BREE Anemia Refs

**Papers on Risk of Anemia** (Those with a red number (4, 5, & 6) are in the BreeOptimization+ERAS-final)

1. Netz A, Hof L, Rumpf F, et al. Adjusting Current Hemoglobin Thresholds: A Way to Improve Outcome in Women Undergoing Major Surgery. J Womens Health (Larchmt) 2024;33(5):678-684. DOI: 10.1089/jwh.2023.0665.

**Material and Methods**: Single-center retrospective analysis of female patients undergoing major surgery.
**Results**: In total, 6,516 patients ‡18 years of age had major surgery between 2018 and 2019 and 2,446 female patients were included in analysis. Mean age was 67.4 – 16.6, 66.4 – 15.6, and 64.5 – 15.5 years in female patients with preoperative Hb levels <12.0, 12.0–12.9 and ‡13.0 g/dL, respectively. The transfusion rate of red blood cells (RBCs) was significantly higher in female patients with Hb <12.0 g/dL (53%) and with Hb 12.0– 12.9 g/dL (31%) compared to female patients ‡13.0 g/dL (22%). Rates of pneumonia, acute kidney injury, and sepsis were significantly higher in patients with Hb <12.0 and 12.0–12.9 g/dL compared to patients with Hb ‡13.0 g/dL. Total length of hospital stay was significantly longer in female patients with Hb <12.0 g/dL than patients with Hb 12.0–12.9 g/dL and Hb ‡13.0 g/dL (10 days vs. 8 days).
**Conclusion**: Taken together, our data show that Hb values below 12.9 g/dL are associated with increased probability of RBC transfusions and increased risk of postoperative complications. In addition, our results indicate that postoperative outcomes for women might be optimized by increasing cut-off values for anemia. The call to revise the anemia threshold for women by the WHO can no longer be disregarded.

2. Baron DM, Hochrieser H, Posch M, et al. Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. British journal of anaesthesia 2014;113(3):416-23. (In eng). DOI: 10.1093/bja/aeu098.

We included 39 309 patients in the analysis. Preoperative anaemia during 28 days before operation had a high prevalence in both men and women (31.1% and 26.5%, respectively). Multivariate analysis showed that patients with severe [odds ratio 2.82 (95% confidence interval 2.06–3.85)] or moderate [1.99 (1.67–2.37)] anaemia had higher in-hospital mortality than those with normal preoperative Hb concentrations. Furthermore, hospital length of stay (P,0.001) and postoperative admission to intensive care (P,0.001) were greater in patients with anaemia than in those with normal Hb concentrations.
Definitions and prevalence of anaemia and polycythaemia.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Severe anaemia | Moderate anaemia | Mild anaemia | Normal haemoglobin |  |
|  |
| Men (g dl-1) | <8 | 8-<11 | 11-<13 | 13-<17 |  |
| Women (g dl-1) | <8 | 8-<10 | 10-<12 | 12-<16 |  |
| Total (N=39,309) | 637 (1.6%) | 3,427 (8.7%) | 7,231 (18.4%) | 27,439 (69.8%) |  |

3. Gabriel RA, Clark AI, Nguyen AP, Waterman RS, Schmidt UH. The Association of Preoperative Hematocrit and Transfusion with Mortality in Patients Undergoing Elective Non-cardiac Surgery. World journal of surgery 2018;42(7):1939-1948. (In eng). DOI: 10.1007/s00268-017-4359-y.

**Methods**: This is a retrospective cohort study using the American College of Surgeons NSQIP database from 2011 to 2013. Cohorts were analyzed based on preoperative hematocrit range—patients with: (1) no anemia, (2) hematocrit >33% and<36% in females or<39% in males, (3) hematocrit >30% and<33%, (4) hematocrit >27% and<30%, (5) hematocrit >24% and<27%, and (6) hematocrit >21% and <24%. Multivariable logistic regression was used to analyze the association of anemia and transfusion with 30-day in-hospital mortality.
**Results**: The odds for 30-day mortality increased incrementally as the hematocrit ranges decreased, in which preoperative hematocrit between 21 and 24% had the highest odds for this outcome (odds ratio [OR] 6.50, p<0.0001) compared to the reference group (no anemia). The use of transfusion increased the odds of mortality even further (OR 5.57, p<0.0001). Among patients that received an intra-/postoperative transfusion, preoperative anemia was not predictive of mortality.

Same association of anemia with mortality after multivariate analysis.

4. Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet (London, England) 2011;378(9800):1396-407. (In eng). DOI: 10.1016/s0140-6736(11)61381-0.

We obtained data for 227 425 patients, of whom 69 229 (30・44%) had preoperative anaemia. After adjustment, postoperative mortality at 30 days was higher in patients with anaemia than in those without anaemia (odds ratio [OR] 1・42, 95% CI 1・31–1・54); this diff erence was consistent in mild anaemia (1・41, 1・30–1・53) and moderate-to-severe anaemia (1・44, 1・29–1・60). Composite postoperative morbidity at 30 days was also higher in patients with anaemia than in those without anaemia (adjusted OR 1・35, 1・30–1・40), again consistent in patients with mild anaemia (1・31, 1・26–1・36) and moderate-to-severe anaemia (1・56, 1・47–1・66). When compared with patients without anaemia or a defined risk factor, patients with anaemia and most risk factors had a higher adjusted OR for 30-day mortality and morbidity than did patients with either anaemia or the risk factor alone.

5. Myles PS, Richards T, Klein A, et al. Postoperative anaemia and patient-centred outcomes after major abdominal surgery: a retrospective cohort study. British journal of anaesthesia 2022;129(3):346-354. (In eng). DOI: 10.1016/j.bja.2022.06.014.

**Results**: A total of 2983 patients met inclusion criteria for this study, of which 78.5% (95% confidence interval [CI], 76.7-80.1%) had postoperative anaemia. Patients with postoperative anaemia had a higher adjusted risk of death or disability up to 90 days after surgery when compared with those without anaemia: 18.2% vs 9.2% (risk ratio [RR]=1.51; 95% CI, 1.10-2.07, P=0.011); lower QoR-15 scores on Day 3 and Day 30, 105 (95% CI, 87-119) vs 114 (95% CI, 99-128; P<0.001), and 130 (95% CI, 112-140) vs 139 (95% CI, 121-144; P<0.011), respectively; higher adjusted risk of a composite of mortality/septic complications, 2.01 (95% CI, 1.55-42.67; P<0.001); unplanned admission to ICU (RR=2.65; 95% CI, 1.65-4.23; P<0.001); and longer median (inter-quartile range [IQR]) hospital stays, 6.6 (4.4-12.4) vs 3.7 (2.5-6.5) days (P<0.001).

The reduction in Hb from baseline to postoperative Day 3 was greater in the anaemic group, 24 (IQR, 13-25) g/L vs nonanaemic group, 13 (4-20) g /L; median difference 11 (95% CI, 8.9-13.1) g/ L (P<0.001). -- In other words, greater blood loss led to more complications.

6. Schatz C, Plötz W, Beckmann J, Bredow K, Leidl R, Buschner P. Associations of preoperative anemia and postoperative hemoglobin values with hospital costs in total knee arthroplasty (TKA). Arch Orthop Trauma Surg 2023;143(11):6741-6751. (In eng). DOI: 10.1007/s00402-023-04929-4.

**Results**: Preoperative anemic women had 426 Euros higher general ward costs (p < 0.01), due to increased LOS. For men, 1 g/dl less Hb loss between the preoperative value and the value before discharge reduced total costs by 292 Euros (p < 0.001) and 161 Euros fewer general ward costs (p < 0.001). Total hospital costs were reduced by 144 Euros with 1 g/dl higher Hb on day 2 postoperatively for women (p < 0.01).

**Papers About Preop Correction of Anemia**

1. Almonacid-Cardenas F, Rivas E, Auron M, et al. Association between preoperative anemia optimization and major complications after non-cardiac surgery: a retrospective analysis. Braz J Anesthesiol 2024;74(2):744474. (In eng). DOI: 10.1016/j.bjane.2023.11.004.

**Conclusion**: Preoperative anemia optimization did not appear to be associated with a composite outcome of major in-hospital postoperative cardiovascular, renal, and pulmonary complications and all-cause in-hospital mortality. There were 5700 “optimized” patients and 8721 “non-optimized" patients studied at the Cleveland Clinic hospitals. Anemia defined as Hgb <12.0 g for women and 13.0 g for men. Confounder-adjusted odds ratio estimate of 0.99 (95% CI
0.86‒1.15) for anemia optimization versus nonoptimization, p=0.90. Intraoperative red blood cell transfusion had a minor mediation effect on the relationship between preoperative anemia optimization and the primary outcome, whereas duration of intraoperative hypotension was not found to be a mediator.

Optimization was defined as treatment with iron or other medications prior to surgery to treat anemia. The median [quartiles] of hemoglobin concentration before optimization for anemia optimized patients was11.4 [9.7,12.6] g/dl(n=3956. The median [quartiles] of preoperative hemoglobin concentration measured on the available closest date before surgery was 11.5 [10.3,12.6] g/dl (n=5686) for anemia optimized patients, and 11.9 [11.0,12.9] g/dl (n=8683) for non-optimized.

2. Ng O, Keeler BD, Mishra A, et al. Iron therapy for preoperative anaemia. The Cochrane database of systematic reviews 2019;12(12):Cd011588. (In eng). DOI: 10.1002/14651858.CD011588.pub3.

**Authors' conclusions**

The use of iron therapy for preoperative anaemia does not show a clinically significant reduction in the proportion of trial participants who received an allogeneic blood transfusion compared to no iron therapy. Results for intravenous iron are consistent with a greater increase in haemoglobin and ferritin when compared to oral iron, but do not provide reliable evidence. These conclusions are drawn from six studies, three of which included very small numbers of participants. Further, well-designed, adequately powered, RCTs are required to determine the true effectiveness of iron therapy for preoperative anaemia. Two studies are currently in progress, and will include 1500 randomised participants.

3. Kaufner L, von Heymann C, Henkelmann A, et al. Erythropoietin plus iron versus control treatment including placebo or iron for preoperative anaemic adults undergoing non-cardiac surgery. The Cochrane database of systematic reviews 2020;8(8):Cd012451. (In eng). DOI: 10.1002/14651858.CD012451.pub2.

**Authors' conclusions**

Moderate-quality evidence suggests that preoperative erythropoietin (rHuEPO) + iron therapy for anaemic adults prior to non-cardiac surgery reduces the need for RBC transfusion and, when given at higher doses, increases the haemoglobin concentration preoperatively. The administration of rHuEPO + iron treatment did not decrease the mean number of units of RBC transfused per patient. There were no important differences in the risk of adverse events or mortality within 30 days, nor in length of hospital stay. Further, well designed, adequately powered RCTs are required to estimate the impact of this combined treatment more precisely.

4. Choi UE, Nicholson RC, Thomas AJ, et al. A Propensity-Matched Cohort Study of Intravenous Iron versus Red Cell Transfusions for Preoperative Iron-Deficiency Anemia. Anesthesia and analgesia 2024;139(5):969-977. DOI: 10.1213/ane.0000000000006974.

**RESULTS**: Compared with RBC transfusion, preoperative IV iron was associated with lower risk of postoperative mortality (n = 2550/77,179 [3.3%] vs n = 4042/77,179 [5.2%]; relative risk [RR], 0.63, 95% confidence interval [CI], 0.60–0.66), and a lower risk of postoperative composite morbidity (n = 14,174/77,179 [18.4%] vs n = 18,632/77,179 [24.1%]; RR, 0.76, 95% CI, 0.75–0.78) (both *P* = .001 after Bonferroni adjustment). Compared with RBC transfusion, IV iron was also associated with a higher hemoglobin in the 30-day postoperative period (10.1 } 1.8 g/dL vs 9.4 } 1.7 g/dL, *P* = .001 after Bonferroni adjustment) and a reduced incidence of postoperative RBC transfusion (n = 3773/77,179 [4.9%] vs n = 12,629/77,179 [16.4%]; RR, 0.30, 95% CI, 0.29–0.31).

**CONCLUSIONS**: In a risk-adjusted analysis, preoperative iron deficiency anemia treatment with IV iron compared to RBC transfusion was associated with a reduction in 30-day postoperative mortality and morbidity, a higher 30-day postoperative hemoglobin level, and reduced postoperative RBC transfusion. This evidence represents a promising opportunity to improve patient outcomes and reduce blood transfusions and their associated risk and costs.

5. Kangaspunta M, Mäkijärvi J, Koskensalo S, et al. Preoperative intravenous iron treatment reduces postoperative complications and postoperative anemia in preoperatively anemic patients with colon carcinoma. Int J Colorectal Dis 2022;37(2):449-455. DOI: 10.1007/s00384-021-04080-9.

**Methods**: In this retrospective cohort study, data were collected from medical records of all 549 colon carcinoma patients who underwent a colon resection in Helsinki University Hospital during the years 2017 and 2018. The patients were divided into two cohorts: one with anemic patients treated with preoperative intravenous iron supplementation therapy (180 patients) and one with anemic patients without preoperative intravenous iron supplementation therapy (138 patients). Non-anemic patients and patients requiring emergency surgery were excluded (231 patients).
**Results**: Patients treated with intravenous iron had less postoperative complications (33.9% vs. 45.9%, *p* = 0.045) and a lower prevalence of anemia at 1 month after surgery (38.7% vs. 65.3%, *p* < 0.01) when compared with patients without preoperative iv iron treatment. No difference was found in the amount of red blood cell transfusions, length of stay, or mortality between the groups.

6. Laso-Morales M, Jericó C, Gómez-Ramírez S, et al. Preoperative management of colorectal cancer-induced iron deficiency anemia in clinical practice: data from a large observational cohort. Transfusion 2017;57(12):3040-3048. DOI: 10.1111/trf.14278.

**STUDY DESIGN AND METHODS**: This was a retrospective analysis of consecutive colorectal cancer resections at two Spanish centers (January 2012 to December 2013). Preoperative anemia was defined as a hemoglobin (Hb) level of less than 13 g/dL and treated with intravenous iron (IVI) or standard care (oral iron or no iron). Red blood cell transfusion (RBCT) requirement was the primary outcome variable. Postoperative infection rate and length of hospital stay (LOS) were secondary outcome variables. Patients were managed with a restrictive transfusion trigger (Hb<8 g/dL). Infection was diagnosed clinically and confirmed by laboratory, microbiologic, and/or radiologic evidence.
**RESULTS**: Overall, 322 of 571 patients (56%) presented with anemia: 232 received IVI and 90 standard care. There were differences in RBCT rate between no anemia and anemia (2% vs. 16%; p<0.01), but not in postoperative infections (19% vs. 22%; p5NS) or LOS. Compared to those on standard care, anemic patients on IVI presented with lower Hb (10.8 g/dL vs. 12.0 g/dL; p<0.001) at baseline, but similar Hb on day of surgery and Postoperative Day 30. There were no between-group differences in RBCT rates (16% vs. 17%; p5NS), but infection rates were lower among IVI-treated patients (18% vs. 29%; p<0.05). No relevant IVI-related side effects were recorded.

7. Ploug M, Kroijer R, Qvist N, Knudsen T. Preoperative Intravenous Iron Treatment in Colorectal Cancer: Experience From Clinical Practice. The Journal of surgical research 2022;277:37-43. DOI: 10.1016/j.jss.2022.03.004.

**Methods**: A registry-based cohort study. Surgical colorectal cancer patients with iron deficiency anemia were compared after division into two groups; those who preoperatively received IV iron treatment and those who did not. Primary outcomes were preoperative changes in Hb and the difference in perioperative red blood cell transfusion (RBCT) rates. Postoperative complications and mortality rates were analyzed and a descriptive analysis on what triggered blood transfusions were performed.
**Results**: A total of 170 patients were included. Of these, 122 had received preoperative IV iron treatment and 48 had not. The perioperative transfusion rate was 45% (55/122) in the treatment group and 40% (19/48) in the control group (non-significant difference). The preoperative changes in Hb levels were not different between the two groups. Transfusion practice appeared more liberal and preceded by higher Hb levels that was guided by the National transfusion guideline. IV iron treated patients had a higher rate of postoperative complications. No differences were found on length of stay (LOS) or postoperative mortality. Conclusions: Preoperative IV iron treatment was neither associated with a rise in Hb concentrations at the time of surgery, nor with a reduction in the likelihood of receiving perioperative red blood cell transfusions (RBCT) in colorectal cancer (CRC) patients with iron deficiency anemia.

8. Richards T, Baikady RR, Clevenger B, et al. Preoperative intravenous iron for anaemia in elective major open abdominal surgery: the PREVENTT RCT. Health Technol Assess 2021;25(11):1-58. DOI: 10.3310/hta25110.

**Design**: A multicentre, double-blinded, randomised, controlled, Phase III clinical trial, with 1 : 1 randomisation comparing placebo (normal saline) with intravenous iron (intravenous ferric carboxymaltose 1000 mg). Randomisation and treatment allocation were by a secure web-based service.
**Setting**: The study was conducted across 46 hospitals in England, Scotland and Wales between September 2013 and September 2018.
**Participants**: Patients aged > 18 years, undergoing elective major open abdominal surgery, with anaemia [Hb level of > 90 g/l and < 120 g/l (female patients) and < 130 g/l (male patients)] who could undergo randomisation and treatment 10–42 days before their operation.
**Intervention**: Double-blinded study comparing placebo of normal saline with 1000 mg of ferric carboxymaltose administered 10–42 days prior to surgery.
**Results**: A total of 487 patients were randomised (243 given placebo and 244 given intravenous iron), of whom 474 completed the trial and provided data for the analysis of the co-primary end points. The use of intravenous iron increased preoperative Hb levels (mean difference 4.7 g/l, 95% confidence interval 2.7 to 6.8 g/l; p < 0.0001), but had no effect compared with placebo on risk of blood transfusion or death (risk ratio 1.03, 95% confidence interval 0.78 to 1.37; p = 0.84; absolute risk difference +0.8%, 95% confidence interval –7.3% to 9.0%), or rates of blood transfusion (rate ratio 0.98, 95% confidence interval 0.68 to 1.43; p = 0.93; absolute rate difference 0.00, 95% confidence interval –0.14 to 0.15). There was no difference in postoperative complications or hospital stay. The intravenous iron group had higher Hb levels at the 8-week follow-up (difference in mean 10.7 g/l, 95% confidence interval 7.8 to 13.7 g/l; p < 0.0001). There were a total of 71 re-admissions to hospital for postoperative complications in the placebo group, compared with 38 re-admissions in the intravenous iron group (rate ratio 0.54, 95% confidence interval 0.34 to 0.85; p = 0.009). There were no differences between the groups in terms of mortality (two per group at 30 days post operation) or in any of the prespecified safety end points or serious adverse events.
**Conclusions**: In patients with anaemia prior to elective major abdominal surgery, there was no benefit from giving intravenous iron before the operation.

9. Ellermann I, Bueckmann A, Eveslage M, et al. Treating Anemia in the Preanesthesia Assessment Clinic: Results of a Retrospective Evaluation. Anesthesia and analgesia 2018;127(5):1202-1210. DOI: 10.1213/ane.0000000000003583.

**METHODS**: Between April 1, 2014, and July 4, 2016, patients scheduled for elective surgery with a risk for RBC transfusions >10% in 2013 were screened for preoperative anemia and, if indicated, treated with intravenous iron (IVI).
**RESULTS**: A total of 1101 patients were seen in the anesthesia/PBM clinic between days −28 and −1 (median [Q1–Q3], −3 days [−1, −9 days]) before elective surgery. Approximately 29% of patients presented with anemia, 46.8% of these anemic patients were treated with ferric carboxymaltose (500–1000 mg).
In the primary analysis, hemoglobin levels at median were associated with a reduction between the visit in the anesthesia/PBM clinic and the surgery in all nonanemic patients on beginning of medical treatment (nonanemic patients at median −2.8 g/dL [−4, −0.9 g/dL], while anemic patients without IVI presented with median differences of −0.8 g/dL [−2, 0 g/dL] and anemic patients with IVI of 0 g/dL [−1.0, 0.5 g/dL]). Hemoglobin levels raised best at substitution 22–28 days before surgery (0.95 g/dL [−0.35, 1.18 g/dL]). Due to the selection criteria, transfusion rates were high in the cohort. Overall, there was no association between IVI treatment and the use of RBC transfusions (odds ratio for use of RBCs in anemic patients, no IVI versus IVI: 1.14; 95% confidence interval, 0.72–1.82).
**CONCLUSIONS**: An anemia clinic within the preanesthesia assessment clinic is a feasible and effective approach to treat preoperative anemia. The IVI supplementation was safe but was associated with decreased RBC transfusions in gynecology/obstetric patients only. The conclusions from this retrospective analysis have to be tested in prospective, controlled trials.

10. Guinn NR, Fuller M, Murray S, Aronson S. Treatment through a preoperative anemia clinic is associated with a reduction in perioperative red blood cell transfusion in patients undergoing orthopedic and gynecologic surgery. Transfusion 2022;62(4):809-816. DOI: 10.1111/trf.16847.

**Study Design and Methods**: Adult patients undergoing elective orthopedic and gynecologic surgery with preoperative anemia were identified and referred for hemoglobin optimization with iron and/or erythropoietin from a single-site academic health center. Treated patients were propensity matched to untreated controls and compared on outcomes of erythrocyte transfusion, length of stay (LOS), and readmission. Changes in hemoglobin relative to treatment time before surgery were also measured in the treated cohort.
**Results**: One thousand three hundred thirty-two patients were evaluated between July 2015 and March 2021, of which 161 underwent optimization through the PAC. After propensity matching, 127 (98 orthopedic and 29 gynecology) PAC-treated patients were compared to 127 (98 orthopedic and 29 gynecology) control patients who did not undergo treatment. The primary outcome of perioperative transfusion was significantly lower in treated patients compared with matched controls (12.60% vs. 26.77%, p = .005). A lower LOS was demonstrated in the gynecologic PAC subgroup (2.2 [1.5, 2.4] vs. 3.1 [2.2, 3.4], p = .002). Each day of treatment time before surgery was associated with an increase of 0.040 g/dL hemoglobin (p < .001) until 65 days, after which further
time did not increase hemoglobin.
**Conclusion**: Treatment through a preoperative anemia clinic is associated with a reduction in perioperative transfusion and possible reduction in LOS and readmission compared with matched controls. Additionally, treatment time before surgery is correlated with a greater increase in hemoglobin up until 2 months prior to surgery.