Original article

The impact of timing of intravenous iron supplementation on preoperative haemoglobin in patients scheduled for major surgery

Vanessa Neef[1], Peter Baumgarten[2,3], Stephanie Noone[1], Florian Piekarski[1], Chris Triphaus[1], Adina Kleinerüschkamp[4], Philipp Helmer[4], Leila Messroghli[1], Kai Zacharowski[1], Suma Choorapoikayil[1], Patrick Meybohm[1,4]

[1]*Department of Anesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Goethe University Frankfurt, Germany;*
[2]*Department of Neurosurgery, University Hospital Frankfurt, Goethe University, Frankfurt, Germany;*
[3]*Department of Neurosurgery, University Hospital, Friedrich Schiller University Jena, Germany;*
[4]*Department of Anesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Wuerzburg, Wuerzburg, Germany*

Background - Anaemia is frequent and an independent risk factor for morbidity and mortality in patients undergoing surgery. Iron deficiency (ID) is the main cause for anaemia and can be corrected by intravenous (IV) iron. The aim of this study was to investigate the timing of preoperative IV iron supplementation on preoperative haemoglobin (Hb) level.

Materials and methods - Surgical patients were screened for the presence of anaemia and ID from November 2015 to January 2020. In case of ID or iron deficiency anaemia (IDA), patients received IV iron supplementation. The timing of IV iron supplementation on preoperative Hb level was analysed by days and time frames clustered by 5 days before surgery.

Results - In total, 404 patients with IV iron supplementation were analysed. In all patients, IV iron was administered with a median (interquartile range [IQR]) of 3.0 (1.0; 9.0) days before surgery. Preoperative Hb level increased steadily starting from 6 days (0.13 [±1.2] g/dL) until 16 days before surgery (1.75 [±1.1] g/dL). Group comparison revealed a median preoperative Hb change of −0.2 (−0.5; 0.2) g/dL for days 1-5, 0.2 (0.0; 0.7) g/dL for days 6-10, 0.7 (0.2; 1.1) g/dL for days 11-15, 0.7 (0.2; 1.8) g/dL for days 16-20, 0.9 (0.3; 1.7) g/dL for days 21-25, 1.5 (0.4; 2.6) g/dL for days 26-30, and 0.6 (0.0; 1.7) g/dL for >31 days. Three patients received multiple administrations of IV iron which resulted in an increase in Hb of >4 g/dL.

Discussion - Supplementation of IV iron to increase Hb concentration preoperatively may be most effective if administered at least ten days before surgery.

Keywords: *Patient Blood Management, intravenous iron, iron deficiency, anaemia, surgery.*

INTRODUCTION

Preoperative anaemia affects up to 48% of patients undergoing major surgery[1] and is associated with increased morbidity and mortality[2,3]. Iron deficiency (ID) is the underlying cause in 30% of patients with preoperative anaemia, making iron supplementation a promising strategy to improve erythropoiesis and reduce blood transfusions. Oral iron is inexpensive and readily available but has poor patient compliance due to gastrointestinal

Arrived: 19 February 2021
Revision accepted: 13 April 2021
Correspondence: Patrick Meybohm
e-mail: meybohm_p@ukw.de

Blood Transfus 2022; 20: 188-197 DOI 10.2450/2021.0058-21
© SIMTIPRO Srl
All rights reserved - For personal use only
No other use without premission
© SIMTIPRO Srl

side effects limiting the efficacy of its use. In addition, long-term treatment of up to 6 months is usually required to replete iron stores adequately. Intravenous (IV) iron supplementation was shown to be beneficial in patients undergoing major surgery[4-6]. A combined administration of IV iron, erythropoietin alpha, vitamin B12, and folic acid increased haemoglobin (Hb) concentration, thereby significantly reducing red blood cell (RBC) transfusion from 1 to 0 units in cardiac surgery patients[6]. The Cardiac and Vascular Surgery Interventional Anemia Response (CAVIAR) study revealed a significant increase in Hb in patients receiving IV iron supplementation by 0.8 (0.5-1.2) g/dL. Furthermore, the authors discovered that an effect on ferritin level on IV iron supplementation appears after 7-9 days and that the Hb increase begins to plateau between 5 and 14 days[7]. Triphaus *et al.* observed a reduced intraoperative transfusion rate in ID anaemic (IDA) patients only if IV iron was supplemented >7 days before surgery[8]. The awareness of the effective role of iron supplementation to treat ID in the preoperative setting is increasing; however, uncertainty remains about the most effective timing of IV iron supplementation. This study addressed in detail the impact of timing of IV iron supplementation on increase of preoperative Hb level in patients undergoing major surgery.

MATERIALS AND METHODS

Data used for this retrospective analysis are part of a multicentre observational epidemiological trial focussing on the implementation of Patient Blood Management (PBM) in surgical patients (clinicaltrials.gov identifier NCT02147795). The study protocol was approved by the Ethics Committee of the University Hospital Frankfurt (ref. 318/17) and the requirement for written informed consent by patients was waived.

Patients and procedures

Data of patients (age ≥18 years) scheduled for major surgery with ≥10% probability of requiring RBC transfusion and screened for preoperative anaemia and ID by the anaemia walk-in clinic of the University Hospital Frankfurt[9] from November 2015 to January 2020 were included in our analysis. Part of the data (November 2015-July 2018) were recently analysed in a pilot project (n=103)[8]. Briefly, IV iron supplementation resulted in a preoperative increase (interquartile range [IQR]) of Hb levels of 0 (–0.2; 0.4) g/dL, 0 (–0.2; 0.6) g/dL, and 0.6 (–0.1;1.3) g/dL in patients with mild (n=52), moderate (n=47), and severe (n=4) anaemia, respectively. A preoperative increase of 0 (–0.3; –0.1) g/dL, 0.2 (–0.2; 0.9) g/dL, and 0.8 (0; 1.6) g/dL was detected in patients with iron substitution 1-7 (n=63), 8-14 (n=18), and ≥15 (n=22) days before surgery (p=0.04 for comparing patients with 1-7 and 8-14 days; and p<0.001 with 1-7 and ≥15 days after IV iron supplementation). In the present follow-up study, we now focussed on the effect of timing of IV iron supplementation by days and time frames clustered by 5 days on preoperative Hb level in a larger number of patients receiving IV iron supplementation prior to major surgery.

Data were extracted from the electronic hospital information system. The patient specific observation period ranged from pre-hospital admission until the day of hospital discharge.

Classification of anaemia and iron deficiency

According to the World Health Organization (WHO), anaemia is defined as Hb concentration <12 g/dL in women and <13 g/dL for men. Iron deficiency was diagnosed by lab results according to Muñoz *et al.*[10] and Anker *et al.*[11]. Briefly, ID was defined as serum ferritin level <100 ng/mL or TSAT <20%. In case of chronic kidney disease or heart failure, ID was diagnosed with ferritin level <300 ng/mL. In addition, a full medical history of the patient was taken into account during diagnosis. Anaemia was categorised into mild (Hb 11-11.9 g/dL for women and Hb 11-12.9 g/dL for men), moderate (Hb 8-10.9 g/dL), and severe (Hb <8 g/dL). Accordingly, patients were assigned to the following groups: patients with IDA or with ID. Other common causes of anaemia such as anaemia of inflammation, anaemia of chronic renal disease, and folate or vitamin B12 deficiency were not primarily addressed in this study.

Iron supplementation

Patients with ID received IV iron (ferric carboxymaltose 50 mg/mL; Vifor, Saint Galene, Switzerland) at a dose of 500 mg in 100 mL saline solution over 15 minutes (min) or 1,000 mg in 250 mL saline solution over 30 min depending on the patient's lab results. Contraindications were pregnancy, history of hypersensitivity reaction, acute infection with antibiotics, iron overload or recovery disorder (e.g. haemochromatosis). The patient's vital signs

© SIMTIPRO Srl

All rights reserved - For personal use only
No other use without premission

were monitored during IV iron administration and for an additional 10-15 min before discharge.

Assessment of sufficient intravenous iron dose

We used the Ganzoni formula[12] to identify patients with insufficient dosing of IV iron. A dose of 10% less than recommended by the Ganzoni formula to reach a Hb of 13 g/dL was considered as insufficiently dosed.

Endpoints

The primary endpoint was the preoperative increase in Hb value by timing of IV iron supplementation. Secondary endpoints were impact of severity of anaemia on Hb increment, hospital length of stay (LOS), adverse or serious events, mortality, prevalence of anaemia at hospital discharge, and efficiency of anaemia walk-in clinics over the years.

Statistical analysis

Descriptive statistical methods expressed as mean ± standard deviation (SD), median, IQR (25%; 75%) were used to analyse the data. The Shapiro-Wilk test was used to assess normality of continuous variables. Normally distributed data were compared with the Student τ-test and non-normally distributed data were compared with the Mann-Whitney U test. Fisher's χ^2 exact test was used for categorical variables. For calculation of Hb increment after IV iron infusion, Hb level at day of supplementation and last Hb level (<24 hours [h]) before surgery were used. In cases in which a patient received multiple IV iron supplementation, Hb level at first IV iron administration and last Hb level (<24 h) before surgery were used to estimate Hb increment in these patients. The Kruskal-Wallis Test was used for group comparison of preoperative Hb increment. After univariate analyses, significant effects were used in multivariate logistic regression model with $p<0.05$ as cut-off. Statistical analysis and graphical illustration were performed using IBM®SPSS® Statistics (Version 26, IBM, Armonk, New York, NY, USA), JMP 14.0 software (SAS Institute, Cary, NC, USA), and Microsoft Excel (Excel 365; Microsoft Corp., Redmond, Washington, WA, USA). $p<0.05$ was considered statistically significant.

RESULTS

Patient's baseline characteristics

Between November 2015 and January 2020, 509 patients received IV iron. In total, 105 patients were excluded from analysis because of minor surgery (n=35), postponed or cancelled surgery (n=27), missing data (n=23), duplicates (n=4), supplementation of IV iron after surgery (n=13), and patients with combined supplementation of IV iron and RBC units (n=3). Of the 404 patients who went forward for analysis, 325 (80.4%) were anaemic (IDA) and 79 (19.6%) were non-anaemic (ID) (**Figure 1**). Mild, moderate and severe anaemia was present in 150 (46.2%), 150 (46.2%), and 25 (7.6%)

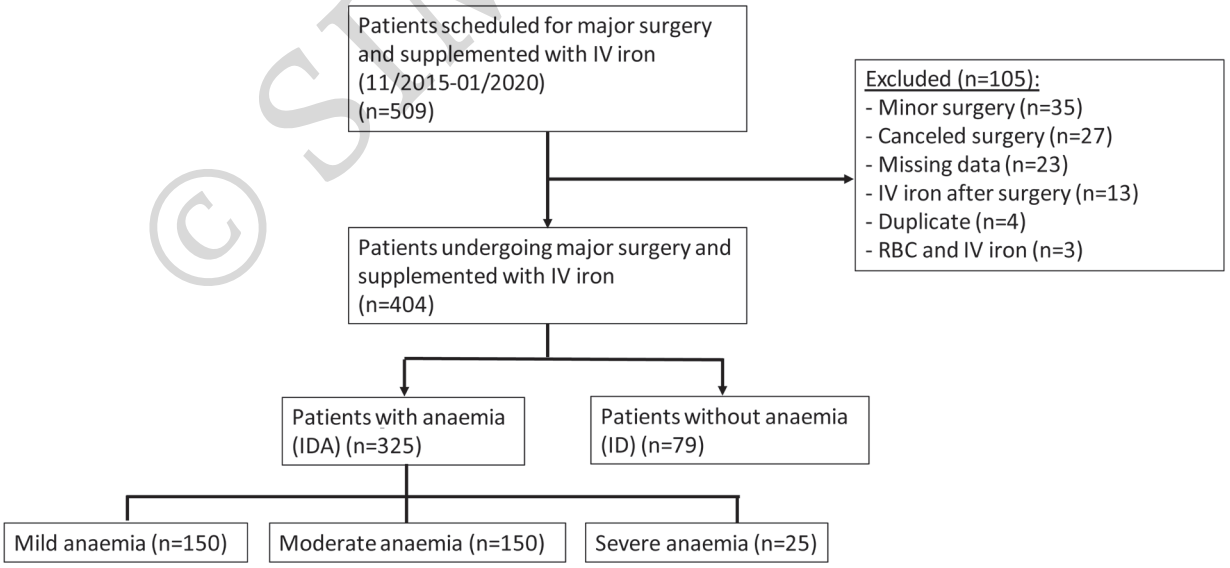


Figure 1 – Flowchart
IV: intravenous; IDA: iron deficiency anaemia; ID: iron deficiency, Hb: haemoglobin; RBC: red blood cell.

© SIMTIPRO Srl

Blood Transfus 2022; 20: 188-197 DOI 10.2450/2021.0058-21

All rights reserved - For personal use only
No other use without premission

patients with IDA, respectively (**Figure 1**). Median age was 69 (58;77) years (**Table I**). Laboratory results are summarised in *Online Supplemental* **Table SI**. The most prevalent comorbidities were cardiovascular disorders, history or present malignant disease, and respiratory diseases (**Table I**). Preoperative Hb level was 11 (±1.8) g/dL and significantly lower in the IDA group compared to the ID group: 10.4 (±1.5) g/dL *vs* 13.3 (±1.1) g/dL; p<0.001 (**Table II**).

Intravenous iron supplementation

In total, among study participants, 404 patients received IV iron supplementation, of whom 3 patients received multiple doses of iron supplementation. Overall, 173 (42.8%) patients received 500 mg IV iron and 228 (56.4%) patients received 1,000 mg. In addition, 3 patients received IV iron twice before surgery: Patient 1 received IV iron on day 16 (1,000 mg) and day 6 (500 mg) before surgery (in total 1,500 mg), Patient 2 received IV iron on day 30

Table I - *Demographic data of the study population*

Data	Total n=404	IDA n=325	ID n=79	p-value#
Gender (female) n (%)	176 (43.6)	134 (41.2)	42 (53.2)	0.037
Age (years)	69.0 (58.0-77.0)*	70.0 (59.5-78.0)*	63.0 (53.0-72.0)*	0.001
BMI (kg/m²)	25.4 (22.7-29.5)*	25.5 (22.6-29.6)*	26.0 (22.8-29.4)*	0.767
ASA 1 n (%) **ASA 2 n (%)** **ASA 3 n (%)** **ASA 4 n (%)**	3 (0.7) 72 (17.8) 168 (41.6) 161 (39.9)	2 (0.6) 58 (17.8) 133 (41.0) 132 (40.6)	1 (1.3) 14 (17.7) 35 (44.3) 29 (36.7)	0.591
Comorbidities n (%)				
Cardiovascular disease	297 (73.5)	242 (74.5)	55 (69.6)	0.382
History of or present cancer	201 (49.8)	162 (49.8)	39 (49.4)	0.939
Respiratory disease	125 (30.9)	105 (32.3)	20 (25.3)	0.228
Endocrine disorders	128 (31.7)	100 (30.8)	28 (35.4)	0.423
Diabetes	113 (28.0)	95 (29.2)	18 (22.8)	0.252
Chronic renal disease	94 (23.3)	82 (25.2)	12 (15.2)	0.048
Gastrointestinal disease	80 (19.8)	67 (20.6)	13 (16.5)	0.405
Chronic inflammation	38 (9.4)	29 (8.9)	9 (11.4)	0.500
Chronic liver disease	22 (5.4)	14 (4.3)	8 (10.1)	0.041
Surgical discipline n (%)				
Abdominal surgery	139 (34.4)	112 (34.5)	27 (34.2)	0.962
Cardiothoracic surgery	132 (32.7)	101 (31.1)	31 (39.2)	0.165
Cardiology	49 (12.1)	44 (13.5)	5 (6.3)	0.078
Urology	36 (8.9)	28 (8.6)	8 (10.1)	0.672
Maxillofacial surgery	21 (5.1)	15 (4.6)	6 (7.6)	0.285
Gynaecology	14 (3.5)	14 (4.3)	0 (0.0)	0.013
Vascular surgery	11 (2.7)	9 (2.8)	2 (2.5)	0.907
Trauma surgery/ Orthopaedics	2 (0.5)	2 (0.6)	0 (0.0)	0.485
Regular medication n (%)				
Beta blockers	158 (39.1)	135 (41.5)	23 (29.1)	0.088
Antiplatelet	136 (33.7)	109 (33.5)	27 (34.2)	0.595
Oral anticoagulation	94 (23.3)	85 (26.2)	9 (11.4)	0.009
Regular oral iron intake	14 (3.5)	13 (4.0)	1 (1.3)	0.265
No regular medication	113 (28.0)	87 (26.8)	26 (32.9)	0.131

*Results are expressed as median (Interquartile Range). #p-value between iron deficiency (ID) and iron deficiency anaemia (IDA); BMI: body mass index; ASA: American Society of Anesthesiologists physical status.

© SIMTIPRO Srl

All rights reserved - For personal use only
No other use without premission

Table II - *Haemoglobin levels, length of hospital stay (LOS) and mortality in the study population*

	Total n (%) 404 (100)	IDA n (%) 325 (80.4)	ID n (%) 79 (19.6)	p-value#
Hb level at IV iron (g/dL)	11.3 (9.8; 12.2)* 11.0 (±1.8)#	10.7 (9.4; 11.6)* 10.4 (±1.5)#	13.1 (12.5; 13.6)* 13.3 (±1.1)#	<0.001
Hb level before surgery (g/dL)	11.2 (9.8; 12.4)* 11.1 (±1.8)#	10.7 (9.6; 11.8)* 10.6 (±1.5)#	13.0 (12.3; 14.0)* 13.2 (±1.3)#	<0.001
Hb level at discharge (g/dL)	9.8 (8.9; 10.7)* 9.8 (±1.3)#	9.7 (8.9; 10.5)* 9.7 (±1.2)#	10.6 (9.6; 11.7)* 10.6 (±1.5)#	<0.001
LOS (days)	14.9 (±13.0)#	15.2 (±13.2)#	13.9 (±12.0)#	0.665
In-hospital mortality, n (%)	14 (3.5)	11 (3.4)	3 (3.8)	0.857

Results are expressed as median (Interquartile Range)* or mean (±SD)#. #p-value between iron deficiency (ID) and iron deficiency anaemia (IDA). Hb: haemoglobin; IV: intravenous.

(1,000 mg) and on day 23 (500 mg) before surgery (in total 1,500 mg), and Patient 3 received IV iron on day 64 (1,000 mg) and on day 55 (1,000 mg) before surgery (in total 2,000 mg). The mean total dose of IV iron was 793.3 (±265.6) mg. Intravenous iron was administered a median 3.0 (1.0; 9.0) days before surgery, while 251 patients (62.1%) received IV iron 1-5 days, 69 (17.1%) 6-10 days, 27 (6.7%) 11-15 days, 15 (3.7%) 16-20 days, 13 (3.2%) 21-25 days, 6 (1.5%) 26-30 days and 23 (5.7%) 31-113 days before surgery.

Impact of iron supplementation on haemoglobin level according to time

Overall, Hb level increased in patients supplemented with IV iron starting from 6 days before surgery (0.13 [±1.2] g/dL) and increased steadily in patients supplemented with IV iron until 16 days before surgery (1.75 [±1.1] g/dL) (**Figure 2**). An Hb increment of 1-1.9 g/dL and ≥2 g/dL were found in 42 and 17 supplemented patients, respectively. In total, 3 patients received IV iron twice before surgery. In these 3 patients, an Hb increment of 4.7 g/dL was observed for a patient with IV iron supplementation (total dose 1,500 mg) 16 and 6 days before surgery, an Hb increment of 4 g/dL was observed for a patient with IV iron supplementation (total dose 2,000 mg) 30 and 23 days before surgery, and an Hb increment of 5.5 g/dL for a patient with IV iron supplementation (total dose 2,000 mg) 64 and 55 days before surgery (**Figure 2**).

For comparison of Hb increment by different time frames before surgery, all patients were grouped in clusters of 5 days. A median preoperative change of –0.2 (–0.5; 0.2) g/dL, 0.2 (0.0; 0.7) g/dL, 0.7 (0.2; 1.1) g/dL, 0.7 (0.2; 1.8) g/dL, 0.9 (0.3; 1.7) g/dL, 1.5 (0.4; 2.6) g/dL and 0.6 (0.0; 1.7) g/dL was detected in patients with iron

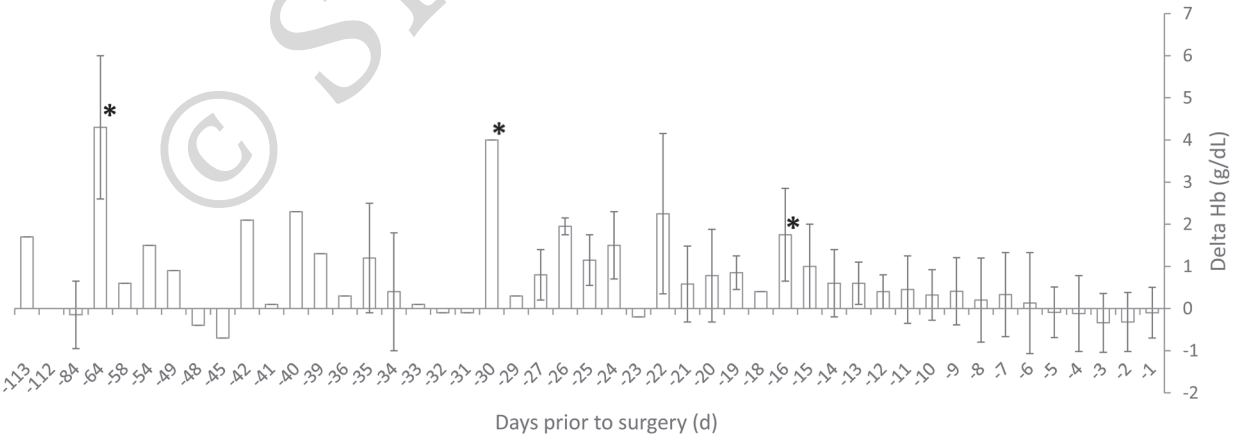


Figure 2 – Haemoglobin (Hb) increment in all patients after intravenous (IV) iron supplementation depending on single days prior to surgery
Mean Hb increment (±SD) from 1-113 days (n=404). *Three patients received IV iron twice before surgery.

Blood Transfus 2022; 20: 188-197 DOI 10.2450/2021.0058-21

© SIMTIPRO Srl
All rights reserved - For personal use only
No other use without premission

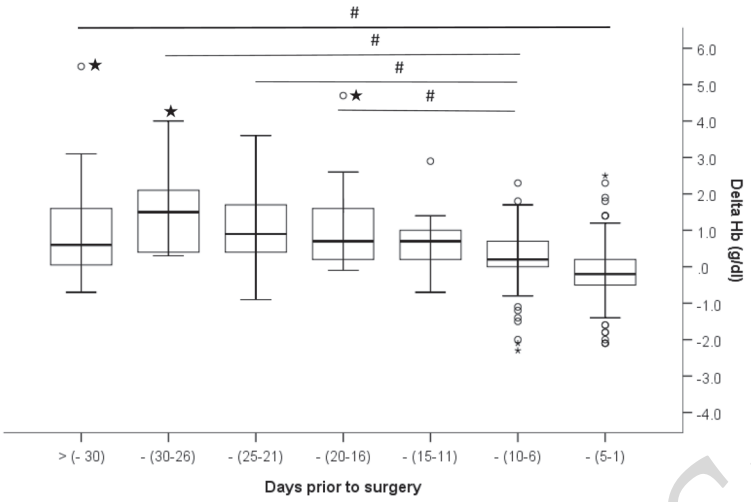


Figure 3 - Haemoglobin (Hb) increment in patients in all patients after iron supplementation depending on different time frames

Within each box, horizontal black lines denote median values; boxes extend from the 25th to the 75th percentile of each group's distribution of values; dots denote observations outside the range of adjacent values. Comparison was performed with the Kruskal-Wallis Test. Star: Three patients received intravenous (IV) iron twice before surgery. p=0.016 for comparing 6-10 *vs* 16-20 days; p=0.038 for 6-10 *vs* 21-25 days; p=0.019 for 6-10 vs 26-30; p<0.001 for 1-5 *vs* all others (6-10, 11-15, 16-20, 21-25, 26-30, ≥31 days). #p <0.05.

supplementation 1-5 (n=251), 6-10 (n=69), 11-15 (n=27), 16-20 (n=15), 21-25 (n=13), 26-30 (n=6), and >31 (n=23) days before surgery, respectively (p=0.016 for comparing patient with 6-10 *vs* 16-20 days; p=0.038 for 6-10 *vs* 21-25 days; p=0.019 for 6-10 *vs* 26-30; p<0.001 for 1-5 *vs* all others (6-10, 11-15, 16-20, 21-25, 26-30, >31 days) (**Figure 3**). Univariate analysis revealed cardiovascular and respiratory disease, gynaecological procedures, use of beta blockers or antiplatelet therapy, no regular intake of medication, severe anaemia, low MCHC/serum iron/soluble transferrin receptor/transferrin saturation or IV iron dose as predictors for Hb increment of ≥0.5 g/dL; however, none of these factors was significant in the multivariate logistic analysis (*Online Supplemental* **Table SII**).

Haemoglobin increment depending on severity of anaemia

Intravenous iron supplementation resulted in a significant preoperative increase of 1.1 g/dL (from 7.3 [±0.6] g/dL to 8.4 [±0.9] g/dL; p<0.001) in patients with severe anaemia (n=25). In patients with moderate (n=150) and mild (n=150) anaemia, an Hb increment of 0.3 g/dL and 0.0 g/dL was observed (**Table III**).

Table III – *Haemoglobin (Hb) increment after intravenous (IV iron) supplementation between different stages of anaemia*

	Patients, n (%)	Hb (g/dL) at IV iron	Hb (g/dL) before surgery	p-value
No anaemia	79 (19.6)	13.1 (12.5; 13.6)* 13.3 (±1.1)#	13.0 (12.3; 14.0)* 13.2 (±1.3)#	0.622
Mild anaemia	150 (37.1)	11.8 (11.4; 12.1)* 11.8 (±0.5)#	11.8 (11.1; 12.4)* 11.8 (±0.9)#	0.950
Moderate anaemia	150 (37.1)	9.8 (9.0; 10.3)* 9.6 (±0.8)#	9.8 (9.2; 10.5)* 9.9 (±1.1)#	0.105
Severe anaemia	25 (6.2)	7.3 (7.1; 7.7)* 7.3 (±0.6)#	8.1 (7.8; 9.1)* 8.4 (±0.9)#	<0.001

Results are expressed as median (Interquartile Range)* or mean (±standard deviation)#.

All rights reserved - For personal use only
No other use without premission

© SIMTIPRO Srl

Impact of iron dose on haemoglobin level

In total, 116 patients received an insufficient dose of whom 43 patients received iron supplementation >7 days. Overall, no significant differences were found for delta Hb between patients with sufficient and insufficient dose of IV iron (*Online Supplemental* **Table SIII**).

Efficiency of anaemia walk-in clinic

Overall, we observed an increase in the number of preoperative IV iron supplemented patients: 1 per week in 2015, 1.8 in 2016, 2.3 in 2018 and 2019.

Safety and tolerability

A total of 407 IV iron infusions were administered and iron was generally well tolerated. No serious adverse events were observed in the context of IV iron supplementation, but one female patient showed a hypersensitivity reaction after infusion of IV iron that disappeared completely within minutes of administration of 50 mg ranitidine, 8 mg dimetiden and 100 mg prednisolone. In addition, one female patient with a history of hypersensitivity reaction on IV iron supplementation received IV iron after a premedication of 250 mg of prednisolone, 8 mg dimetiden and 50 mg ranitidine. Intravenous iron was well tolerated without any adverse events.

Length of hospital stay, mortality and prevalence of anaemia at hospital discharge

Overall, patients with preoperative IV iron supplementation were discharged after 14.9 (±13) days. LOS was higher in patients with IDA (15.2 [±13.2] days) compared to patients with ID (13.9 [±12.0] days; p=0.665). By the time of hospital discharge, Hb values were significantly lower in patients with IDA (9.7 [±1.2] g/dL) compared to patients with ID (10.6 [±1.5]; p<0.001). Regarding surgical disciplines, the lowest Hb values by time of hospital discharge were observed in trauma surgery (8.9 [±1.5] g/dL), followed by cardiothoracic surgery (9.6 [±1.3] g/dL), cardiology (9.7 [±1.1] g/dL), urology (9.8 [±1.3] g/dL), and abdominal surgery (10.0 [±1.3] g/dL). Patients in vascular surgery (10.1 [±1.8] g/dL), gynaecology (10.3 [±1.6] g/dL), and maxillofacial surgery (10.7 [±1.4] g/dL) had the highest Hb values at hospital discharge. In total, 11 (3.4%) patients with IDA and 3 (3.8%) patients with ID died during their hospital stay (**Table II**).

DISCUSSION

Preoperative anaemia in surgical patients is associated with increased RBC transfusion and prolonged hospital stay. Iron deficiency is the main cause for anaemia and can be reversed by iron supplementation. Several guidelines have emerged from the need to combat preoperative anaemia. For example, the National Institute for Health and Care Excellence[13] and consensus statements recommend treatment of ID patients at least four weeks before surgery[10,14] leading to the implementation of anaemia walk-in clinics[8,9,15-18]. However, the time span between anaemia management and surgery varies between patients even within the same hospital. Therefore, there is still a degree of uncertainty as to the most effective timing of IV iron supplementation. In accordance with the implementation of a Patient Blood Management programme, a nurse-led anaemia walk-in clinic was established at the University Hospital Frankfurt in 2014[9].

Part of the data (November 2015-July 2018) were recently analysed in a pilot project (n=103). However, analysing the effect of time of preoperative IV iron supplementation on preoperative Hb level increase in detail was not feasible because of the low number of patients[8]. Between November 2015 and January 2020, 404 ID patients scheduled for major surgery received IV iron supplementation. Of the 404 ID patients, 325 were anaemic. The time span for iron supplementation before surgery varied between 1 and 113 days. In total, 62.1% of the patients received iron supplementation 1-5 days before surgery with only a minor effect on preoperative Hb level. The majority of these patients were from the cardiothoracic department and were scheduled for surgery with a short preoperative waiting time. Triphaus *et al.* demonstrated that ID patients supplemented with IV iron less than 7 days before surgery have most benefit in the postoperative period. In these patients, the transfusion rate decreased from 42.5 to 31.5%[8]. Similarly, Spahn *et al.* revealed a significantly reduced number of RBC transfusions in cardiac surgery patients supplemented with IV iron/erythropoietin/vitamin B12/folic acid one day before cardiac surgery[6]. Overall, we found a steady increase in Hb value in patients with IV iron supplementation from 6 days onwards. Considering that iron-dependent maturation from erythroblasts to differentiated RBC takes up to 4-6 days, a therapeutic effect of IV iron supplementation can presumably be expected after 5-7 days[19]. Froessler *et al.* administrated IV iron to patients undergoing abdominal surgery 8 (6; 13) days before surgery and found an Hb increment of

©SIMTIPRO Srl

Blood Transfus 2022; 20: 188-197 DOI 10.2450/2021.0058-21

All rights reserved - For personal use only
No other use without premission

0.8 g/dL at hospital admission[20]. Our grouped comparison of treatment days before surgery revealed an Hb increase of 0.2 g/dL (0.0; 0.7 g/dL) at 6-10 days before surgery with an increment of 1.5 g/dL (0.4; 2.6 g/dL) until 26-30 days before surgery, suggesting that IV iron supplementation should be administrated in patients with ID as early as possible before surgery.

Besides IDA, ID is also a significant risk factor for postoperative complications. Rössler an colleagues analysed 730 cardiac surgery patients, of which 119 suffered from ID and these showed an increase in mortality rate from 2 to 5%, serious adverse events from 16 to 35%, major cardiac and cerebrovascular events from 5 to 8%, and the transfusion rate of RBC units increased in patient with anaemia from 2.5 (±3) to 3.5 (±4.2)[21]. Interestingly, we found a similar Hb increment between patients with IDA or ID, indicating that also in patients with ID and normal Hb level, administration of IV iron is associated with increased erythropoiesis. This supports the use of IV iron in these patients.

Patients with severe anaemia showed a significant increase of >1 g/dL compared to patients with mild or moderate anaemia, suggesting that IV iron supplementation immediately activates erythropoiesis. An increased endogenous erythropoietin level in these patients may be associated with the generation of RBCs. In total, 3 patients with moderate and severe anaemia received multiple doses of IV iron supplementation before surgery and showed an Hb increase >4 g/dL. Overall, our results indicate that patients with severe anaemia benefit most from IV iron supplementation, particularly from multiple infusions. RBC units are often administrated to treat patients with severe anaemia. However, it is noteworthy that RBC transfusion only achieves a temporary reversal of the anaemia. Ideally, a single unit of RBCs (300-350 mL) increases Hb by 1 g/dL (3% change in Hct) and at least 4 units would have been required to an Hb increase >4 g/dL[22].

In general, cardiothoracic and abdominal surgical interventions are mostly of an urgent nature and preoperative IV iron is often administrated shortly before surgery. Of all surgical disciplines, patients undergoing major maxillofacial surgery are often supplemented with IV iron in advance, which may explain their Hb values at hospital discharge.

Identifying the correct dose of IV iron is challenging. In our anaemia walk-in clinic, a full medical history of the patient was taken into account during diagnosis and treatment. We retrospectively used the Ganzoni formula to assess the optimal dose for replacing patient's iron stores[10,12]. Interestingly, no significant differences were found for delta Hb between patients with sufficient and insufficient dose of IV iron. Most of the patients received IV iron less than ten days before surgery, and the apparent dose-independency effect could be the consequence of the short interval between administration and surgery. However, insufficient dose of IV iron might impede Hb increment postoperatively.

This study has some limitations. Our analysis revealed that Hb increment varied in patients with IV iron supplementation ≥31 days. Intravenous iron was supplemented in an outpatient setting and co-founding factors such as ongoing occult bleeding due to oral anticoagulants or tumour bleeding could have limited the increase in Hb. In addition, our dosing regimen of 500 or 1,000 mg FCM was established for pragmatic reasons but might have been too low to substitute severe ID in some patients and therefore may have weakened the study results. To address this, assessment of ferritin level is recommended; however, this has not yet been standardised at our hospital. A recent consensus statement suggested reviewing the classic WHO criteria in adults by aligning the Hb cut-off to 13 g/dL for both genders[10]. Females have a lower circulating blood volume and reduced RBCs compared to males but experience similar blood loss during surgery. Therefore, accepting an Hb level of 12 g/dL or less for women in the pre-surgery assessment, compared with a higher threshold of 13 g/dL for men, makes transfusion, with all the associated side effects and complications, more likely in women. However, changing long-established workflows is challenging. In addition, to assess the effect of IV iron supplementation, iron parameters and Ret-He values should be evaluated at hospital discharge at the latest.

CONCLUSIONS

Supplementation of IV iron to increase Hb concentration preoperatively is probably most effective if administered at least ten days, but preferably 3-4 weeks, before surgery, while short-term IV iron may improve postoperative

All rights reserved - For personal use only
No other use without premission

© SIMTIPRO Srl

erythropoiesis. Iron supplementation was most effective in severely anaemic patients with ID and in patients receiving multiple supplementation doses. Furthermore, postponing elective surgery in patients with a short preoperative waiting time to facilitate adequate and, if necessary, multiple IV iron supplementation should be considered.

ACKNOWLEDGEMENTS

We thank the following nurses for their support: Rebecca Meier, Sadaf Arefi-Shamsi, and Sabine Isik.

AUTHORSHIP CONTRIBUTIONS

SC and PM contributed equally to this work as co-senior Authors.

VN helped with substantial contributions to the conception and design of the work; data collection; analysis, and interpretation of the data; and wrote the manuscript. PB helped with data analysis and revised the manuscript critically for important intellectual content. SN helped with data collection and revised the manuscript critically for important intellectual content. FP helped with interpretation of the data and revised the manuscript critically for important intellectual content. CT helped with interpretation of the data and revised the manuscript critically for important intellectual content. LM helped with interpretation of the data and revised the manuscript critically for important intellectual content. AK And PH revised the manuscript critically for important intellectual content. KZ helped with substantial contributions to the conception and design of the work; interpretation of the data and revised the manuscript critically for important intellectual content. PM helped with substantial contributions to the acquisition to the conception and design of the work; and revised the manuscript critically for important intellectual content. SC helped with substantial contributions to the conception and design of the work; data analysis; interpretation of the data; and wrote the manuscript.

DISCLOSURE OF CONFLICTS OF INTEREST

KZ: The Department of Anaesthesiology, Intensive Care Medicine & Pain Therapy of the University Hospital Frankfurt received support from B. Braun Melsungen, CSL Behring, Fresenius Kabi, and Vifor Pharma for the implementation of Frankfurt's Patient Blood Management program and KZ received honoraria for scientific lectures from CSL Behring, implatcast GmbH, med Update GmbH, Pharmacosmos and Vifor Pharma. PM: received honoraria for scientific lectures from Belgien Red Cross, Biotest, CSL Behring GmbH, Bundesamt für Bevölkerungsschutz und Katastrophenhilfe (BKK), Fresenius, Haemonetics, Landesärztekammer Sachsen, Landesärztekammer Hessen, Masimo, Radiometer, Schöchl medical Education, Thieme-Verlag, Trillium Diagnostik, Werfen GmbH, ViforPharma GmbH. FP received honoria from Pharmacosmos for scientific lectures. PB received travel grants from Roche and Medac not related to this work.

All other Authors declare no conflicts of interest.

REFERENCES

1. Muñoz M, Gomez-Ramirez S, Campos A, et al. Pre-operative anaemia: prevalence, consequences and approaches to management. Blood Transfus 2015; **13**: 370-9.
2. 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.
3. Baron DM, Hochrieser H, Posch M, et al. Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. Br J Anaesth 2014; **113**: 416-23.
4. Theusinger OM, Leyvraz PF, Schanz U, et al. Treatment of iron deficiency anemia in orthopedic surgery with intravenous iron: efficacy and limits: a prospective study. Anesthesiology 2007; **107**: 923-7.
5. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. BMJ 2013; **347**: f4822.
6. Spahn DR, Schoenrath F, Spahn GH, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial. Lancet 2019; **393**: 2201-12.
7. Klein AA, Chau M, Yeates JA, et al. Preoperative intravenous iron before cardiac surgery: a prospective multicentre feasibility study. Br J Anaesth 2020; **124**: 243-50.
8. Triphaus C, Judd L, Glaser P, et al. Effectiveness of preoperative iron supplementation in major surgical patients with iron deficiency: a prospective observational study. Ann Surg 2021; **274**: e212-e219.
9. Meybohm P, Goehring MH, Choorapoikayil S, et al. Feasibility and efficiency of a preoperative anaemia walk-in clinic: secondary data from a prospective observational trial. Br J Anaesth 2017; **118**: 625-6.
10. Muñoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia 2017; **72**: 233-47.
11. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009; **361**: 2436-48.
12. Ganzoni AM. [Intravenous iron-dextran: therapeutic and experimental possibilities]. Schweiz Med Wochenschr 1970; **100**: 301-303. [In German.]
13. NICE. Blood Transfusion. 2015; Available at: https: //www.nice.org.uk/guidance/ng24/resources/blood-transfusion-pdf-1837331897029. Accessed on 18/01/2019.
14. Muñoz M, Acheson AG, Bisbe E, et al. An international consensus statement on the management of postoperative anaemia after major surgical procedures. Anaesthesia. 2018; **73**: 1418-31.
15. Diez-Lobo AI, Fisac-MartÍN MP, Bermejo-Aycar I, Muñoz M. Preoperative intravenous iron administration corrects anemia and reduces transfusion requirement in women undergoing abdominal hysterectomy. Transfus Altern Transfus Med 2007; **9**: 114-9.

All rights reserved - For personal use only
No other use without premission

©SIMTIRED Srl

16. Enko D, Wallner F, von-Goedecke A, et al. The impact of an algorithm-guided management of preoperative anemia in perioperative hemoglobin level and transfusion of major orthopedic surgery patients. Anemia 2013; **2013**: 641876.
17. Quintana-Diaz M, Fabra-Cadenas S, Gomez-Ramirez S, et al. A fast-track anaemia clinic in the Emergency Department: feasibility and efficacy of intravenous iron administration for treating sub-acute iron deficiency anaemia. Blood Transfus 2016; **14**: 126-33.
18. Van Wyck DB, Mangione A, Morrison J, et al. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. Transfusion 2009; **49**: 2719-28.
19. Besarab A, Horl WH, Silverberg D. Iron metabolism, iron deficiency, thrombocytosis, and the cardiorenal anemia syndrome. Oncologist 2009; **14** (Suppl 1): 22-33.
20. Froessler B, Palm P, Weber I, et al. The important role for intravenous iron in perioperative Patient Blood Management in major abdominal surgery: a randomized controlled trial. Ann Surg 2016; **264**: 41-6.
21. Rössler J, Schoenrath F, Seifert B, et al. Iron deficiency is associated with higher mortality in patients undergoing cardiac surgery: a prospective study. Br J Anaesth 2020; **124**: 25-34.
22. Elzik ME, Dirschl DR, Dahners LE. Correlation of transfusion volume to change in hematocrit. Am J Hematol 2006; **81**: 145-6.

© SIMTIPRO Srl

All rights reserved - For personal use only
No other use without premission