Risk of Anemia

4

Christian von Heymann and Lutz Kaufner

Case Vignette

A 76-year-old female is scheduled for elective aortic valve replacement for severe aortic valve stenosis. From her history the patient complained of progressive shortness of breath for the last 12 months. Past medical history included a 10-year history of orally treated diabetes mellitus and chronic obstructive pulmonary disease associated with an ongoing longstanding nicotine abuse. Additionally, she suffered from chronic anemia that was treated with a course of oral iron about 1 year ago, but it was discontinued due to gastrointestinal discomfort. The patient is stable without symptoms of disease or complaints on low intensity physical exertion. Blood screening on admission reveals a hemoglobin of 10.1 g/dL (6.3 mmol/L), a hematocrit of 31%, a mean cellular volume (MCV) of 75 fL, and a mean corpuscular hemoglobin of 25.9 pg. No further anemia studies have been ordered yet. Does anemia increase the risk of the patient suffering adverse outcomes including mortality after cardiac surgery?

C. von Heymann (✉)
Department of Anesthesia, Intensive Care Medicine, Emergency Medicine and Pain Therapy, Vivantes Klinikum im Friedrichshain, Berlin, Germany
e-mail: christian.heymann@vivantes.de

L. Kaufner
Department of Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
e-mail: lutz.kaufner@charite.de

C. von Heymann, C. Boer (eds.), *Patient Blood Management in Cardiac Surgery*,
https://doi.org/10.1007/978-3-030-15342-7_4

Why Is It Important?

According to the WHO about 1.93 billion people—27% of the world's population—suffered from anemia in 2013 [1].The age-adjusted prevalence of anemia was 19,748 per 100,000 inhabitants in developed countries. Prevalence by age shows a marked increase (up to 30,000 per 100,000) in the elderly population > 65 years of age [2].

In cardiac surgery, between 20% and 45% of patients present with anemia of any cause prior to surgery [3–7]. Preoperative anemia has been identified as a risk factor for a variety of adverse outcomes in different surgical specialties [8] and is frequently the reason for blood transfusion in various settings [9].

Patient blood management (PBM) is a multidisciplinary concept that aims to tailor the administration of blood products to the need and clinical situation of each particular patient. Furthermore, PBM intends to sharpen the consciousness for the reasons underlying the need for blood transfusions. Within the first pillar of the clinical concept of PBM the detection and treatment of preoperative anemia plays a prominent role [10].

Cardiac surgery continues to use a high percentage of the national blood supply [11] and anemia either pre- or perioperative as well as acute or chronic is the major underlying cause. For this reason, the assessment of the impact of preoperative anemia in patients undergoing cardiac surgery is warranted. In this context the impact of perioperative transfusion on postoperative outcomes and the interaction with causative factor anemia has to be acknowledged.

The purpose of this chapter is to review the data of the impact of preoperative anemia on the outcome of patients scheduled for cardiac surgery. A second chapter of this book will focus on diagnostics and treatment of preoperative anemia.

Evidence

A literature search using the following query (((Cardiac surgery) NOT (Children OR Pediatric))) AND (anemia AND (preop* OR pre-op* OR before OR prior)) was performed, to identify studies investigating the impact of preoperative anemia on the clinical outcome of patients undergoing cardiac surgery. Sixty-one publications on preoperative anemia in adult cardiac surgery published between 2001 and January 2017 were identified. After the exclusion of case reports, editorials, studies investigating postoperative anemia, or the treatment of anemia that did not report the risk associated with preoperative anemia, 48 studies reporting patient outcomes remained. Of these, 21 studies were observational, one was a national audit, 5 were matched cohort, and 21 retrospective studies in design.

Forty-five of these 48 studies reported that preoperative anemia was associated with worse outcome after on-pump or off-pump cardiac surgery. Worse outcomes ranged from the need for blood transfusions and acute kidney injury to mortality. In contrast, only 3 studies did not describe preoperative anemia as a risk factor for adverse clinical outcomes after cardiac surgery [12–14].

Without assessing the quality of evidence from each study of this literature search, these numbers suggest that preoperative anemia seems to be a risk factor for adverse clinical outcomes after cardiac surgery rather than it conveys no risk for the patient. These results are in line with data from non-cardiac surgery that also indicated the independent impact of preoperative anemia on adverse outcomes [15, 16]. The remaining question is whether preoperative anemia is simply a surrogate for the severity of comorbidities of the patients or a risk factor that is independent of other factors conveying a risk for the cardiac surgery patient? This question is difficult to answer, but the literature provides data suggesting that anemia is an independent risk factor in cardiac surgery.

The study by Williams and colleagues collected data from more than 180.000 isolated coronary artery bypass graft procedures and reported that preoperative anemia, as defined by a hematocrit <33%, was an independent predictor of perioperative mortality, renal failure, and deep sternal wound infection [3]. These results were confirmed by other large and more recent analyses from different countries [4, 6, 7, 17].

Hence, some national and international guidelines have addressed preoperative anemia as a risk factor in cardiac surgery: The 2017 Patient Blood Management Guideline of the European Association of Cardiothoracic Anaesthesiologists (EACTA) in conjunction with the European Association of Cardiothoracic Surgery (EACTS) acknowledges preoperative anemia as a significant risk factor for cardiac surgical procedures and recommends preoperative treatment according to the underlying cause of anemia (Class IIb and IIa recommendations) [18].

Moreover, the increased risks of preoperative anemia in patients undergoing surgery were acknowledged by the British Committee for Standards in Haematology Guidelines [19] which recommend that healthcare pathways should be structured to ensure anemia screening and correction before surgery (Grade 2b).

In addition, the first update of the European Society of Anaesthesiology (ESA) Guideline on the Management of Severe Perioperative Bleeding states that preoperative anemia in adults and children is a strong risk factor for perioperative blood transfusion in different surgical specialties and may be associated with adverse outcomes (B) and recommends anemia assessment in patients with a risk of bleeding within 3–8 weeks before operation (1C).

Furthermore, adapted to the results of the blood work up, a causal treatment is recommended (strong recommendation either 1B or 1C depending on the treatment option and the quality of evidence for the treatment modality) [20].

The recently published German Guidelines on Preoperative Anemia investigated the risk of anemia before cardiac and non-cardiac surgery using the GRADE system to assess the published evidence until early 2015 [21]. This guideline attempted to quantify the risk with preoperative anemia for different outcome variables and patient groups. The included meta-analysis showed that preoperative anemia increased the risk for mortality by a factor 2.72 [95%CI: 2.28, 3.24] (Fig. 4.1, panel (**a**)), the risk to be transfused by 1.97 [95%CI: 1.59, 2.44] (panel (**b**)), and the hospital stay after cardiac surgery to be in median prolonged by 2.3 days [95%CI: 0.39, 4.24] (panel (**c**)). The confidence intervals indicate that all results were statistically significant [21].

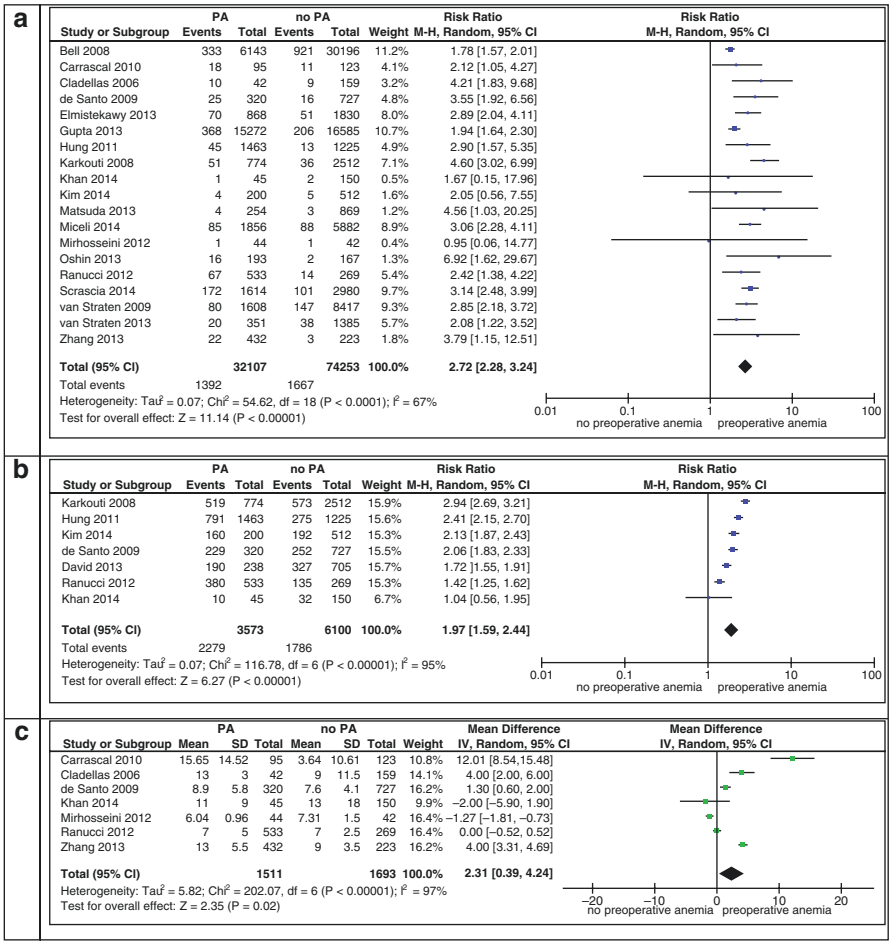

Fig. 4.1 The risk of mortality (panel (**a**)) and perioperative red cell transfusion (panel (**b**)) with anemia before cardiac surgery and the impact of preoperative anemia on hospital stay (panel (**c**)) are shown as forest plots of observational studies [21]

The guideline group, including representatives of 18 different medical societies, stated that the abovementioned risks of preoperative anemia refer to the untreated preoperative anemia in cardiac and non-cardiac surgery irrespective of the underlying cause of anemia as the causes were mainly not investigated in the studies included in the meta-analysis.

Risk of Anemia in Certain Patient Populations

Cardiac surgery with CPB induces hemodilution which is usually more pronounced in women due to a lower body weight and circulating blood volume. This increases the risk to be transfused for women during or after cardiac surgery, especially when

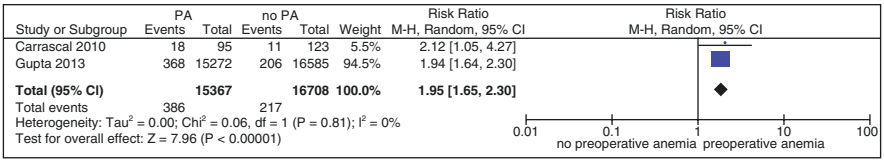

Fig. 4.2 The impact of anemia in patients >65 years of age on mortality [21]

patients are anemic preoperatively. Until 2015, only one study in gynecological surgery investigated the risk of preoperative anemia. This study showed a 4.7 times higher risk to be transfused in patients with preoperative anemia [22]. However preoperative anemia was not identified as an independent risk factor for other clinical outcomes such as the rate of complications or length of hospital stay. Perioperative transfusion, however, was significantly associated with a higher risk in the adjusted analysis, so that the authors concluded that patients should be systematically screened for preoperative anemia and treated according to the results [22].

Another group at risk are elderly patients undergoing cardiac surgery, in whom the prevalence of anemia is already increased [1, 2]. Pooled data from 2 studies show that the risk of mortality is increased by the factor 1.95 in anemic patients >65 years of age undergoing cardiac surgery (Fig. 4.2) [21]. Another study showed that elderly and anemic patients stayed longer in the hospital and the ICU than non-anemic elderly patients, although these results did not reach significance (median hospital stay 15.6 ± 14.5 vs. 3.6 ± 10.6 days, $p = 0.23$, and ICU stay 7.2 ± 10.7 vs. 4.9 ± 8.0 days, $p = 0.069$) [23].

The Independent Impact of Anemia

Preoperative anemia is frequently associated with a higher demand of intra- or perioperative blood transfusions as demonstrated in the majority of studies. Blood transfusions themselves are considered a risk factor for adverse outcomes after cardiac surgery [24, 25] and so it is difficult to estimate the independent impact of preoperative anemia. Three studies confirmed that there is an interaction between anemia and transfusion and described an almost two-fold higher risk of mortality anemic in patients who were transfused [6, 7], although in one study the risk associated with blood transfusions seemed to be stronger than that with anemia [8].

The authors of all studies suggested that the treatment of preoperative anemia as a modifiable risk factor should be considered as it may also influence the risk associated with blood transfusions in cardiac surgery.

Implications for Daily Practice

A large body of literature and separate analyses from different national guidelines show that preoperative anemia is a risk factor for adverse outcomes after cardiac surgery. Preoperative treatment may not only improve anemia, but also reduce

allogenic transfusion requirements, which show a significant interaction with anemia on outcome after cardiac surgery. However, it needs to be proven in a pragmatic and prospective randomised, sufficiently powered trial whether preoperative anemia treatment is superior to blood transfusion.

Answering the question of the case vignette, current evidence from a large number of studies and some recent meta-analyses and guidelines suggest that this lady with an isolated aortic stenosis has an increased risk for mortality (by factor of 2) and other adverse outcomes associated with her anemia. Due to her stable clinical condition, the attending clinicians should consider to identify the cause of anemia and treat the patient accordingly.

References

1. Kassebaum NJ. The global burden of anemia. Hematol Oncol Clin North Am. 2016;30:247–308.
2. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood. 2004;104:2263–8.
3. Williams ML, He X, Rankin JS, Slaughter MS, Gammie JS. Preoperative hematocrit is a powerful predictor of adverse outcomes in coronary artery bypass graft surgery: a report from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thorac Surg. 2013;96:1628–34.
4. Scrascia G, Guida P, Caparrotti SM, et al. Incremental value of anemia in cardiac surgical risk prediction with the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II model. Ann Thorac Surg. 2014;98:869–75.
5. Engoren M, Schwann TA, Habib RH, et al. The independent effects of anemia and transfusion on mortality after coronary artery bypass. Ann Thorac Surg. 2014;97:514–20.
6. von Heymann C, Kaufner L, Sander M, et al. Does the severity of preoperative anemia or blood transfusion have a stronger impact on long-term survival after cardiac surgery? J Thorac Cardiovasc Surg. 2016;152:1412–20.
7. LaPar DJ, Hawkins RB, McMurry TL, Investigators for the Virginia Cardiac Services Quality Initiative, et al. Preoperative anemia versus blood transfusion: which is the culprit for worse outcomes in cardiac surgery? J Thorac Cardiovasc Surg. 2018;156:66–74.e2.
8. Glance LG, Dick AW, Mukamel DB, et al. Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology. 2011;114:283–92.
9. Boening A, Boedeker RH, Scheibelhut C, et al. Anemia before coronary artery bypass surgery as additional risk factor increases the perioperative risk. Ann Thorac Surg. 2011;92:805–10.
10. Hofmann A, Farmer S, Shander A. Five drivers shifting the paradigm from product-focused transfusion practice to patient blood management. Oncologist. 2010;16:3–11.
11. Bennett-Guerrero E, Zhao Y, O'Brien SM, et al. Variation in use of blood transfusion in coronary artery bypass graft surgery. JAMA. 2010;304:1568–75.
12. Cutrell JB, Barros N, McBroom M, et al. Risk factors for deep sternal wound infection after cardiac surgery: influence of red blood cell transfusions and chronic infection. Am J Infect Control. 2016;44:1302–9.
13. Matsuda S, Fukui T, Shimizu J, et al. Associations between preoperative anemia and outcomes after off-pump coronary artery bypass grafting. Ann Thorac Surg. 2013;95:854–60.
14. Zhang L, Hiebert B, Zarychanski R, Arora RC, Cardiovascular Health Research in Manitoba (CHaRM) Investigator Group. Preoperative anemia does not increase the risks of early surgical revascularization after myocardial infarction. Ann Thorac Surg. 2013;95:542–7.

15. Beattie WS, Karkouti K, Wijeysundera DN, Tait G. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. Anesthesiology. 2009;110:574–81.
16. Musallam KM, Tarnim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet. 2011;378:1396–407.
17. Klein AA, Collier TJ, Brar MS, Association of Cardiothoracic Anaesthetists (ACTA), et al. The incidence and importance of anaemia in patients undergoing cardiac surgery in the UK - the first Association of Cardiothoracic Anaesthetists national audit. Anaesthesia. 2016;71:627–35.
18. Boer C, Meesters MI, Milojevic M, et al. 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. J Cardiothorac Vasc Anesth. 2017;25:1–34.
19. Kotze A, Harris A, Baker C, et al. British committee for standards in hematology guidelines on the identification and management of pre-operative anaemia. Br J Haematol. 2015;171:322–31.
20. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. Eur J Anaesthesiol. 2017;34:332–95.
21. S3 Guideline on Preoperative Anaemia. AWMF registernummer 001 – 024. . 2018. www.awmf.org/.../tx_szleitlinien/001-024l_S3_Praeoperative-Anaemie_2018-04.pdf.
22. Browning RM, Trentino K, Nathan EA, Hashemi N. Preoperative anaemia is common in patients undergoing major gynaecological surgery and is associated with a fivefold increased risk of transfusion. Aust N Z J Obstet Gynaecol. 2012;52:455–9.
23. Carrascal Y, Maroto L, Rey J, et al. Impact of preoperative anemia on cardiac surgery in octogenarians. Interact Cardiovasc Thorac Surg. 2010;10:249–55.
24. Paone G, Likosky DS, Brewer R, et al. Transfusion of 1 and 2 units of red blood cells is associated with increased morbidity and mortality. Ann Thorac Surg. 2014;97:87–94.
25. Koch CG, Li L, Duncan AI, Mihaljevic T, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med. 2006;34:1608–16.