, (SD)
Prasad et al. [27]	G1: Oral iron	32	NR	NR	Pre: NS	NR	2 patients (constipation)	NR	NR
	G2: No Intervention	34			POD1: NS				
					POW4: S				
Parker [28]	G1: Oral iron	120	NR	6(4%)	Pre: NS	NR	26 (abdominal pain or alteration in bowel habits)	NR	NR
	G2: No intervention	123		3(2%)	POD1: NS				
					POW6: NS				
Karkouti et al. [30]	G1: IV iron	11	27.3% (3)	NR	Pre: NS	Hb < 70 g/L or clinical indication of transfusion	No serious events	NR	NR
	G2: PBM	10	20% (2)		POD1: NS				
					POD7: NS				
	G3: No intervention	10	40% (4)		POW6:NS/trend favouring PBM				
Serrano-Trenas et al. [29]	G1: IV iron	86	33.3%	NR	Pre: NS	Preoperatively hb < 10 g/L, postoperatively < 8 of 9 in patients with known cardiorespiratory history or any Hb in patients with symptoms of untreated anaemia	3 pts, 1 skin rash 2 discomfort	NS	NS
	G2: No intervention	90	41.3%		POD1: NS				
					POD7: NS (haematocrit)				
Panarese et al. [38]	G1: PBM	55	0	NR	Pre: NR	NR	NR	NR	10.23
	G2: No intervention	55	47 intra operatively, 11 postoperatively		POD1: NR				11
Blanco-Rubio et al. [31]	G1: IV iron	57	28.6% (16)	1 (0.8%)	Pre: NS	Transfusion when Hb < 80 g/L or < 90 g/L, if clinical symptoms of anaemia	NR	NS	NR
	G2: No intervention	63	71.4% (45)	5 (8.3%)					
Izuel-Rami et al. [32]	G1: IV iron	68	67.6% (46)	NR	Pre: NS	Restrictive transfusion, Hb < 70 g/L, in non-cardiopathic patients.	NR	NS, favouring PBM	11.9 (±7.4)
	G2: PBM	63	36.5% (23)		POD1: NS				12.7 (±7.5)
					POD2: S favouring no treatment over both PBM or IV iron				
	G3: No intervention or oral iron	196	52.0% (102)		POD7: NS				13.1 (±7.4)

Table 2 continued

Study	Comparison	N	ABT, % (n)	Mortality (30 d)	Reported Hb	Transfusion policy	Treatment-related events	Postsurgical infection	LOS, days, mean, (SD)
Muñoz et al. [18]	G1: IV iron	1000	32.4% (324)	4.8% (48)	Admission: NS	Transfusion when Hb < 8D g/L or < 90 g/L, if clinical symptoms of acute anaemia or actKre cardiac disease	None	S, favouring treatment	11.9 (±6.1)
	G2: No intervention	361	43.3% (176)	9.4% (34	PAD1:S				12.7 (±7.4)
					POD1: NS				13.4 (±6.3)
					POD7: S favouring control				
Cuenca Esplerrez et al. [33]	G1: IV iron	23	9 (39.1%)	3 (13.0%)	Pre: NS	Restrictive transfusion, Hb < 90 g/L.	None	S, favouring treatment	13.7 (±3.6)
	G2: No intervention	104	59 (56.7%)	17(16.3%)	POD2: NS				14.3 (±3.6)
Cuenca et al. [34]	G1: IV iron	20	3(15%)	0 (55.0%)	Admission: NS	Restrictive transfusion, considered if Hb < 90 g/L	None	NS, trend favouring treatment	11.9 (±2.1)
	G2: No intervention	57	21 (36.8%)	11 (19.3%)	Pre: NS				14.1 (±3.1)
					POD2: NS				
Cuenca et al. [35]	G1: IV iron	55	24 (43.6%)	5 (8.9%)	Admission: NS	Restrictive transfusion, considered If Hb < 90 g/L	None	S, favouring treatment	12.6 (±4.4
	G2: No intervention	102	57 (55.9%)	17(16.7%)	POD2: NS				14.3 (±3.6)
Garcla-Erce et al. [36]	G1: PBM	83	20 (24.1%)	6 (7.23%)	Pre: NS	Transfusion when H < 80 g/L or < 90 g/L, if clinical symptoms of acute anaemia or active cardiac disease	NR	S, favouring treatment	15.3 (±0.6)
	G2: No intervention	41	29 (70.7%)	6 (14.6%)	POD1: NS				15.0 (±0.8)
					POD2: NS				
					POD7: NS				
Armand-Ugón et al. [37]	G1: Oral Iron	14	O(-)	NR	Pre: S favouring oral	Clinical assessment by physician	None	NR	7.6 (±1.5)
	G2: IV iron	14	1 (7.1%)		POD1: S favouring oral				7.5 (±1.9)
					POD7: NS				

ABT allogenic blood transfusion; *d* day; *Hb* haemoglobin; *LOS* length of stay; *n* number; *NR* not reported; *NS* not significant; *PBM* patient blood management protocol; *POD* postoperative day; *POW* postoperative week; *Pre* preoperatively; *S* significant; *SD* standard deviation

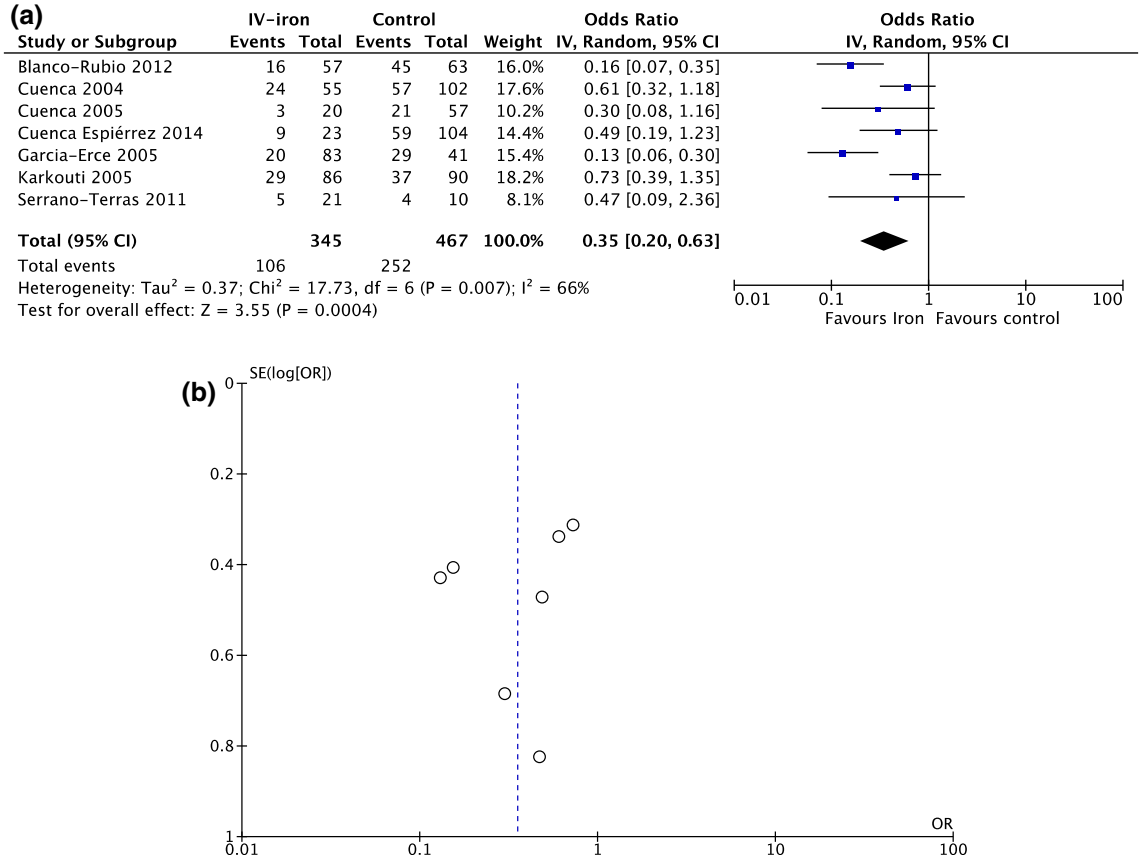

Fig. 2 **a** Meta-analysis of studies reporting on the rate of allogenic blood transfusion (ABT). Inverse variance random-effects model was used, and results are reported as odds ratio with 95% CIs. Treatment consisted of IV iron versus a control groups with no intervention. **b** Funnel plot: Studies included in the meta-analysis on allogenic blood transfusion: Funnel plot: Studies included in the meta-analysis on allogenic blood transfusion

Results from observational studies varied with respect to both timing of measurement and whether the studies included EPO. Only one observational study found a significant result: haemoglobin of controls 10.7 g/L (± 1.1) exceeding haemoglobin of the intervention group of 10.3 g/L (± 1.3) ($p < 0.01$) at POD7 [18].

Secondary outcome analysis

Mortality

Seven studies reported on 30-day postoperative mortality. One RCT showed a difference in mortality, 4.0% ($n = 6$) in the intervention group versus 2.0% ($n = 3$) in the control group [28]. This difference was not present after 1 year, where the mortality was 17.3% ($n = 29$) in both groups.

Five observational studies were eligible for a meta-analysis (Fig. 4a). All reported the 30-day postoperative mortality with additional EPO being administered in two. One study reported a mortality of 0.8%, with 57 patients in the study group [31]. This does not equal a meaningful number, and the study was excluded from the meta-analysis. Thus, the meta-analysis included four studies and showed a favourable effect of iron supplementation OR 0.50 (CI 95% 0.26–0.96) $p = 0.04$, $I^2 = 0\%$. A pooled retrospective analysis reported a mortality of 4.8% in 1000 patients receiving either iron or iron + reHuEPO, against 9.4% in the control population of 361 patients ($p < 0.01$) [18].

Length of stay

LOS was reported in one RCT, where no difference between groups was found. LOS was described in eight of the observational studies (Table 2, Fig. 5). Meta-analysis was not possible, due to large heterogeneity in study design and local differences in discharge criteria. Overall, treatment with iron leads to a reduced LOS. Only in one study [32], an insignificant increase from 12.7 to 13.1 days in LOS was seen when treated with IV iron alone—in this

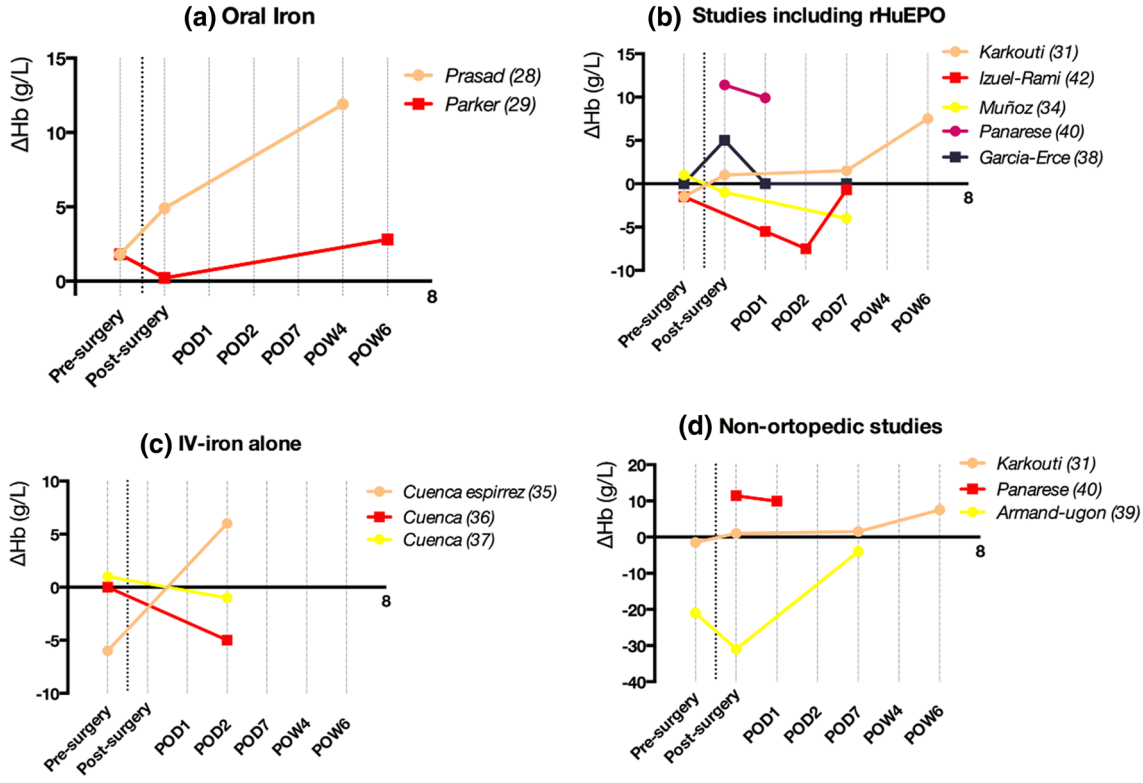

Fig. 3 **a**–**d** Differences in haemoglobin (Hb) for the treatment vs control cohort, at respective follow-up times ($\Delta Hb = Hb_{study} - Hb_{control}$). Positive values indicate a higher haemoglobin level in the intervention group compared with the control group. A positive slope is in favour of the intervention. **a** shows the effect of oral iron, **b** shows the effect of iron with additional rHuEPO, **c** shows the effect of intravenous (IV) iron alone, and **d** shows the effect of iron therapy in the non-orthopaedic studies; POD = postoperative day, POW = postoperative week, rHuEPO = recombinant human erythropoietin

study a decrease was found, when patients were part of a PBM protocol instead. The decreased LOS when included in PBM was not repeated in a 2005 study [36], where a PBM protocol leads to a non-significant increase from 15.0 (0.8) to 15.3 (0.6) days. In the largest study, a pooled observational study [18], a significant reduction was found. Only one observational study could repeat this finding [34].

Adverse events

Among all studies, treatment-related events were rare: oral iron caused mild adverse events in 28 patients out of 152 treated, mainly abdominal discomfort [27, 28]. IV iron caused no serious adverse events (SAEs) in RCTs, and few mild adverse events in one RCT [29]. In five observational studies reported on adverse events, none were observed [18, 33–35, 37].

A total of eight studies reported on postoperative infections. Four of these [29, 31, 32, 34]—hereof one RCT [29]—found no decrease in infection rates when treated with IV iron. One study found a trend towards a reduction only in the PBM group [32]. Four observational studies [18, 33, 35, 36] found a significant reduction in infection rates, (26.9% to 10.7% ($p = 0.001$)) [18], (35.4% to 20.3% $p = 0.04$) [35], (34% to 9% $p < 0.001$) [36], and (13% to 10% $p = 0.016$) [33], respectively.

Discussion

The key finding of this review was that iron therapy in relation to acute major non-cardiac surgery had a possible beneficial effect on the risk of allogenic blood transfusion (ABT). No clear effect of iron therapy was found on the postoperative haemoglobin levels. The effect on mortality as well as LOS was not clear, but pointed towards a benefit of treatment. No serious adverse events with respect to iron in immediate relation to acute major non-cardiac surgery were described in the included studies. A reduction in infections was found in the observational studies.

The effect of iron therapy on the risk of ABT was ambiguous. Our meta-analysis showed an OR of 0.35 CI

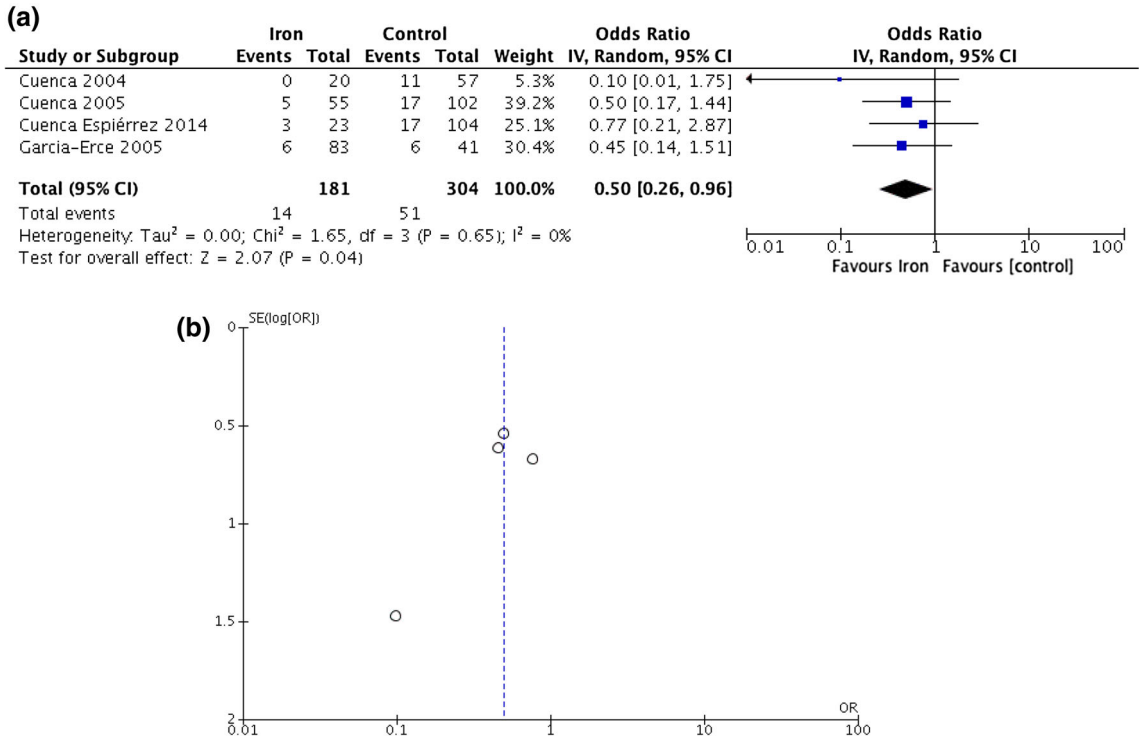

Fig. 4 **a** Meta-analysis of studies reporting on the 30-day mortality. Inverse variance random-effects model was used, and results are reported as odds ratio with 95% CIs. Treatment consisted of IV iron versus a control group receiving no intervention. **b** Funnel plot: Studies included in the meta-analysis on 30-day mortality

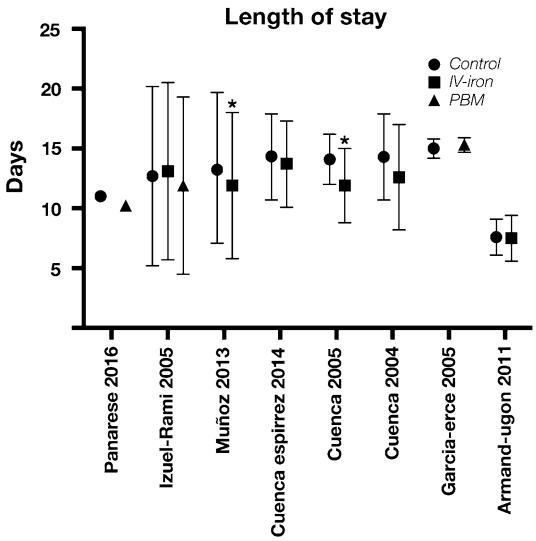

Fig. 5 Length of stay described in eight studies. One study (Panarese 2016) did not report standard deviation. All studies were observational studies. *Significant difference

95% (0.20–0.63), I2 = 66% $p = 0.0004$, with great heterogeneity among the studies. An unincluded large pooled observational study on patients undergoing surgery for hip fracture also found a significant reduction in ABT when treated with IV iron [18]. However, the only two prospective studies reporting on ABT failed to show a significant reduction in a meta-analysis, OR = 0.69 CI 95% (0.39–1.22), $p = 0.2$. Thus, our findings rely mainly on observational studies in orthopaedic emergency surgical patients.

ABT has been found to be an independent risk factor for inferior outcomes in acute surgery [4] and is known to have a negative impact on the immune system with potential multiple hazards [39]. When using a restrictive transfusion strategy, there may be a significant reduction in cardiac events, rebleeding, bacterial infections, and total mortality [40]. The proposed reduction of ABT is in accord with an earlier review [9], including 72 both surgical and non-surgical RCTs. This review stated that IV iron therapy was effective in increasing haemoglobin concentration and reducing the risk of ABT (RR 0.74 95% CI (0.62–0.88)) but included elective as well as acute patients and effectively only investigated the effect of IV iron in itself. The potential benefit was counterbalanced by a potential increased risk of infection. In contrast, our review pointed towards a reduction in the risk of postsurgical infections in relation to IV iron therapy.

A 2015 review of the safety of IV iron found no increased risk of SAEs including infection (relative risk [RR], 1.04; 95% CI, 0.93–1.17; I^2 = 9%) and concluded that intravenous iron therapy was neither associated with an increased risk of SAEs nor infections [41]. In our review, no serious adverse events were observed across all studies. Milder adverse events were seldom reported, in accord with previous studies.

Both pre- and postoperative anaemia are an obvious risk factor for inferior patient-related clinical outcomes in relation to surgery [3, 42, 43]. We were not able to find a clinically relevant effect of iron on the haemoglobin levels. Oral iron seemed to produce a long-term positive effect on the haemoglobin levels (Fig. 2), but it is unknown whether this finding was associated with clinical outcomes such as complications or mortality [27, 28]. Regarding treatment with IV iron, it was not possible to make any firm conclusions, as the only significant postoperative finding favoured the control-over the treatment group [18]. In a single RCT, 1-year mortality did not improve after treatment with oral iron; however, across the observational studies, the meta-analysis showed a markedly reduced risk with an OR 0.50 (CI 95% 0.26–0.96) p = 0.04 on 30-day mortality.

Oral and IV iron therapy administered at different times with respect to surgery has been extensively investigated in elective surgical patients. The emergency surgical population is different, offering no time for preoperative optimization [44], as well as an altered level of physiological stress [3, 45]. A 2017 international consensus statement on perioperative management of anaemia called upon postponing major non-urgent surgery until after treatment of anaemia [44]. This is not an opportunity in emergent surgical cases. The consensus statement did not mention specific treatments in acute surgical settings and, however, suggested that postoperative anaemia should be treated with intravenous iron.

The strength of this review mainly lies in the methodology, as we have made an effort to use a rigid set-up. Both our analyses and study selection are previously described by a protocol registered at PROSPERO, adhering to a sound methodology.

The limitations of this review include that the majority of studies is primarily comprised of patients undergoing surgery for hip fractures, making it difficult to generalise the findings to other surgical patient groups. Patients admitted to the hospital with hip fractures are typically elderly and frail patients, often with multiple comorbidities. These patients will often be in need of blood transfusions [46], which induces a risk of bias. However, the magnitude of surgical stress conveyed by hip fracture surgery is similar to other types of surgery [47]. A further limitation lies in the study size of the included studies. Most of the included observational studies are small, which potentially could lead to an increased risk of small-study effect in our meta-analyses. The same limitation applied goes for the included RCTs, rendering it difficult to make substantial unifying conclusions. Throughout the studies, different criteria towards iron deficiency were used in patient inclusion. The inflammatory process of the emergency patients has a substantial impact on the iron metabolism [48], and as such, it would be appropriate to address the iron status in said patients. As we found great heterogeneity towards this in our review, it was not possible to discuss this aspect.

Perioperative iron therapy has increasingly been getting attention, and recent consensus statements called upon a more consistent use of iron therapy in relation to surgery [44, 49]. Our review shows a lack of good studies in emergency surgery and implies that further studies should be conducted before inclusion of iron into treatment routines. The potential benefits described in our study could have a significant impact in this vulnerable patient population. Considering the small number of studies included opposed to the number screened, there is a lack of good-quality randomized clinical trials in multiple different surgical fields as well as large-scale prospective studies comparing IV iron alone to standard of care in an acute surgical setting.

In conclusion, this review identified 13 studies investigating iron treatment in relation to acute surgery. Studies included a variety of surgical patients, primarily patients with hip fracture, and were mainly observational in character. In a meta-analysis, IV iron showed a lower 30-day mortality and a reduction in ABT largely due to the observational studies. Furthermore, iron treatment showed a lower risk of postoperative infection. No significant effect was found with respect to postoperative haemoglobin levels or LOS. Based on the current evidence, the review does not have the power to recommend addition of iron therapy to acute major non-cardiac surgical patients and calls for further studies.

Author's contributions AS helped in study design, study selection, data collection, data analysis, data interpretation, drafting of manuscript, and critical revision. AAB helped in study selection and critical revision. SE contributed to study design, data interpretation, and critical revision. IG participated in data interpretation and critical revision. JB performed study design, data analysis, data interpretation, and critical revision.

Appendix 1

Search strategy

(((((((((((((((((Abdomen) OR abdominal) OR Surgery) OR Abdomen, Acute) OR Digestive System Surgical Procedures) OR General Surgery) OR Specialties, Surgical) OR ((Bloodless Medical and Surgical Procedures)))) OR Abdominal Cavity/surgery)) OR Blood Loss, Surgical)))) AND (((((((((Postoperative) OR Perioperative) OR Perioperative period) OR Postoperative care) OR Preoperative Care) OR Emergency) OR Emergencies)) OR acute))) AND ((((((((iron) OR Iron therapeutic) OR Iron administration) OR Ferric Compounds) OR Ferrous Compounds)) OR hematinics)))) AND (((((((((Perioperative outcomes) OR Postoperative complications) OR Long term outcomes) OR Short term outcomes) OR Mortality) OR Treatment outcome) OR Blood transfusion) OR Length of Stay))

Appendix 2

References	Prasad et al. [27]	Parker [28]	Karkouti et al. [30]	Serrano-Trenas et al. [29]
Random sequence generation	Low	Low	Low	Low
Allocation concealment	Low	Low	Low	Low
Selective reporting	Unclear	Low	Unclear	Low
Other bias	Low	Low	Unclear	Low
Blinding of participants and personnel	Low	High	Low	Low
Blinding of outcome assessment	Low	Unclear	Low	Low
Incomplete outcome data	Low	Low	Low	Low
Quality	High	Fair	High	High

Quality assessment of randomized clinical trials, using Cochrane risk of bias assessment tool [25]

Appendix 3

References	Panarese et al. [38]	Blanco-Rubio et al. [31]	Izuel-Rami et al. [32]	Muñoz et al. [18]	Cuenca Espiérrez et al. [33]	Cuenca et al. [34]	Cuenca et al. [35]	Garcla-Erce et al. [36]	Armand-Ugón et al. [37]
Selection (max 4)	*	***	***	****	***	**	**	***	**
Comparability (max 2)		*	*					**	*
Outcome (max 3)	**	*	*	***	***	**	**	***	**
Total (max 9)	***	*****	*****	*******	******	****	****	********	*****

Quality assessment of observational studies, Newcastle–Ottawa Scale [26]

References

1. Musallam KM et al (2011) Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet (London, England) 378:1396–1407
2. Lopes AM et al (2017) Postoperative haematocrit and outcome in critically ill surgical patients. Acta Med Port 30:555–560
3. Matsuyama T et al (2013) Risk factors for postoperative mortality and morbidities in emergency surgeries. J Anesth 27:838–843
4. Havens JM et al (2016) Explaining the excess morbidity of emergency general surgery: packed red blood cell and fresh frozen plasma transfusion practices are associated with major complications in nonmassively transfused patients. Am J Surg 211:656–663.e4
5. Muñoz M, Gómez-Ramírez S, Campos A (2014) Iron supplementation for perioperative anaemia in patient blood management. EMJ Rev 1:123–132
6. Lidder PG et al (2007) Pre-operative oral iron supplementation reduces blood transfusion in colorectal surgery—a prospective, randomised, controlled trial. Ann R Coll Surg Engl 89:418–421
7. Rogers BA, Cowie A, Alcock C, Rosson JW (2008) Identification and treatment of anaemia in patients awaiting hip replacement. Ann R Coll Surg Engl 90:504–507
8. Theusinger OM, Leyvraz P-F, Schanz U, Seifert B, Spahn DR (2007) Treatment of iron deficiency anemia in orthopedic surgery with intravenous iron: efficacy and limits: a prospective study. Anesthesiology 107:923–927
9. Litton E, Xiao J, Ho KM (2013) Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. BMJ 347:f4822
10. Muñoz M et al (2009) Usefulness of the administration of intravenous iron sucrose for the correction of preoperative anemia in major surgery patients. Med Clin 132:303–306
11. Gonzalez-Porras JR et al (2009) An individualized pre-operative blood saving protocol can increase pre-operative haemoglobin levels and reduce the need for transfusion in elective total hip or knee arthroplasty. Transfus Med 19:35–42
12. Ingraham AM, Haas B, Cohen ME, Ko CY, Nathens AB (2012) Comparison of hospital performance in trauma vs emergency and elective general surgery: implications for acute care surgery quality improvement. Arch Surg 147:591–598
13. Vester-Andersen M et al (2014) Mortality and postoperative care pathways after emergency gastrointestinal surgery in 2904 patients: a population-based cohort study. Br J Anaesth 112:860–870
14. Havens JM et al (2015) The excess morbidity and mortality of emergency general surgery. J Trauma Acute Care Surg 78:306–311
15. Leal-Noval SR et al (2013) Spanish consensus statement on alternatives to allogeneic blood transfusion: the 2013 update of the 'Seville document'. Blood Transfus 11:585–610
16. Beris P et al (2008) Perioperative anaemia management: consensus statement on the role of intravenous iron. Br J Anaesth 100:599–604
17. Torres S et al (2006) Intravenous iron following cardiac surgery does not increase the infection rate. Surg Infect (Larchmt) 7:361–366
18. Muñoz M et al (2013) Very-short-term perioperative intravenous iron administration and postoperative outcome in major orthopedic surgery: a pooled analysis of observational data from 2547 patients. Transfusion 54:289–299
19. Muñoz M et al (2014) Cost of post-operative intravenous iron therapy in total lower limb arthroplasty: a retrospective, matched cohort study. Blood Transfus 12:40–49
20. Jeong O, Park YK (2014) Effect of intravenous iron supplementation for acute postoperative anemia in patients undergoing gastrectomy for gastric carcinoma: a pilot study. Ann Surg Oncol 21:547–552
21. Titos-Arcos JC et al (2012) Is intravenous iron useful for reducing transfusions in surgically treated colorectal cancer patients? World J Surg 36:1893–1897. https://doi.org/10.1007/s00268-012-1589-x
22. Nagaraju SP, Cohn A, Akbari A, Davis JL, Zimmerman DL (2013) Heme iron polypeptide for the treatment of iron deficiency anemia in non-dialysis chronic kidney disease patients: a randomized controlled trial. BMC Nephrol 14:64
23. Giordano G et al (2011) Intravenous iron support vs oral liposomal iron support in patients with refractory anemia treated with Epo alpha. Monocentric prospective study. 11th Int Symp Myelodysplastic Syndr MDS Edinb U. K. 35:S137
24. Moher D et al (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4:1
25. Higgins JPT et al (2011) The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928
26. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P (2013) The Newcastle–Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
27. Prasad N, Rajamani V, Hullin D, Murray JM (2009) Post-operative anaemia in femoral neck fracture patients: does it need treatment? A single blinded prospective randomised controlled trial. Injury 40:1073–1076
28. Parker MJ (2010) Iron supplementation for anemia after hip fracture surgery. J Bone Jt Surg Am 92:265–269
29. Serrano-Trenas JA et al (2011) Role of perioperative intravenous iron therapy in elderly hip fracture patients: a single-center randomized controlled trial. Transfusion 51:97–104
30. Karkouti K et al (2006) Intravenous iron and recombinant erythropoietin for the treatment of postoperative anemia. Can J Anesth 53:11–19
31. Blanco Rubio N et al (2013) Hierro intravenoso preoperatorio como estrategia de ahorro de sangre en cirugía de fractura de cadera. Med Clin (Barc) 141:371–375
32. Izuel-Rami M et al (2005) Efectividad de distintas pautas de tratamiento de la anemia perioperatoria en pacientes ancianos con fractura de cadera. Farm Hosp 29:250–257
33. Cuenca Espiérrez J, Antonio García Erce J, Martínez Martín ÁA, Manuel Solano V, Javier Modrego Aranda F (2004) Seguridad y eficacia del hierro intravenoso en la anemia aguda por fractura trocantérea de cadera en el anciano. Med Clin (Barc) 123:281–285
34. Cuenca J et al (2005) Role of parenteral iron in the management of anaemia in the elderly patient undergoing displaced subcapital hip fracture repair: preliminary data. Arch Orthop Trauma Surg 125:342–347
35. Cuenca J et al (2004) Patients with pertrochanteric hip fracture may benefit from preoperative intravenous iron therapy: a pilot study. Transfusion 44:1447–1452
36. García-Erce JA et al (2005) Perioperative stimulation of erythropoiesis with intravenous iron and erythropoietin reduces transfusion requirements in patients with hip fracture. A prospective observational study. Vox Sang 88:235–243
37. Armand-Ugón R et al (2011) Efficacy of intravenous iron for treating postpartum anemia in low-resource african countries: a pilot study in Malawi. J Women's Heal 20:123–127
38. Panarese A et al (2016) Can bloodless surgery be applied to every patient undergoing major abdominal surgical intervention? Arch Hell Med 33:826–830

39. Clevenger B, Kelleher A (2014) Hazards of blood transfusion in adults and children. Contin Educ Anaesth Crit Care Pain 14:112–118
40. Salpeter SR, Buckley JS, Chatterjee S (2014) Impact of more restrictive blood transfusion strategies on clinical outcomes: a meta-analysis and systematic review. Am J Med 127:124–131.e3
41. Avni T et al (2015) The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc 90:12–23
42. Hallward G, Balani N, McCorkell S, Roxburgh J, Cornelius V (2016) The relationship between preoperative hemoglobin concentration, use of hospital resources, and outcomes in cardiac surgery. J Cardiothorac Vasc Anesth 30:901–908
43. Elhenawy AM, Meyer SR, Bagshaw SM, MacArthur RG, Carroll LJ (2015) Role of preoperative intravenous iron therapy to correct anemia before major surgery: study protocol for systematic review and meta-analysis. Syst Rev 4:29
44. Muñoz M et al (2017) International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia 72:233–247
45. Huddart S, Peden C, Quiney N (2013) Emergency major abdominal surgery—'the times they are a-changing'. Colorectal Dis 15:645–649
46. Foss NB, Kehlet H (2006) Hidden blood loss after surgery for hip fracture. J Bone Jt Surg Br 88:1053–1059
47. Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ (1992) Systemic cytokine response after major surgery. Br J Surg 79:757–760
48. Prakash D (2012) Anemia in the ICU. Anemia of chronic disease versus anemia of acute illness. Crit Care Clin 28:333–343
49. Muñoz M et al (2018) An international consensus statement on the management of postoperative anaemia after major surgical procedures. Anaesthesia. https://doi.org/10.1111/anae.14358