REVIEW ARTICLE

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Anemia and Patient Blood Management in Hip and Knee Surgery

A Systematic Review of the Literature

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ABSTRACT

A systematic search was conducted to determine the characteristics of perioperative anemia, its association with clinical outcomes, and the effects of patient blood management interventions on these outcomes in patients undergoing major orthopedic surgery. In patients undergoing total hip or knee arthroplasty and hip fracture surgery, preoperative anemia was highly prevalent, ranging from 24 ± 9% to 44 ± 9%, respectively. Postoperative anemia was even more prevalent (51% and 87 ± 10%, respectively). Perioperative anemia was associated with a blood transfusion rate of 45 ± 25% and 44 ± 15%, postoperative infections, poorer physical functioning and recovery, and increased length of hospital stay and mortality. Treatment of preoperative anemia with iron, with or without erythropoietin, and perioperative cell salvage decreased the need for blood transfusion and may contribute to improved patient outcomes. High-impact prospective studies are necessary to confirm these findings and establish firm clinical guidelines.

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PRE- and postoperative anemia is highly prevalent in surgical patients.[1] Anemic patients are more likely to receive allogeneic blood transfusions (ABT) than nonanemic patients.[2–4] It has been suggested that preoperative anemia and increased ABT rates were independently[5,6] associated with an increased risk of perioperative adverse outcomes, such as increased postoperative infections, increased hospital length of stay (LOS), and increased mortality.[1,7–11]

A survey of the demographics of blood use in north England in the year 2000 showed that 52% of the transfused blood units were given to medical patients, 41% to surgical patients, and the remainder to obstetric and gynecology patients. Major orthopedic hip and knee surgery (total hip arthroplasty [THA], total knee arthroplasty [TKA], and surgical hip fracture repair) consumed 8% of all transfused units and was the leading indication for blood transfusions in surgical patients.[12]

The need for perioperative patient blood management measures aiming at improving patient outcomes and reducing the need for ABTs is increasingly recognized.[13] Early detection, evaluation, and management of preoperative anemia (hemoglobin < 12 g/dl for females and < 13 g/dl for

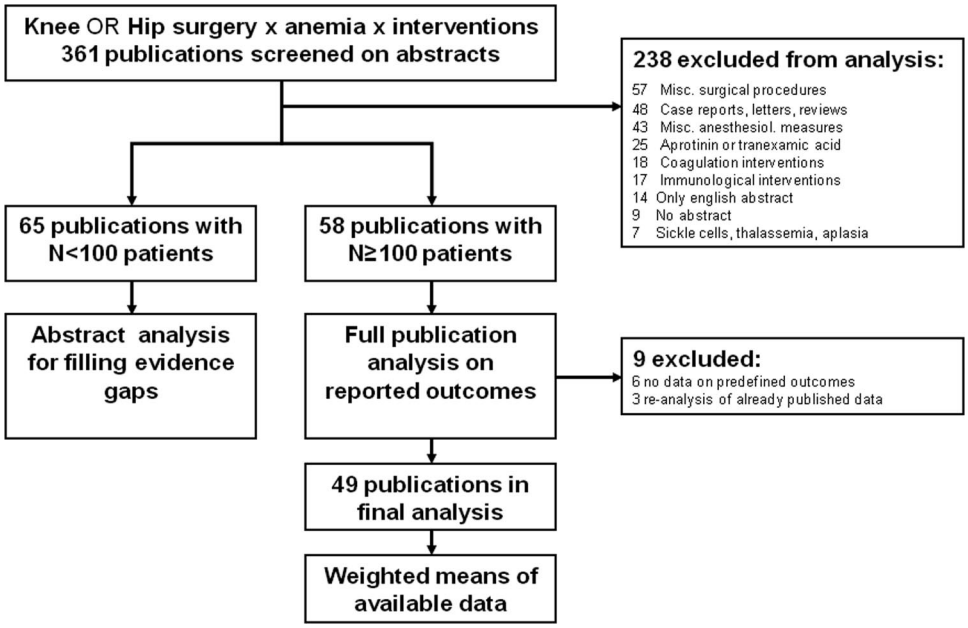

Fig. 1. Search method for determining the epidemiologic characteristics of anemia, the associations of anemia with clinical outcomes, and the effect on outcomes of selected patient blood management interventions in patients undergoing knee or hip surgery.

males) were identified as an unmet medical need, and it was even strongly suggested that preoperative anemia should be corrected, that is, the red cell mass optimized, before elective surgery is undertaken.[14] Preoperative anemia correction with supplemental intravenous or oral iron or recombinant human erythropoietin (rHuEPO) therapy and autologous transfusion techniques, such as preoperative autologous blood donation (PAD) and intra- or postoperative cell salvage (CS), have been proposed to reduce the need for ABT.[15]

The aim of this review was to aggregate the epidemiologic characteristics of anemia in patients undergoing hip or knee surgery, to identify the associations between anemia and patient outcomes, and to report the evidence-based effects on clinical outcomes of selected patient blood management interventions.

Materials and Methods

A Medline search (PubMed, U.S. National Library of Medicine of the National Institutes of Health) was performed on May 7, 2009. For consistent information retrieval, the following basic search strings based on medical subject headings (MeSH) terminology used in the controlled vocabulary of the U.S. National Library of Medicine for indexing articles were used: "Arthroplasty, Replacement, Hip" OR "Hip Prosthesis" OR "Hip Fractures" and "Arthroplasty, Replacement, Knee" OR "Knee Prosthesis." The epidemiologic characteristics of anemia and the associations of anemia with clinical outcomes were obtained by restricting the search results to ("Anemia" NOT "Anemia, Sickle cell"). In addition, search results on selected patient blood management interventions were obtained by combining the basic search strings with the following MeSH terms: "Erythropoietin, Recombinant," "Ferric Compounds," and "Ferrous Compounds." For the latter, search results were restricted to randomized controlled trials, cohort studies, meta-analyses, practice guidelines, and reviews in humans.

Preoperative was defined as any characteristic or measure reported before surgery. Postoperative was used for the time interval between surgery and discharge. The following epidemiologic parameters of interest were predefined: prevalence of pre- and postoperative anemia, prevalence of iron-deficiency anemia and anemia of inflammation, pre- and postoperative hemoglobin levels, blood volume loss, blood transfusion rate, and number of blood units transfused. For the study of associations with anemia, the following clinical outcomes were predefined: physical function, infections, LOS, mortality, and quality of life (QoL). The selected patient blood management interventions were analyzed with regard to their effects on pre- and postoperative hemoglobin levels, ABT rate, and the predefined clinical outcomes that are found associated with perioperative anemia listed earlier.

As shown in figure 1, the search retrieved 361 publications, all of which were screened for appropriateness based on abstracts. Two hundred thirty-eight publications were excluded from the analysis for the following reasons: other surgical procedures (57), case reports or letters (48), miscellaneous anesthesiological measures (43), use of aprotinin or tranexamic acid (25), interventions in coagulation (18), immunologic interventions (17), publications in foreign language with English abstract only (14), no abstract (9), sickle-cell anemia or, thalassemia or aplasia (7). Of the remaining 123 publications, 65 reporting results in less than 100 patients were used to fill possible evidence gaps. Fifty-eight

publications reported results in 100 patients or more and underwent full-text review. Of these, nine were excluded for the following reasons: no numerical data on predefined outcomes (6) and reanalysis of already published data (3).

Statistical analysis was purely descriptive based on results as reported. When appropriate, weighted means (arithmetical means adjusted for different study and group sizes) and corresponding standard deviations were calculated. An initially planned formal meta-analysis of the published results was precluded by inconsistencies in variable reporting.

Results

Forty-nine publications matching with the selection criteria and reporting results in the predefined areas were included in the final analysis.

Epidemiology of Anemia in Patients Undergoing Hip or Knee Surgery

Nineteen prospective and retrospective cross-sectional cohort studies reporting the epidemiologic characteristics of anemia in patients undergoing elective total hip or knee arthroplasty (THA/TKA, 13 studies including 29,068 patients) or hip fracture surgery (6 studies, 6,366 patients) were identified. Patients undergoing elective hip or knee arthroplasty were generally younger than patients hospitalized for surgical repair of hip fracture (weighted mean ±SD): 68.5 ± 3.2 and 79.1 ± 1.8 yr old, respectively. Only 10 publications reported the criteria used for the diagnosis of anemia. These varied across publications ranging from stringent (hemoglobin level less than 10 g/dl)[16] to liberal (hemoglobin level less than 13 g/dl for both women and men)[17] thresholds. In addition, the definition was gender-specific in some studies,[18–22] but not in others,[16,17,23–25] it was based on the hematocrit level less than 30%[25] instead of a hemoglobin threshold.

Weighted mean (±SD) hemoglobin levels decreased from 13.6 ± 0.4 (preoperative) to 10.6 ± 0.8 g/dl (postoperative) in THA/TKA patients and from 12.5 ± 0.2 to 8.2 ± 2.1 g/dl in hip fracture patients. According to the definitions of anemia retained by the different authors, preoperative and postoperative anemia was present in 24 ± 9% and 51% (single record) of the THA/TKA patients and in 44 ± 9% and 87 ± 10% of the hip fracture patients, respectively. The weighted mean volume of blood loss was 1,004 ± 302 ml in patients undergoing THA/TKA and was not reported for hip fracture patients. ABT rates were similar in both patient groups: 45 ± 25% (range, 10–69%) and 44 ± 15% (range, 34–69%) for THA/TKA and hip fracture patients, respectively. They were similar in patients undergoing hip and knee replacement and in patients undergoing primary and revision arthroplasty.[17,26–28] The lowest transfusion rate was achieved in the study with the most stringent transfusion trigger (hemoglobin level < 8 g/dl or clinical symptoms of anemia). The weighted mean number of blood units transfused per transfused patient was 2.6 ± 0.6 (range, 2.2–3.8 units) and was similar in THA/TKA and hip fracture patients, although the latter single report did not mention whether this figure applied to included patients or to transfused patients. Detailed findings by study are shown in table 1. Results from studies reporting characteristics of interest in patients after THA or TKA did not usually provide sufficient granularity for comparative analysis between these two procedures, with the exception of ABT rates. The weighted average ABT rates and ranges were 46% (10–92%) and 44% (9–84%) for THA and TKA, respectively.

Only three studies attempted to differentiate between anemia of inflammation and iron-deficiency anemia.[21,22,24] Consolidated results are shown in table 2. Of note, the study by Saleh *et al.*[21] included a high proportion of elderly patients with rheumatoid arthritis, which was proposed by the authors as a possible explanation for the high proportion of normocytic normochromic anemia in their patient population.

Associations of Anemia with Selected Patient Outcomes

Seven studies reported the association of anemia with one or more prespecified clinical outcomes, wherein six of these studies were performed in patients undergoing hip fracture repair,[16,18–20,23,29] one in patients undergoing elective THA,[10] and none in patients with TKA. Detailed results are shown in table 3.

Physical Function. Functional mobility in the early postoperative phase after a hip fracture surgery was impaired by early postoperative (first 3 days postsurgery) anemia (hemoglobin less than 10 g/dl) in a prospective study with 487 consecutive hip fracture patients treated according to a multimodal rehabilitation program. In this study, anemia was significantly associated with an impaired ability to walk on each of the first 3 days after surgery and was identified as an independent risk factor for not being able to walk on the third postoperative day in an adjusted multiple regression analysis (odds ratio 0.41, $P = 0.002$).[16] These observations confirmed earlier findings of a retrospective cohort study with 5,793 patients who underwent surgical hip repair, in which lower postoperative hemoglobin level was independently associated with shorter walking distance at time of hospital discharge ($P < 0.001$).[29]

In contrast, three studies reported the absence of an association between anemia and poorer physical functioning. Halm *et al.*[23] found a significant association between the Functional Independence Motor score and hemoglobin level at admission ($P = 0.04$). However, this significance disappeared after adjustment for prefracture patient characteristics (such as mobility, age, and degree of independence), clinical status at admission (RAND comorbidity index[30] and Acute Physiology and Chronic Health Evaluation score[31]), discharge status, and blood transfusions. In a retrospective analysis of prospectively collected data of 844 community-dwelling patients who had undergone hip (neck or trochanter) fracture surgical repair, those with postoperative anemia (hemoglobin level less than 12.0 g/dl in women and 13.0 g/dl in men) or with anemia at discharge were more likely to experience a decline in instrumental activities of daily living com-

Table 1. Characteristics of Anemia in Patients Undergoing Elective THA, Elective TKA, or Hip Fracture Surgery

Reference	Year of Publication	Study Design	Total No.	Type of Surgery (No.)	Mean Age (yr)	Definition of Anemia (Hb in g/dl or Hct)	Prevalence of Preoperative Anemia, %	Prevalence of Postoperative Anemia, %
Saleh *et al.*[21]	2007	Retrospective	1,142	THA (621)	68	M < 13; F < 11.5	20	
				TKA (521)				
Basora *et al.*[24]	2006	Prospective	218	THA (50)	71	MF < 13	39	
				TKA (168)				
Myers *et al.*[22]	2004	Prospective	225	THA (225)	64	M < 12.5; F < 11.5	15	
Rosencher *et al.*[17]	2003	Prospective	3,464	THA (2346)	69	MF < 13	31	51
				TKA (1118)				
Steinitz *et al.*[101]	2001	Retrospective	1,206	THA (1206)				
Boralessa *et al.*[102]	2001	Prospective	101	TKA (101)	70			
Borghi *et al.*[103]	2000	Prospective	2,884	THA (2404)	63			
				TKA (480)				
Capraro *et al.*[104,105]	2000	Retrospective	1,161	THA (764)	69			
				TKA (397)	71			
Churchill *et al.*[106]	1998	Retrospective	2,590	THA (1002)	66			
				TKA (926)				
Hasley *et al.*[25]	1995	Retrospective	7,173	THA (4131)	71	Hct < 30%	21	
				TKA (3042)	69		20	
Borghi *et al.*[26]	1995	Retrospective	1,576	THA (1356)	64			
				TKA (220)				
Toy *et al.*[27]	1992	Retrospective	324	THA (324)	63			
Surgenor *et al.*[28]	1991	Retrospective	6,472	THA (2730)	68			
				TKA (1978)	69			
				Hemiarthroplasty hip (1764)	78			
Weighted mean ± SD					68.5 ± 3.2		24 ± 9	51

Reference	Type of Surgery (No.)	Mean Preoperative Hb Level, g/dl	Mean Postoperative Hb Level, g/dl	Estimated Blood Loss Volume, ml	Transfusion Trigger (Hb Level in g/dl)	Transfusion Rate, %	Number of Units Transfused per Transfused Patient
Saleh *et al.*[21]	THA (621)				< 13 (M) or < 11.5(F)	21	
	TKA (521)						
Basora *et al.*[24]	THA (50)						
	TKA (168)						
Myers *et al.*[22]	THA (225)					20	
Rosencher *et al.*[17]	THA (2346)	13.6	10.8	750		36	
	TKA (1118)			800		32	
Steinitz *et al.*[101]	THA (1206)				8	27	2.7
Boralessa *et al.*[102]	TKA (101)	13.6	10.7	1,092	< 9 or symptoms	30	
Borghi *et al.*[103]	THA (2404)			1,275	< 8 or symptoms	10	
	TKA (480)			1,280		9	
Capraro *et al.*[104,105]	THA (764)	13.9	11.5	1,350		92	4.0
	TKA (397)	13.6	11.5	1,200		84	3.0
Churchill *et al.*[106]	THA (1002)					65	2.4
	TKA (926)						
Hasley *et al.*[25]	THA (4131)					69	2.6
	TKA (3042)					51	2.2
Borghi *et al.*[26]	THA (1356)	13.8	9.2			11	
	TKA (220)					9	
Toy *et al.*[27]	THA (324)	12.8	10.8	640		29	2.2
Surgenor *et al.*[28]	THA (2730)					70	2.9
	TKA (1978)					45	2.3
	Hemiarthroplasty hip (1764)					47	2.6
Weighted mean ± SD		13.6 ± 0.4	10.6 ± 0.8	1,004 ± 302		45 ± 25	2.6 ± 0.6

(*continued*)

Table 1. Continued

Hip Fracture Surgery							
Reference	Year of Publication	Study Design	No.	Mean Age, yr	Definition of Anemia (Hb in g/dl)	Prevalence of Preoperative Anemia, %	Prevalence of Postoperative Anemia, %
Foss *et al.*[16]	2008	Prospective	487	82	MF < 10		74
Hutton *et al.*[107]	2005	Retrospective	3,945	78			
Su *et al.*[18]	2004	Retrospective	844	80	M < 13; F < 12	44	90
Halm *et al.*[23]	2004	Prospective	550	82	MF < 12	46	93
Dharmarajan *et al.*[19]	2004	Retrospective	145	82	M < 13; F < 12	28	
Gruson *et al.*[20]	2002	Prospective	395		M < 13; F < 12	46	
Weighted mean ± SD				79.1 ± 1.8		44 ± 9	87 ± 10

Reference	Mean Preoperative Hb Level, g/dl	Mean Postoperative Hb Level, g/dl	Estimated Blood Loss Volume, ml	Transfusion Trigger (Hb Level in g/dl)	Transfusion Rate, %	Number of Units Transfused*
Foss *et al.*[16]	12.7			< 10	69	
Hutton *et al.*[107]		7.8			34	
Halm *et al.*[23]	12.3	10.8			56	2.3
Dharmarajan *et al.*[19]	12.7					
Gruson *et al.*[20]					44	
Weighted mean ± SD	12.5 ± 0.2	8.2 ± 2.1			44 ± 15	

* Whether the number of units transfused applies to the mean number of units transfused per patient included or per transfused patient is not reported.

F = female; Hb = hemoglobin; Hct = hematocrit; M = male; THA = total hip arthroplasty; TKA = total knee arthroplasty.

pared with those without anemia, although this difference did not reach statistical significance. Hemoglobin values were available for 714 patients of which 643 (90%) were anemic at discharge and 312 (44%) were anemic at discharge but not at admission.[18] Finally, in a prospective study with 395 hip fracture patients, the difference in recovery of ambulatory activity and of basic and instrumental activities of daily living status at 3, 6, or 12 months after surgical intervention did not reach statistical significance, although it was numerically in favor of patients without anemia.[20]

Infection. In a prospective analysis of 225 patients undergoing elective THA of which 15% were anemic on admission, preoperative anemia compared with no anemia was associated with an increased incidence of postoperative urinary tract infections (28 *vs.* 14%, $P = 0.039$) and numerically more frequent respiratory tract infections.[22] In parallel, the postoperative ABT rate in the anemic group was 71.0% compared with 10.5% in the nonanemic group.[22]

Length of Hospital Stay. Anemia on admission[20,23] and postoperative anemia[16,22] were both associated with a significantly increased LOS of the same order of magnitude in all four prospective cohort studies reporting this clinical outcome. In anemic patients compared with nonanemic patients, mean LOS was 18 *versus* 11 days ($P < 0.001$),[22] 13 *versus* 8 days ($P < 0.001$),[16] and 16 *versus* 8 days ($P < 0.01$).[23] Finally, Gruson *et al.*[20] reported without quantifying their findings that anemia at hospital admission was significantly associated with an increased hospital LOS ($P < 0.01$).

Mortality. Preoperative[20,23] and postoperative[16] anemia were both associated with a significantly increased mortality

Table 2. Type of Anemia in Patients Undergoing Hip or Knee Surgery

						Type of Anemia		
Reference	Type of Surgery	No.	Mean Age, yr	Definition of Anemia (Hb in g/dl)	Prevalence of Anemia, %	Hypochromic Microcytic, %	Normochromic Normocytic, %	Other, %
Saleh *et al.*[21]	THA/TKA	1,142	68	M < 13; F < 11.5	20	23	64	13
Basora *et al.*[24]	THA/TKA	218	71	MF < 13	39	70*	30	
Myers *et al.*[22]	THA	225	64	M < 12.5; F < 11.5	15	60	34	4

* Defined as serum-soluble transferring receptor level < 1.76 mg/l.

F = female; Hb = hemoglobin; M = male; THA = total hip arthroplasty; TKA = total knee arthroplasty.

Table 3. Clinical Outcomes Associated with Anemia in Patients Undergoing Hip or Knee Surgery

Reference	Type of Surgery	Study Design	Definition of Anemia (Hb Level in g/dl)	No.	Mean Age, yr	Predefined Clinical Outcomes Associated with Anemia vs. No Anemia				
						Quality of Life	Physical Function	Infections	LOS	Mortality
Foss *et al.*[16]	Hip fracture	Prospective	MF < 10	487	82	NR	Poorer (cumulated ambulatory score)	NR	13 vs. 8 days ($P <$ 0.001)	12.6 vs. 6.3% at 30 days ($P < 0.05$)
Su *et al.*[18]	Hip fracture	Retrospective	M < 13; F < 12	844	80	NR	No difference (activities of daily living)	NR	NR	No difference
Halm *et al.*[23]	Hip fracture	Prospective	MF < 12	550	82	NR	No difference after adjustment (functional independence motor score)	NR	Higher preoperative hemoglobin levels associated with shorter LOS (OR = 0.67, $P <$ 0.001)	Higher preoperative hemoglobin levels associated with lower risk for death (OR = 0.69, $P < 0.05$)
Dharmarajan *et al.*[19]	Hip fracture	Retrospective	M < 13; F < 12	145	82	NR	NR	NR	NR	NR
Lawrence *et al.*[29]	Hip fracture	Retrospective		5,793	79	NR	Poorer (distance walked at discharge)	NR	NR	NR
Gruson *et al.*[20]	Hip fracture	Prospective	M < 13; F < 12	395	65–84: 74% ≥ 85: 26%	NR	No difference (activities of daily living)	NR	Not quantified, $P <$ 0.01	OR = 5.0, $P = 0.01$ if Hb level < 10 g/dl
Myers *et al.*[22]	THA	Prospective		225	64	NR	NR	Increased urinary tract infection rate (28 vs. 14%, $P =$ 0.039)	18 vs. 11 days, no *P* value published	NR

F = female; Hb = hemoglobin; LOS = length of stay; M = male; NR = not reported; OR = odds ratio; THA = total hip arthroplasty.

in all three prospective studies that investigated this association. In anemic patients compared with nonanemic patients, 30-day postoperative mortality after hip fracture repair was 13 *versus* 6% ($P < 0.05$),[16] the adjusted odds ratio for death within 60 days after discharge was 1.5 ($P < 0.05$),[23] and the overall odds ratios for death at 6 and 12 months after discharge were 2.9 ($P = 0.02$) and 2.6 ($P = 0.01$), respectively.[20] Interestingly, in the latter study, patients with severe anemia (hemoglobin < 10 g/dl) were five times more likely to die within 6 and 12 months after discharge ($P \leq 0.01$) than patients with mild anemia (defined as hemoglobin level from 10 to 11.9 g/dl for women and to 12.9 g/dl for men).[20] Only one retrospective study found no association between anemia and mortality.[18]

Quality of Life. None of the selected studies reported the effects of anemia on QoL in patients undergoing hip or knee surgery. Among studies including fewer than 100 patients, one found a positive correlation between hemoglobin levels at discharge and change in QoL scores during 2 months after primary hip arthroplasty (N = 87),[32] whereas another one (n = 30) found no evidence of such an association during 56 days after surgery.[33]

Evidence-based Effects of Selected Patient Blood Management Interventions on Predefined Outcomes

Iron and/or rHuEPO-based Treatments. Detailed findings on clinical outcomes are shown in table 4. Two cohort studies reported the effects of preoperative treatment with oral iron before primary TKA[34] and intravenous iron given 4 days or less before surgical hip fracture repair.[35] Iron therapy was shown to reduce the need for ABT.[34,35] Iron therapy also significantly reduced the postoperative infection rate.[35] Although mean LOS and 30-day mortality were numerically reduced with iron therapy, the difference did not reach statistical significance.

Another study exploring the effects of iron in orthopedic surgery patients was not included in the table because of its peculiar design.[36] In a prospective series of 322 patients undergoing THA, those identified as anemic (hemoglobin < 12 g/dl) were provided oral iron therapy while on the waiting list (n = 26). The ABT rate was 3% in the nonanemic group *versus* 23% in the anemic group treated with oral iron ($P <$ 0.05). Within the latter, the transfusion rate was 9% in those who responded to iron therapy and increased their preoperative hemoglobin level more than 12 g/dl (n = 11) *versus* 33% in those who did not ($P < 0.05$). The mean LOS was significantly ($P < 0.05$) higher in nonresponder anemic patients (8.6 days) than in anemic responders (6.1 day) and in nonanemic patients (6.6 days).[36]

Eight studies reported the effects of rHuEPO in patients undergoing major orthopedic surgery.[37–44] With the exception of two studies using a placebo as comparator,[43,44] all other used an active control group (CS, PAD, and/or iron therapy). rHuEPO was given in combination with oral or intravenous iron in all studies. The weighted mean hemoglobin levels in gram per deciliter at first consultation, pre- and postsurgery were 12.7 ± 0.6 g/dl, 14.3 ± 0.3 g/dl, and 11.4 ± 0.1 g/dl in the rHuEPO-based treatment groups and 12.7 ± 0.6, 12.4 ± 0.4, and 9.7 ± 0.1 g/dl in the control groups, respectively.[37,38,41,43,44] rHuEPO-based treatments consistently reduced the need for ABT, the effect being more

Table 4. Effects on Outcomes of Iron- or Erythropoietin-based Patient Blood Management Interventions in Randomized Controlled Trials and Cohort Studies

Reference	Study Design	Duration of Observation	Type of Surgery	Study Groups		No. Included		Transfusion Trigger	Allogeneic Blood Transfusion Rate		
				Active	Control	Active	Control		Active	Control	*P* Value
Moonen *et al.*[37]	RCT	4 weeks	THA/TKA with pretreatment Hb level 10–13 g/dl	rHuEPO 40,000 IU weekly (4×) + ferrofumerate 200 mg tid during 3 weeks before surgery	Cell salvage	50	50	Hb < 8.1 or < 8.9 or < 9.7 g/dl depending on the ASA score	4%	28%	0.002
Keating *et al.*[38]	RCT	3 weeks	THA/TKA with pretreatment Hb level 11–14 g/dl	rHuEPO 45,000 IU weekly (4×) + polysaccharide iron complex or the equivalent of 300 mg elemental iron/day per os during 3 weeks before surgery	PAD + polysaccharide iron complex or the equivalent of 300 mg elemental iron/d per os during 3 weeks presurgery	146	132	Hb < 8 g/dl or higher if clinical symptoms	3%	14%	0.002
Weber *et al.*[41]	RCT	4–6 weeks	THA/TKA/spine surgery with pretreatment Hb level 10–13 g/dl	rHuEPO 40,000 IU weekly (4×) + oral iron (type and dose NA)	Usual care, including oral or IV iron (type and dose NA)	467	237	Hb < 8 g/dl	9%	37%	< 0.05
Faris *et al.*[43]	RCT	4 weeks	Major orthopedic surgery	rHuEPO 7,500 to 22,500 IU/d during 15 days + ferrous sulfate 325 mg tid per os	Placebo + ferrous sulfate 325 mg tid per os	131	69	NA	21%	54%	< 0.001
Canadian study group[44]	RCT	3 weeks	THA with pretreatment Hb level 11–16 g/dl	rHuEPO 7,500 to 22,500 IU/d during 14 days + iron sulfate 300 mg tid per os	Placebo + ferrous sulfate 300 mg tid per os	130	78	Hb < 9 g/dl	27%	44%	NA
Garcia *et al.*[39]	Cohort study	30 days	TKA	rHuEPO 40,000 IU (1× if Hb < 13 g/dl) + 2 × 200 mg original iron sucrose IV	2 × 200 mg original iron sucrose IV if Hb ≥ 13 g/dl	19	129	Hb < 8 g/dl	0%	5%	NS
Garcia *et al.*[40]	Cohort study	30 days	Hip fracture	rHuEPO 40,000 IU 1× if Hb < 13 g/dl + original iron sucrose 3 × 200 mg/48 h	Historical hip fracture patients with usual care	83	41	Hb < 8 g/dl or < 9 g/dl in the presence of cardiac disease or acute anemia symptoms	24%	71%	< 0.001
Couvret *et al.*[42]	Cohort study	3 weeks	THA/TKA	rHuEPO 44,000 IU weekly (3×) + ferrous sulfate 320 mg bid per os during 3 weeks before surgery	PAD + ferrous sulfate 320 mg bid per os during 3 weeks presurgery	708	182	Hematocrit < 24% or between 24 and 30% if clinical symptoms	10%	13%	NS
Cuenca *et al.*[34]	Cohort study	Up to 45 days after surgery	Primary TKA and pretreatment Hb < 13 g/dl	Ferrous sulfate 256 mg/d + vitamin C and folic acid 30 to 45 days before surgery	Historical TKA patients with usual care	156	156	Hb < 9 g/dl	6%	32%	< 0.01
Cuenca *et al.*[35]	Cohort study	30 days after surgery	Hip fracture	Original iron sucrose 200–300 mg at admission (0–4 days before surgery)	Historical hip fracture patients with usual care	55	102	Hb < 9 g/dl	44%	56%	NS

(*continued*)

Table 4. Continued

Reference	Infection Rate (%)			Mean Length of Stay (days)			30-day Mortality (%)		
	Active	Control	*P* Value	Active	Control	*P* Value	Active	Control	*P* Value
Moonen *et al.*[37]	2%	2%	NS						
Keating *et al.*[38]	7%	7%	NS						
Weber *et al.*[41]	9.4%	10.6%	NS		10.8	NS			
Canadian Study group[44]					11.7	NS			
Garcia *et al.*[39]				7.5	7.7	NS			
Garcia *et al.*[40]	12.5%	31.4%	0.016	15.3	15.0	NS	7.3%	15.0%	NS
Couvret *et al.*[42]				10.4	10.3	NS			
Cuenca *et al.*[34]				11	12	NS			
Cuenca *et al.*[35]	16.4%	33.3%	< 0.001	12.6	14.3	NS	5%	17%	NS

ASA = American Society of Anesthesiologists; Hb = hemoglobin; IU = International Units; LOS = length of stay; NA = not available; NS = nonsignificant; PAD = preoperative autologous donation; RCT = randomized controlled trial; rHuEPO = recombinant human erythropoietin; THA = total hip arthroplasty; TKA = total knee arthroplasty.

pronounced when more liberal transfusion triggers were used. The clinical outcomes of postoperative infections, LOS, and 30-day mortality were generally not significantly different between rHuEPO-based regimens and the active control groups. However, none of the studies was adequately designed or powered for these outcomes.

Two studies reported physical function endpoints (data not shown). Keating *et al.*[38] showed that the mean overall change in a previously validated vigor score (similar to a combined activities of daily living and QoL score)[45] was significantly greater with an rHuEPO-based treatment than with PAD after adjusting for baseline hemoglobin, gender, age, weight, height, and baseline scores ($P = 0.001$). However, changes in handgrip strength were not significantly different between groups.[38] Weber *et al.*[41] found that time to ambulation (3.3 ± 2.7 days) and time to discharge (10.8 ± 5.5 days) did not differ significantly when a rHuEPO-based treatment was compared with usual care in patients undergoing major orthopedic surgery. However, these parameters were significantly higher in transfused than in nontransfused patients (3.8 *vs.* 3.1 day, $P = 0.004$ and 12.9 *vs.* 10.2 days, $P < 0.001$, respectively) in both the rHuEPO and the control group.[41]

Cell Salvage. Detailed findings are shown in table 5. Eleven studies reporting the effects of CS compared with standard drain without retransfusion of autologous blood and including 100 patients or more who underwent knee or hip arthroplasty were identified.[46–56] Of these, only three included THA patients.[46,48,49] CS measures consisting of retransfusion of washed or nonwashed shed blood generally reduced the need for ABT, independent of the study site-specific transfusion trigger. Reported reductions in infection rates were not significant. Mean LOS was numerically lower in patients after CS and reached statistical significance in two studies.[52,57] Time to ambulation was reduced after CS compared with standard drain in two studies: 6.0 *versus* 7.0 days ($P < 0.01$)[53] and 4.6 *versus* 5.1 day ($P = 0.395$),[46] respectively. Thirty-day mortality was not reported in any study.

Interestingly, del Trujillo *et al.*[46] noted that although the overall differences in postoperative infection rates, time to ambulation, and mean LOS were not statistically significant with CS compared with standard drain, they were in patients having received an ABT compared with those who had not: postoperative infection rate, 12.1 *versus* 2.6%, $P = 0.046$; time to ambulation, 4.4 *versus* 5.7 days, $P = 0.013$; and mean LOS, 9.6 *versus* 13.5 days, $P = 0.001$.[46]

Preoperative Autologous Blood Donation. Four cohort studies,[58–61] including 100 patients or more, reported the effects of PAD on the ABT rate. PAD was compared with either usual care with no PAD[58,59,61] or with PAD restricted to 2 units of blood.[60] In studies comparing PAD with no PAD, ABT rates were reduced from 40 to 3%,[59] 52 to 18%,[58] and 91 to 9%[61] corresponding to a weighted average reduction (±SD) from 73% (±27) to 8% (±8). PAD of 4 units of blood was not significantly superior to PAD of 2 units.[60] The effects of PAD on the other predefined clinical outcomes were not reported in any study.

Other Patient Blood Management Measures. Wong *et al.*[62] evaluated the effectiveness of a blood conservation algorithm aiming at reducing the need for ABT (patient and physician education, use of iron or rHuEPO or PAD in accordance with predefined preoperative hemoglobin level categorized) in patients undergoing THA in 30 hospitals randomly assigned to implement the algorithm or to continue with usual care. Transfusion triggers were set at hemoglobin less than 7 g/dl or hemoglobin between 7 and 10 g/dl and symptoms. The allogeneic transfusion rate was substantially reduced in hospitals randomized to the blood conservation algorithm compared with usual care (16.5% *vs.* 26.1%, $P = 0.02$) with no difference in the use of autologous blood. Mean LOS was numerically but not significantly lower in hospitals randomized to the blood conservation algorithm (5.8 *vs.* 6.3 days).

Eindhoven *et al.*[63] performed a cohort study to compare the implementation of conservative blood transfusion triggers (6–8-10 g/dl Flexinorm) in one hospital with continued usual care (hemoglobin less than 10 g/dl or hematocrit less than 30%) in another. The allogeneic transfusion rate over 12 months was 14 and 40% ($P < 0.0001$), respectively. No data on clinical outcomes were reported.

Intraoperative hemodilution may be a measure of interest for patient blood management in patients undergoing elective hip surgery. Our search retrieved eight studies, all randomized controlled trials, reporting results of acute normo-

Table 5. Effects on Outcomes of Patient Blood Management Interventions Based on Cell Salvage (Autologous Retransfusion of Salvaged Blood Cells) in Randomized Controlled Trials and Cohort Studies

Reference	Study Design	Type of Surgery	Study Groups		No. Included		Transfusion Trigger	Allogeneic Blood Transfusion Rate		
			Active	Control	Active	Control		Active	Control	*P* Value
Amin *et al.*[47]	RCT	TKA	Autologous retransfusion drain (Bellovac)	Standard drain	86	92	Hb < 8 g/dl or symptoms of acute anemia	13%	15%	NS
Smith *et al.*[48]	RCT	THA	Autologous retransfusion drain (ABTrans)	Standard drain	76	82	Hb < 8 g/dl or Hb between 8 and 10 g/dl and symptoms of acute anemia	8%	21%	0.022
Moonen *et al.*[49]	RCT	THA/TKA with preoperative Hb level 13 to 14.6 g/dl	Autologous retransfusion drain (ABTrans)	Standard drain	80	80	Hb < 8.1 or <8.9 or <9.7 g/dl depending on the ASA score	6%	19%	0.015
Tsumara *et al.*[50]	RCT	TKA	Autologous retransfusion drain (ConstaVac)	Standard drain	106	106	NA	3%	1%	NS
Kirkos *et al.*[51]	RCT	TKA	Autologous retransfusion drain	Standard drain	78	77	Hb < 10 g/dl	NA	NA	
Thomas *et al.*[55]	RCT	TKA	Washed shed blood salvage and reinfusion (Cell Saver 5)	Standard drain	115	116	Hb < 9 g/dl	7%	28%	< 0.001
Shenolikar *et al.*[56]	RCT	TKA with preoperative Hb > 10 g/dl	Washed shed blood salvage and reinfusion (Cell Saver 3)	Standard drain	50	50	Hb < 9 g/dl	16%	80%	NA
del Trujillo *et al.*[46]	Cohort study	THA	Washed shed blood salvage and reinfusion (OrthoPAT)	Standard drain	60	48	Hb < 8 g/dl or symptoms of acute anemia	15%	48%	0.001
Cuenca *et al.*[52]	Cohort study	TKA	Autologous retransfusion of unwasged shed blood if admission Hb < 13 g/dl + rHuEPO 40'000 IU (1x if Hb < 13 g/dl) + 2x 200mg IV iron	rHuEPO 40,000 IU (1x if Hb < 13 g/dl) + 2x 200 mg IV iron	173	139	Hb < 8 g/dl or symptoms of acute anemia	3%	5%	NS
Munoz *et al.*[53]	Cohort study	TKA	Autologous retransfusion drain	Standard drain	200	100	NA	11%	48%	< 0.01
Steinberg *et al.*[54]	Cohort study	TKA	Autologous retransfusion drain (SureTrans)	Standard drain	194	171	Hb < 8 g/dl or symptoms of acute anemia	19%	52%	< 0.01

Reference	Infection Rate (%)			Mean Length of Stay (days)		
	Active	Control	*P* Value	Active	Control	*P* Value
Amin *et al.*[47]				6.6	7.0	NS
Smith *et al.*[48]	4	6	NS	6.4	7.0	NS
Shenolikar *et al.*[56]				15.6	16.7	NS
del Trujillo *et al.*[46]	2	10	NS	10.1	11.6	NS
Cuenca *et al.*[52]	2	2	NS	8.0	10.0	0.001
Munoz *et al.*[53]				13.0	16.0	< 0.01

ASA = American Society of Anesthesiologists; Hb = hemoglobin; NA = not available; NS = nonsignificant; RCT = randomized controlled trial; rHuEPO = recombinant human erythropoietin; THA = total hip arthroplasty; TKA = total knee arthroplasty.

volemic hemodilution.[64–71] As the largest study enrolled 49 patients,[68] they were excluded from detailed analysis. Briefly, in these studies, the primary endpoint of interest generally was the ABT rate. Three studies showed a significantly lower ABT rate with hemodilution,[65,67,70] the remainder showed no significant difference *versus* controls.

Discussion

A systematic literature search identified preoperative anemia and even more so postoperative anemia after intraoperative blood loss as highly prevalent in patients undergoing major elective orthopedic surgery (THA/TKA) and surgical repair of hip fractures. In these patients, anemia was associated with significant adverse clinical outcomes, such as increased allogeneic transfusion rates, decreased physical functioning, increased infection rates, increased LOS, and increased mortality. In randomized controlled trials and cohort studies, patient blood management interventions based on preoperative iron or erythropoietin therapy and postoperative retransfusion of salvaged cells

generally allowed a statistically significant and clinically relevant reduction of ABTs.

In the prospective and retrospective cohort studies included in the present review, preoperative anemia was prevalent in approximately 25% of the patients undergoing elective THA/TKA and 50% of the patients undergoing surgical hip fracture repair. This is consistent with the observation that hip fracture patients were 10 yr older than THA/TKA patients on average and with the increasing incidence of anemia with age.[72] However, the definition of anemia used for assessing its prevalence was often not reported or deviated from the definition of World Health Organization (hemoglobin level less than 13 g/dl in men and less than 12 g/dl in women),[73] possibly reflecting the ongoing debate about the validity of these values, especially in an elderly population.[74] Independent of the authors' beliefs with regard to the appropriate definition of anemia, postoperative hemoglobin levels were consistently much lower than before surgery (on average 3.0 g/dl after THA/TKA and 4.3 g/dl after surgical hip fracture repair) and the prevalence of anemia further increased consistently after surgery, reaching 51% after THA/TKA and 87% after hip fracture repair.

In patients with iron deficiency, anemia develops once iron stores are depleted. Iron loss due to surgical bleeding will exaggerate a possibly preexisting iron deficiency and may aggravate postoperative anemia. The marked postoperative increase in the prevalence of anemia after major orthopedic surgery suggests that preoperative iron store depletion may be widespread in this patient population. Although preoperative iron therapy contributes to increase in preoperative hemoglobin levels and thereby to decrease in the risk of postoperative anemia requiring ABT,[34,35] postoperative iron administration aims at correcting anemia by supporting erythropoiesis and at replenishing the iron stores. However, this has not yet been studied clinically so far. By assuming that circulating erythrocytes contain 1,800 mg of iron in 5,000 ml of blood,[75] the loss of 1,000 ml of blood during major hip or knee surgery corresponds to a net loss of 360 mg of hemoglobin-bound iron. Patients perioperatively administered 360 mg of elemental iron will therefore be discharged with iron stores at the level they were before surgery, thus possibly with persisting iron deficiency.

Transfusion triggers varied across studies and were inconsistently reported. Accordingly, the ABT rates ranged from 10 to 89%. However, the average ABT rates and the average number of blood units transfused were similar after THA, TKA, and hip fracture repair (44–45% and 2.3–2.6 units, respectively), indicating possible differences in the perception of the severity of postoperative anemia between these two patient groups, that is, lower postoperative hemoglobin levels seemingly being more acceptable in elderly than in younger patients. At the time of writing this manuscript, the publication of the results of the recently completed FOCUS outcome trial was still pending. The FOCUS trial was designed to compare an aggressive erythrocyte transfusion strategy (transfusions to maintain hemoglobin levels at or more than 10 g/dl through hospital discharge or up to 30 days after randomization) with a more conservative strategy (transfusions withheld until the patient develops symptoms from anemia and permitted if hemoglobin level falls less than 8 g/dl) in patients with cardiovascular disease who had undergone surgical repair for a hip fracture with the following outcome measures: time to ambulation (primary endpoint); myocardial infarction or death, postoperative complications, survival, nursing home placement, and function (secondary endpoints).[76] The only randomized controlled clinical endpoint trial that assessed the effects of ABT in anemic adult patients was performed in the critically ill.[77] In this study, a restrictive strategy of transfusion (ABT if hemoglobin less than 7.0 g/dl and hemoglobin level maintained at 7.0–9.0 g/dl) compared with a liberal strategy (ABT if hemoglobin less than 10.0 g/dl and hemoglobin level maintained at 10.0–12.0 g/dl) lead to a numerically lower 30-day mortality rate in the overall population of critically ill patients, which reached statistical significance in patients who were less acutely ill and among patients younger than 55 years of age.[77] Supported by the recently reviewed results from retrospective and prospective studies and by many pathophysiologic observations of deleterious effects of storage on red blood cells,[78,79] this array of consistent and accumulating evidence strongly suggests that ABT are a risk factor for poorer clinical outcomes and triggered a growingly acknowledged need for patient blood management interventions aiming at minimizing the need for ABT.[13,80]

Preoperative anemia is a major risk factor for adverse outcome in major surgery.[5,9,10,81,82] Preoperative anemia is also one of the most important risk factor for perioperative blood transfusions.[2,5,17,83] The question thus arises as to whether preoperative anemia or perioperative ABT is responsible for the observed adverse outcome. Despite its complexity, this has been investigated in cardiac and general surgery.[5,9,10,81,82] With various multivariate statistics and propensity score matching in some studies, the authors unanimously found that preoperative anemia and perioperative ABT were both independent risk factors for postoperative mortality, ischemia, and infections.[5,9,10,81,82] Unfortunately, no such big observational studies exist in orthopedic surgery. However, the probability of such fundamental associations being different in orthopedic surgery should be considered as reasonably low. Therefore, treatment modalities aimed at reducing preoperative anemia and perioperative erythrocyte transfusion seem justified already today, although only the final proof that such measures will indeed improve outcome is pending the results of future randomized controlled trials.

The categorization of anemia as iron-deficiency anemia and anemia of inflammation or chronic disease was reported in three studies only, with a prevalence of hypochromic microcytic anemia ranging from 23 to 70%. The clinical relevance of such a categorization has been recently underlined by the discovery of hepcidin as the iron gatekeeper.[84–86] As opposed to patients with pure iron-deficiency anemia, patients with anemia of chronic inflammation have high serum

hepcidin levels. By inducing the internalization of ferroportin in enteric cells and macrophages, the presence of high serum levels of hepcidin plays a key role in the development of anemia of chronic inflammation by impairing the absorption of orally administrated iron and by leading to iron sequestration in macrophages.[84] In contrast, intravenous iron has been recently shown to overcome hepcidin-induced iron-restricted erythropoiesis in iron-replete patients.[87] The practical relevance of these findings is that patients with anemia of chronic disease should be expected to be nonresponders to oral iron therapy[88] and may need higher doses of erythropoietin to trigger sustained erythropoiesis.[89] Conversely, intravenous iron therapy overcomes oral absorption blockade because of inflammation-reduced rHuEPO need and dose, as shown in dialyzed[90–92] and nondialyzed[93–95] anemic patients with chronic kidney disease and in anemic cancer patients.[96–98]

The present review identified several clinically important outcomes that were significantly associated with anemia in patients undergoing major orthopedic surgery. Systematic reviews have the advantage of being reproducible while preventing study selection bias. Conversely, they are limited by the publication bias itself (negative outcomes being less likely to be reported than significant findings[99,100]) and by the quality of MeSH term coding. As an example, the multicentric Austrian benchmark study[2] reporting blood use in elective surgery and included 1,401 patients with primary THA and 1,296 patients with TKA among 3,622 elective surgical procedures was not retrieved by the present search. MeSH term coding ("Surgical Procedures, Elective") preempted retrieval by a focused indication driven search. However, the variability in ABT rates, number of units transfused, perioperative blood loss volumes, and overall conclusions of this study were consistent with those reported here.

The selected patient blood management interventions (preoperative iron or erythropoietin therapy, CS, and PAD) were generally powered for the primary endpoints of pre- or postoperative hemoglobin levels or postoperative ABT rates. None of the studies was adequately powered for QoL, physical functioning, LOS, or mortality endpoints. Although the numerical trends were in favor of outcome improvement, solid scientific evidence based on statistically significant differences in adequately designed and powered primary endpoint trials is still lacking. The heterogeneity and inconsistencies in data reporting precluded a meaningful meta-analysis of the reported findings. However, published results available to date are sufficient for generating hypotheses and power calculations required for clinical endpoint trials of patient blood management interventions. For future research, a framework for standardized reporting of clinical trial results in the field of anemia and orthopedic surgery should be developed and implemented to ensure comparability of results across studies and to allow for meta-analyses. As already recommended earlier by other authors,[1] the definition of anemia and transfusion triggers should be unified across studies or results published according to preoperative hemoglobin level strata. Anemia should be categorized as anemia of inflammation or iron-deficiency anemia and results shown accordingly. ABT rates should refer to the number of units transfused per transfused patient, or, alternatively, the total number of patients transfused and the total number of units transfused should be published. A standardized set of clinical endpoints and their minimal variation considered as clinically (or economically) meaningful should be defined. Among such endpoints of interest, the ABT rate, infection rate, LOS, time to ambulation, QoL, as well as 30-day, 6-month, and 12-month mortality deserve appropriate attention. Finally, perioperative patient blood management interventions should be categorized into pre-, per-, and postoperative measures because different effects on outcomes may be expected from the same intervention (*e.g.*, iron supplementation) performed at a different point in time (*e.g.*, pre- *vs.* postoperative).

Conclusion

Anemia in the orthopedic perioperative setting was frequent and was associated with increased ABT rates and with adverse clinical outcomes. Patient blood management interventions aiming at decreasing the need for ABTs and at improving patient outcomes deserve increased medical attention.

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