Preoperative Anaemia in Primary Hip and Knee Arthroplasty

Präoperative Anämie in der Hüft- und Kniegelenkendoprothetik

Authors

Patrick Meybohm[1*], Hendrik Kohlhof[2*], Dieter Christian Wirtz[2], Ingo Marzi[3], Christoph Füllenbach[1], Suma Choorapoikayil[1], Maria Wittmann[4], Ursula Marschall[5], Josef Thoma[6], Klaus Schwendner[7], Patrick Stark[8], Ansgar Raadts[9], Jens Friedrich[10], Henry Weigt[11], Patrick Friederich[12], Josef Huber[13], Martin Gutjahr[14], Elke Schmitt[1,15**], Kai Zacharowski[1**]

Affiliations

1 Department of Anesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt
2 Department of Orthopedics and Trauma Surgery, University Hospital Bonn
3 Department of Trauma, Hand and Reconstructive Surgery, University Hospital Frankfurt am Main
4 Department of Anesthesiology and Operative Intensive Care Medicine, University Hospital Bonn
5 Head of Department Medicine/Health Care Research, Barmer, Wuppertal
6 Department of Anesthesiology and Operative Intensive Medicine, ORTENAU KLINIKUM Offenburg-Kehl, Offenburg
7 Department of Anesthesiology and Operative Intensive Care Medicine, Martha-Maria Hospital Nuremberg
8 Department of Visceral and Vascular Surgery, Klinikum Mittelmosel, Zell
9 Department of Anesthesiology and Intensive Care Medicine, University Hospital Jena
10 Department of Anesthesiology and Operative Intensive Care Medicine, Klinikum Leverkusen gGmbH
11 Department of Anesthesiology, SLK-Kliniken Heilbronn GmbH
12 Department of Anesthesiology, Operative Intensive Medicine and Pain Therapy, München Klinik Bogenhausen
13 Institute for Laboratory Diagnostics and Transfusion Medicine, Donauisar Klinikum Deggendorf
14 Department for Anesthesiology, Intensive Medicine and Pain Therapy, Marienhausklinik Ottweiler
15 Institute for Biostatistics and Mathematical Modelling, Goethe University Frankfurt

Correspondence

Prof. Patrick Meybohm
Department of Anesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt
Theodor-Stern-Kai 7, 60590 Frankfurt am Main
Phone: 069/6301-87226, Fax: 069/6301-5881
patrick.meybohm@kgu.de

Key words

anaemia, blood loss, blood transfusion, orthopaedic surgery

Schlüsselwörter

Anämie, Blutverlust, Bluttransfusion, Orthopädie

Bibliography

DOI https://doi.org/10.1055/a-0974-4115
Published online 18.09.2019 | Z Orthop Unfall 2020; 158: 194–200 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 1864-6697

ABSTRACT

Introduction Approximately one in three patients has untreated preoperative anaemia, which in turn is associated with an increased need for transfusion of allogenic red blood cell concentrates (RBC) and complications in the context of a surgical intervention. Here, the prevalence of preoperative and postoperative anaemia as well as their effects on transfusion rate, hospital length of stay and hospital mortality in primary hip and knee arthroplasty has been analysed.

Methods From January 2012 to September 2018, 378,069 adult inpatients from 13 German hospitals were analysed on the basis of an anonymized registry. Of these, n = 10,017 patients had a hip and knee joint primary arthroplasty. The primary endpoint was the incidence of preoperative anaemia, which was analysed by the first available preoperative haemoglobin value according to the WHO definition. Secondary endpoints included in-hospital length of stay, number of patients with red blood cell concentrate transfusion, incidence of hospital-acquired anaemia, number of deceased patients, and postoperative complications.

Results The preoperative anaemia rate was 14.8% for elective knee joint arthroplasty, 22.9% for elective hip joint arthroplasty and 45.0% for duo-prosthesis implantation. Preoperative anaemia led to a significantly higher transfusion rate (knee: 8.3 vs. 1.8%; hip: 34.5 vs. 8.1%; duo-prosthesis: 42.3 vs. 17.4%), an increased red blood cell concentrate consumption (knee: 256 ± 107 vs. 29 ± 5 RBC/1000 patients; hip: 929 ± 60 vs. 190 ± 16 RBC/1000 patients; duo-prosthesis: 1411 ± 98 vs. 453 ± 42 RBC/1000 patients). Pre-operative anaemia was associated with prolonged hospital stay (12.0 [10.0; 17.0] d vs. 11.0 [9.0; 13.0] d; p < 0.001) and increased mortality

* Shared first authorship
** Shared last authorship

(5.5% [4.6–6.5%] vs. 0.9% [0.7–1.2%]; Fisher p < 0.001) compared to non-anaemic patients. In patients aged 80 years and older, the incidence of preoperative anaemia and thus the transfusion rate was almost twice as high as in patients under 80 years of age.

Summary Preoperative anaemia is common in knee and hip primary arthroplasty and was associated with a relevant increase in red blood cell concentrate consumption. In the context of patient blood management, a relevant potential arises, especially in elective orthopaedic surgery, to better prepare elective patients, to avoid unnecessary transfusions and thus to conserve the valuable resource blood.

ZUSAMMENFASSUNG

Einleitung Präoperativ liegt bei etwa jedem 3. Patienten eine nicht therapierte Anämie vor, die wiederum im Kontext eines chirurgischen Eingriffs mit einem erhöhten Transfusionsbedarf von allogenen Erythrozytenkonzentraten (EK) sowie Komplikationen einhergeht. In der vorliegenden Arbeit soll die Prävalenz einer prä- und postoperativen Anämie und deren Einfluss auf den Transfusionsbedarf von EK, Krankenhausverweildauer sowie Krankenhaussterblichkeit in der primären Hüft- und Kniegelenkendoprothetik analysiert werden.

Methoden Basierend auf einem anonymisierten Register wurden von Januar 2012 bis September 2018 378 069 erwachsene stationäre Patienten aus 13 deutschen Krankenhäusern analysiert, von denen n = 10 017 Patienten eine Hüft- und Kniegelenkprimärimplantation hatten. Der primäre Endpunkt war die Inzidenz einer präoperativen Anämie, die über den 1. präoperativ verfügbaren Hämoglobinwert entsprechend der WHO-Definition analysiert wurde. Zu den sekundären Endpunkten zählte die Krankenhausverweildauer, Anzahl Patienten mit EK-Transfusion, Inzidenz einer postoperativen krankenhauserworbenen Anämie, Anzahl verstorbener Patienten sowie verschiedene postoperative Komplikationen.

Ergebnisse Die präoperative Anämierate betrug bei elektiver Kniegelenkendoprothetik 14,8%, bei elektiver Hüftgelenkendoprothetik 22,9% und bei Duokopfprothesenimplantation sogar 45,0%. Eine präoperative Anämie führte zu einer signifikant höheren EK-Transfusionsrate (Kniegelenkprothese: 8,3 vs. 1,8%; Hüftgelenksprothese: 34,5 vs. 8,1%; Duokopfprothese: 42,3 vs. 17,4%) sowie einem erhöhten EK-Verbrauch (Kniegelenk: 256 ± 107 vs. 29 ± 5 EK/1000 Patienten; Hüftgelenk: 929 ± 60 vs. 190 ± 16 EK/1000 Patienten; Duokopfprothese: 1411 ± 98 vs. 453 ± 42). Im Gesamtkollektiv war eine präoperative Anämie gegenüber nicht anämischen Patienten mit einer verlängerten Krankenhausverweildauer (12,0 [10,0; 17,0] d vs. 11,0 [9,0; 13,0] d; p < 0,001) sowie einer erhöhten Sterblichkeit assoziiert (5,5% [4,6–6,5%] vs. 0,9% [0,7%–1,2%]; Fisher p < 0,001). Bei Patienten mit einem Alter von 80 Jahren und höher war die Inzidenz einer präoperativen Anämie und damit die Transfusionsrate nahezu doppelt so hoch wie bei den unter 80-Jährigen.

Zusammenfassung Eine präoperative Anämie kommt bei Knie- und Hüftgelenkprimärimplantation häufig vor und ist mit einem relevant erhöhten EK-Verbrauch assoziiert. Vor diesem Hintergrund könnte sich in der Zukunft vor allem in der elektiven orthopädischen Chirurgie ein relevantes Potenzial ergeben, im Sinne von Patient Blood Management die elektiven Patienten besser vorzubereiten, um unnötige Transfusionen zu vermeiden und so die wertvolle Ressource Blut zu schonen.

Introduction

A haemoglobin concentration of < 12 g/dl in women and < 13 g/dl in men is defined as anaemia according to the World Health Organisation (WHO) with an increased need for transfusion of allogeneic red blood cell (RBC) concentrates. Baron and colleagues [1] recently analysed about 40,000 surgical patients from 28 European countries. Surprisingly, almost one in three patients showed anaemia associated with prolonged hospital stay and increased risk of hospital mortality prior to surgery. In the PREPARE study by Lasocki and colleagues [2], a total of 1,534 patients were evaluated in 17 European centres for elective knee and hip joint endoprosthetics and spinal surgery. The prevalence of anaemia before surgery was 14.1% and even increased to over 85.0% at the time of hospital discharge.

In the meantime, numerous studies have proven the effectiveness of pre-operative anaemia management [3–9]. Likewise, the directive 'Hemotherapy 2017' of the German Medical Association [10] requires that 'prior to substitution treatment with blood products, patients must be examined individually on the basis of current findings whether other measures are suitable to remedy chronic or acute deficiencies. These include optimising the volume of red blood cells, minimising bleeding and blood loss as well as increasing and fully exploiting anaemia tolerance (Patient Blood Management)'.

In this study the incidence of pre-operative anaemia and its influence on the transfusion needs of RBC, hospital stay and hospital mortality in primary hip and knee joint endoprosthetics shall be analysed.

Patients and Methods

Anonymous register data from 13 hospitals of the accompanying epidemiological research project of the German PBM Network [11] were used as a data basis [11]; the protocol was approved by the respective local ethics committees (lead ethics committee: University Hospital Frankfurt 380/12). Data of adult inpatients (over 18 years of age) undergoing surgery were recorded (ClinicalTrials.gov Identifier: NCT02147795). In addition, a data protection vote of the Hessian data protection officer has been obtained (Ref: 43.60; 60.01.21-ga). The data were extracted from the respective electronic hospital information systems and anonymised for further analysis. Patient-specific observation period ranged from hospital admission to discharge.

Patient Population

Patients with hip and knee joint primary implantation in gonarthrosis, coxarthrosis and femoral neck fracture coded with the following Operationen- und Prozedurenschlüssel (OPS) codes (as of June 2019) were included in the analysis. No exclusion criteria were defined.

1. Knee joint (elective primary implantation in gonarthrosis): 5-822.00-02, 5-822.83-87, 5-822.g0-g2, 5-822.j0-j2, 5-822.k0-k2.
2. Hip joint (elective primary implantation in coxarthrosis): 5-820.00-02, 5-820.30-31, 5-820.80-82, 5-820.92-96.
3. Hip joint (dual head prosthesis in femoral neck fracture): 5-820.40-41.

Endpoints

The primary endpoint was the incidence of pre-operative anaemia, which was analysed by the first available pre-operative haemoglobin value according to the WHO definition.

Secondary endpoints included hospital stay, number of patients with RBC transfusions, number of transfused RBC per 1000 patients, incidence of post-operative hospital-acquired anaemia, number of patients deceased in hospital (death of any cause as discharge reason), number of patients with acute renal failure (ICD-10: N17.0, N17.1, N17.2, N17.8, N17.9, N19, N99.0) and pneumonia (viral pneumonia (J12.0 – J12.3, J12.8, J12.9), pneumonia caused by Streptococcus pneumonia (J13), pneumonia caused by *Haemophilus influenzae* (J14), pneumonia caused by bacteria (J15.0 – J15.9), pneumonia caused by other infectious agents (J16.0, J16.8), pneumonia, pathogen not specified (J18.0 – J18.2, J18.8, J18.9)).

The results were also broken down by age (< 80 and ≥ 80 years).

Statistical analysis

The statistical evaluation included for all endpoints a detailed descriptive analysis broken down by three surgical groups and two age groups (mean values ± standard error, medians with first and third quartile, percentage rates with 95% confidence interval).

Furthermore, non-parametric significance tests (Mann–Whitney or Fisher's exact test, p values) for differences between the relevant subgroups (with/without RBC transfusion or pre-operative anaemia) were performed for the endpoints mortality and hospital stay as well as for the estimation of the magnitude of RBC transfusion or pre-operative anaemia (Spearman's rank correlation coefficient, r).

Finally, to investigate the dependence of the endpoints mortality and hospital stay on the influencing factors RBC transfusion and pre-operative anaemia, an evaluation was performed using a multi-variate mixed regression model which included the hospitals as random effects to calculate the hospital-specific cluster effects as well as RBC transfusion and pre-operative anaemia as the fixed effects in addition to age, gender and surgery group (if significant) as influencing variables. Potential influence variables for each model were set *a priori* and then tested with univariate analysis (non-parametric and in the regression model) for significance before being included in the final model.

Results

From January 2012 to September 2018, routine data from a total of 378,069 patients from 13 German hospitals were analysed, of which 10,017 patients underwent hip and knee joint primary endoprosthetics. One patient was excluded from the analysis because he was marked as both an elective hip joint and dual head prosthesis.

The incidence of pre-operative anaemia was 14.8% in elective knee joint endoprosthetics, 22.9% in elective hip joint endoprosthetics and 45.0% in implantation of a dual head prosthesis (▶ **Tab. 1**). Pre-operative anaemia resulted in a significantly higher rate of RBC transfusion (32.7% *vs.* 7.3%, Fisher p < 0.001) (knee joint prosthesis): 8.3% *vs.* 1.8%, p < 0.001; hip joint prosthesis: 34.5% *vs.* 8.1%, p < 0.001; dual head prosthesis: 42.3% *vs.* 17.4%, p < 0.001) and RBC consumption (989 ± 50 *vs.* 174 ± 11 RBC/1000 patients, Mann–Whitney p < 0.001) (knee joint: 256 ± 107 *vs.* 29 ± 5, p < 0.001; hip joint: 929 ± 60 *vs.* 190 ± 16, p < 0.001; dual head prosthesis: 1411 ± 98 *vs.* 453 ± 42, p < 0.001). In multivariate regression analysis, rates of RBC transfusion and RBC consumption were also significantly higher in the presence of pre-operative anaemia (p < 0.001).

Compared with non-anaemic patients, those with pre-operative anaemia showed significantly prolonged hospital stay [hospital stay: 12.0 (10.0–17.0) days *vs.* 11.0 (9.0–13.0) days; Mann–Whitney and multi-variate regression model p < 0.001] and increased mortality [5.5% (4.6–6.5%) *vs.* 0.9% (0.7–1.2%); Fisher and multi-variate regression model p < 0.001]. Likewise, the transfusion of at least one RBC was significantly correlated to prolonged hospital stay [15.0 (11.0–22.0) days *vs.* 11.0 (9.0–13.0) days; Mann–Whitney and multi-variate regression model p < 0.001] and increased mortality rate [7.4% (6.1–9.0%) *vs.* 1.1% (0.9–1.4%); Fisher and multi-variant regression model p < 0.001].

Patients aged 80 years and older showed a significantly higher overall RBC transfusion rate (24.2% *vs.* 8.7%, Fisher p < 0.001), higher RBC consumption (601 ± 29 *vs.* 256 ± 152 RBC/1000 patients; Mann–Whitney p < 0.001), longer hospital stay (14.6 ± 0.2 *vs.* 12.1 ± 0.1 days; Mann–Whitney p < 0.001) and higher mortality rate (5.1% *vs.* 0.8%; Fisher p < 0.001) than patients under 80 years of age (▶ **Fig. 1**).

Discussion

In about every third patient, untreated pre-operative anaemia can be observed [1, 12]. Various observational studies have concluded that pre-operative anaemia must be considered an independent risk factor for RBC transfusion, potential complications and post-operative mortality [1, 13, 14]. In our analysis, the prevalence of pre-operative anaemia was 14.8% for elective knee joint endoprosthetics, 22.9% for elective hip joint endoprosthetics and 45.0% for dual head prosthesis implantation. In the literature, different anaemia definitions are frequently used and the surgery on the hip or knee are only analysed collectively. A meta-analysis of 19 studies including 35,000 patients showed anaemia and transfusion rates of 24% ± 9% and 45% ± 25%, respectively, for elective hip and knee endoprosthetics and 51% and 44% ± 15%, respec-

▶ **Table 1** Demographic data, anaemia rate, transfusion rate, RBC consumption and clinical endpoints.

Primary implantation	Knee prosthesis (n = 3162)	Hip prosthesis (n = 4813)	Dual head prosthesis (n = 2041)
Age, years	70.0 [62.0–76.0]	71.0 [62.0–78.0]	84.0 [78.0; 89.0]
Gender, male, %	39.7	44.2	33.2
Hb pre-operative,* g/dl	13.7 [12.8–14.7]	13.5 [12.4; 14.5]	12.4 [11.1; 13.6]
Pre-operative anaemia (WHO), % (n)*	14.8 [13.5–16.2] (398)	22.9 [21.7–24.2] (974)	45.0 [42.7–47.3] (822)
Hb post-operative,** g/dl	11.0 [10.0; 12.1]	10.2 [9.3–11.2]	10.0 [9.0–10.9]
Hospital-acquired anaemia (WHO), % (n)*	81.2 [79.6–82.6] (2184)	93.6 [92.8–94.3] (3996)	93.2% [92.0–94.3] (1764)
Length of hospital stay, days	10.0 [9.0–12.0]	11.0 [9.0–13.0]	13.0 [10.0–18.0]
Hospital mortality, % [95% CI] (n)	0.1 [0.0–0.2] (2)	0.8 [0.6%–1.1] (39)	7.4 [6.3–8.7] (152)
Pneumonia, % [95% CI] (n)	0.4 [0.2–0.7] (14)	1.7% [1.4–2.1] (83)	10.5 [9.2–11.9] (214)
Renal failure, % [95% CI] (n)	3.1% [2.5–3.8] (98)	4.7% [4.2–5.4] (228)	14.3 [12.8–15.9] (291)
RBC transfusion rate, % [95% CI] (n)			
No Pre-operative anaemia	1.8 [1.3–2.5] (42)	8.1 [7.2–9.1] (265)	17.4 [15.1–19.9] (175)
Pre-operative anaemia	8.3 [5.8–11.4]# (33)	34.5% [31.5–37.6]# (336)	42.3 [38.9–45.8]# (348)
RBC/1000 patients; mean ± standard error			
No pre-operative anaemia	29 ± 5	190 ± 16	453 ± 42
Pre-operative anaemia	256 ± 107##	929 ± 60##	1411 ± 98##

* n = 1251 (12.5%) no pre-operative Hb values; ** n = 1163 (11.6%) no post-operative Hb values; # p < 0.001 no anaemia *vs.* anaemia (Fisher), p < 0.001 in all individual surgical groups and in the total cohort; ## Mann–Whitney p < 0.001 in all individual surgical groups and in the total cohort. Hb = haemoglobin; WHO = World Health Organization

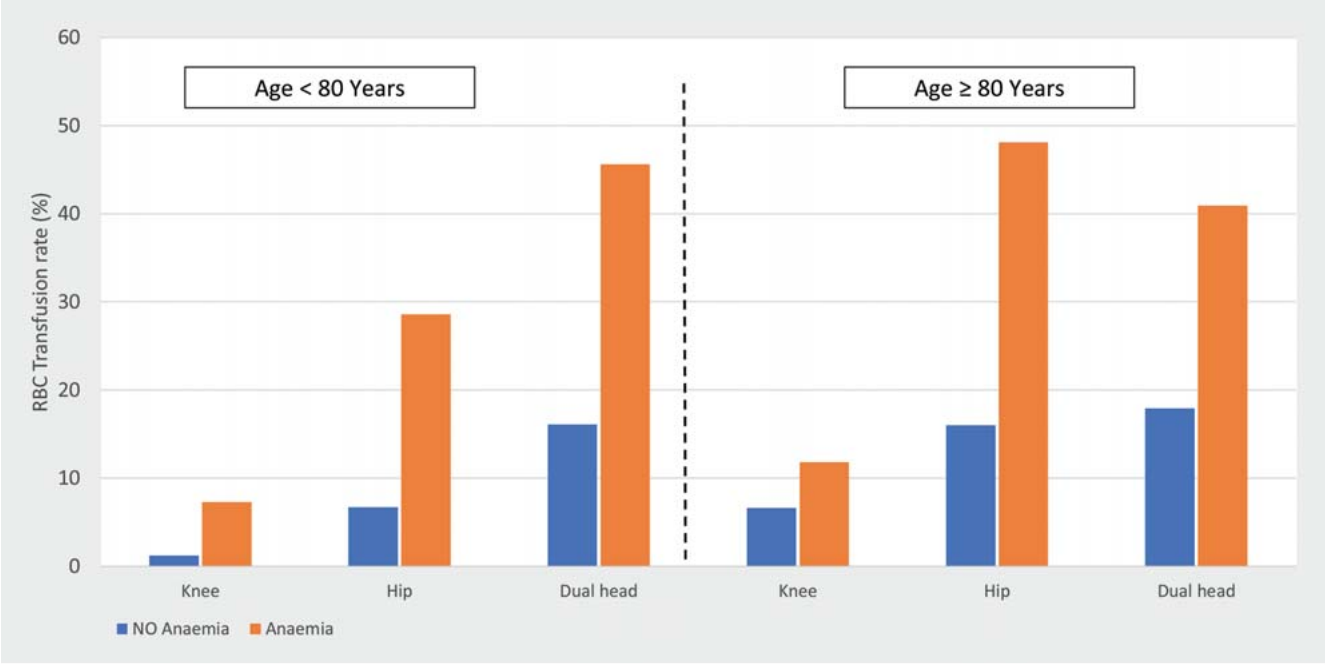
tively, for hip fracture [14]. In our analysis, pre-operative anaemia was associated with up to 10-fold increased RBC consumption, whereas other studies have shown 4–11-fold increased probability for RBC transfusions [2, 15–17].

In this context, there is great potential for pre-operative anaemia management, as required by various international guidelines [18–20], by the current S3 guideline 'Preoperative Anemia' [21] and by the directive 'Hemotherapy 2017' [10].

The causes of anaemia in orthopaedic/trauma patients are multifaceted [6, 22–24]. At least in a subgroup of these patients, anaemia is caused by an iron deficiency. In a recent Danish study of orthopaedic knee and hip patients, Jans et al. reported that >40% of the anaemic patients presented with iron deficiency [15]. Possible causes of iron deficiency include malnutrition (vegetarians, vegans or alcohol addicts); dysfunctional enteral iron absorption (e.g. *Helicobacter pylori* gastritis, gastrectomy, atrophic gastritis, chronic inflammatory bowel disease, medication with NSAIDs or proton pump inhibitors) or chronic blood loss (e.g. angiodysplasia, neoplasia, ulcers, diverticula, or increased menstruation).

Based on the current S3 guideline [21], anaemia diagnosis should be initiated preoperatively in a timely manner. In this respect, early identification (at least 2–4 weeks preoperatively) of anaemic patients is crucial in the context of preparations for surgery. If iron deficiency has been diagnosed, therapy should be started primarily with iron based on the cause. However, quite a few patients discontinue oral iron substitution due to gastrointestinal problems and intolerances [25]. If oral iron therapy is ineffective or unsuitable, such as in the case of urgency of the procedure (<6 weeks), parenteral iron therapy is recommended in principle, whereby the available preparations differ from each other, particular in their complex stability and safety [5, 26–28]. In case of chronic anaemia or renal anaemia (erythropoietin deficiency), treatment with erythropoietin alone or, in case of additional iron deficiency, in combination with iron is recommended [21]. Theusinger et al. [16], for instance, have confirmed the benefit of pre-operative anaemia management, particularly in patients undergoing orthopaedic elective procedures. In elective knee joint endoprosthetics, the anaemia rate was reduced from 15.5% to 7.8% and the transfusion rate from 19.3% to 4.9%. In elective hip joint endoprosthetics the anaemia rate was reduced from 17.6% to 12.9% and the transfusion rate from 21.8% to 15.7% [16]. Kotze et al. have found similar achievements in pre-operative anaemia management in orthopaedic patients [17]. This study now focusses on the demographic change of the geriatric orthopaedic patient population. Our analysis shows that in the field of elective orthopaedic patient care, the pre-operative anaemia rate in patients over 80 years of age is significantly higher than that in patients under 80 years of age (knee prosthesis: 23.9% *vs.* 13.4%; hip prosthesis: 37.2% *vs.* 19.7%). These data support the need to diagnose and treat pre-operative anaemia as part of future geriatric orthopaedic concepts in elective surgery.

Unlike elective patients, patients with an acute femoral fracture who received dual head prosthesis in an emergency within 24–48 hours pose a particular challenge. In these cases, anaemia rate was as high as 45% and EC transfusion rate over 40%. Since pre-operative time is very limited, new concepts for perioperative anaemia management are warranted. A simple laboratory diag-



▶ **Fig. 1** Transfusion rate of red blood cell (RBC) concentrates in patients without (blue) and with anaemia (orange) in elective knee and hip joint endoprosthetics as well as implantation of a dual head prosthesis at the age of < 80 or and ≥ 80 years.

nostic using ferritin on the day of surgery would be conceivable here, for example, in order to be able to conduct parenteral substitution with iron indicated at the end of the surgery or postoperatively, particularly in cases of perioperative blood loss of > 500 ml [29, 30]. At least in the field of cardiac surgery, it has recently been demonstrated that an ultra-short term combined administration of intravenous iron, erythropoietin alpha, vitamin B12 and folic acid could reduce post-operative RBC consumption by 1 day preoperatively [31].

A substantial advantage of the current analysis is the comprehensive representative analysis of routine data of more than 10,000 patients with primary hip and knee joint endoprosthetics at 13 German hospitals. Anonymous data from an established clinical patient register were used as the data basis. Clinical registries are increasingly being used in healthcare to gain knowledge. Existing data sources can thus be used and evaluated comprehensively. However, the current register analysis has the limitation that unknown factors for RBC transfusion or post-operative complications could not be ruled out (e.g. use of ischaemia, tranexamic acid, duration of drainage stay or wound and joint infections) although risk adjustments have been performed. In some patients, pre-operative anaemia management may even have been performed locally as part of patient blood management. However, since pre-operative anaemia management cannot be coded based on either OPS or the International Classification of Diseases, the potential influence of any anaemia management could not be taken into account.

Conclusion

In summary, the current analysis reported pre-operative anaemia rate of 14.8% in elective knee joint endoprosthetics, 22.9% in elective hip joint endoprosthetics and as high as 45.0% in (emergency) dual head prosthesis implantation. Pre-operative anaemia led to a relevant increase in RBC consumption and was associated with prolonged hospital stay and increased mortality. In patients aged 80 years and older, the incidence of pre-operative anaemia and consequent transfusion rate were almost two times higher than in patients under 80 years of age. In this context, a relevant potential could arise in the future, particularly in elective geriatric orthopaedics, to better prepare elective patients in terms of patient blood management, to avoid unnecessary RBC transfusions and to thus conserve the valuable resource blood [32].

Acknowledgement

The German Patient Blood Management Network with the associated registry was awarded the Lohfert Prize 2014 by the Lohfert Foundation, the German Prize for Patient Safety 2016 by Aktionsbündnis Patientensicherheit e. V., and the MSD Health Prize (3rd place) 2018.

We would also like to thank Professor Eva Herrmann (Biostatistical Institute of the University of Frankfurt, Department of Medicine) for her supportive statistical advice and the IT staff of the participating hospitals for providing the data.

Conflict of Interest

P. M. and K. Z. received funding from B. Braun Melsungen, CSL Behring, Fresenius Kabi and Vifor Pharma for an examiner-initiated study to implement the Patient Blood Management Program at four university hospitals. P. M. and/or K. Z. received grants or travel expense funding for consultations and lectures from the following companies: Abbott GmbH &Co KG, Aesculap Akademie GmbH, AQAI GmbH, Astellas Pharma GmbH, AstraZeneca GmbH, Aventis Pharma GmbH, B, Braun Melsungen AG, Baxter Deutschland GmbH, Biosyn Arzneimittel GmbH, Biotest AG, Bristol-Myers Squibb GmbH, CSL Behring GmbH, Dr, F, Köhler Chemie GmbH, Dräger Medical GmbH, Essex Pharma GmbH, Fresenius Kabi GmbH, Fresenius Medical Care, Gambro Hospal GmbH, Gilead Sciences GmbH, GlaxoSmithKline GmbH, Grünenthal GmbH, Hamilton Medical AG, HCCM Consulting GmbH, Heinen + Löwenstein GmbH, Janssen-Cilag GmbH, med Update GmbH, Medivance EU B. V., MSD Sharp & Dohme GmbH, Novartis Pharma GmbH, Novo Nordisk Pharma GmbH, P. J. Dahlhausen & Co. GmbH, Pfizer Pharma GmbH, Pulsion Medical Systems S. E., Siemens Healthcare, Teflex Medical GmbH, Teva GmbH, TopMed-Medizintechnik GmbH, Verathon Medical, Vifor Pharma GmbH. K. S. received grants or travel expense funding for lectures from the companies HAEMA AG and Vifor Pharma GmbH.

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