

# Anemia and Transfusion After Subarachnoid Hemorrhage

Peter D. Le Roux · The Participants in the International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage

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**Abstract** Delayed cerebral ischemia after subarachnoid hemorrhage (SAH) may be affected by a number of factors, including cerebral blood flow and oxygen delivery. Anemia affects about half of patients with SAH and is associated with worse outcome. Anemia also may contribute to the development of or exacerbate delayed cerebral ischemia. This review was designed to examine the prevalence and impact of anemia in patients with SAH and to evaluate the effects of transfusion. A literature search was made to identify original research on anemia and transfusion in SAH patients. A total of 27 articles were identified that addressed the effects of red blood cell transfusion (RBCT) on brain physiology, anemia in SAH, and clinical management with RBCT or erythropoietin. Most studies provided retrospectively analyzed data of very low-quality according to the GRADE criteria. While RBCT can have beneficial effects on brain physiology, RBCT may be associated with medical complications, infection, vasospasm, and poor outcome after SAH. The effects may vary with disease severity or the presence of vasospasm, but it remains unclear whether RBCTs are a marker of disease severity or a cause of worse outcome. Erythropoietin data are limited. The literature review further

suggests that the results of the Transfusion Requirements in Critical Care Trial and subsequent observational studies on RBCT in general critical care do not apply to SAH patients and that randomized trials to address the role of RBCT in SAH are required.

**Keywords** Anemia · Erythropoietin · Oxygen delivery · Vasospasm

## Introduction

Aneurysm rupture causing subarachnoid hemorrhage (SAH) occurs in about 10/100,000 people each year [1, 2]. Nearly half of these individuals are dead within 30 days [1–5]. Among survivors, only one-third make a full recovery and approximately half who appear to experience a favorable outcome have neuropsychological and cognitive deficits and difficulties in their daily activities [6–10]. Poor outcome after SAH may be associated with two preventable factors delayed cerebral ischemia (DCI) and extracerebral organ dysfunction (e.g., medical complications and infection) [11–19]. The mortality rate from extracerebral organ dysfunction is 20–40% [17, 18]. DCI occurs in about 30% of patients, is often associated with arterial vasospasm that begins about 3 days after SAH, is maximal days 7–8, resolves after 14 days, and is identified radiographically in about 70% of patients [20–24]. Clinical trials to prevent vasospasm seldom have improved clinical outcome, despite reduced vessel narrowing [21, 25, 26]. This dissociation between clinical outcome and vasospasm has refocused efforts to limit brain injury rather than vessel narrowing and has renewed interest in intensive care strategies to prevent DCI and medical complications.

DCI is caused by impaired cerebral blood flow (CBF) and O<sub>2</sub> delivery (DO<sub>2</sub>). Cerebral circulation compensates

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for reduced CBF by increasing oxygen extraction fraction (OEF) to maintain the amount of oxygen available for metabolism and to prevent ischemia. When OEF is increased (oligemia), tissues may not compensate for further DO<sub>2</sub> reductions and, if not corrected, infarction may occur. Therefore, avoiding critical DO<sub>2</sub> reductions is central to SAH care. CBF and CaO<sub>2</sub> determine cerebral DO<sub>2</sub>, and since hemoglobin (Hb) levels primarily determine CaO<sub>2</sub>, anemia may impair cerebral DO<sub>2</sub>. After SAH, more than half the patients develop anemia [27, 28] that maybe associated with worse outcome. Clinical studies also suggest that Hb > 11 g/dL may be associated with improved SAH outcome [29–31]. However, higher Hb may increase blood viscosity and, with autoregulatory vasoconstriction in response to increased CaO<sub>2</sub>, further reduce CBF, countering any DO<sub>2</sub> benefit. Furthermore, RBCT (red blood cell transfusion) has been associated with organ dysfunction and mortality [32–35]. This effect may be mediated by inflammatory mediators or altered nitric oxide (NO) metabolism among other factors in transfused cells [36–41]. Both inflammation and NO influence vasospasm [21, 42]. Limited data are available to guide anemia management and RBCT after SAH.

This literature review was designed to present available published evidence on the occurrence and outcome of anemia in SAH patients. The role of RBCT and erythropoietin on brain physiology and clinical outcome also was explored.

## Methods

A literature search was made to identify clinical or experimental studies published between 1980 and August 2010 in the English literature that described and compared RBCT strategies and Hb levels after rupture of a cerebral aneurysm. Candidate articles were identified from electronic databases, including Medline and EMBASE, *Index Medicus*, bibliographies of pertinent articles, and expert consultation. Additional articles were identified through review of textbooks, bibliographies from retrieved articles, and the “Related Articles” feature of PubMed. For electronic searches, the following key words were used: “subarachnoid hemorrhage,” “subarachnoid hemorrhage outcome,” “anemia,” “hemoglobin,” “transfusion,” “packed red blood cells,” “vasospasm,” “delayed cerebral ischemia,” “blood products,” and “erythropoietin.” This search was supplemented by also identifying randomized trials that have compared transfusion strategies in general critical care, recent review articles on transfusion in neurocritical care, transfusion guidelines, and studies that have evaluated transfusion and hemoglobin in traumatic brain injury (TBI).

Original research studies were selected for detailed review if they addressed incidence and/or outcome of

anemia and treatment with RBCT or erythropoietin after SAH. Selected studies were evaluated for quality of evidence using the GRADE system [43].

## Summary of the Literature

Five hundred and twelve manuscripts were identified. There is no high-quality evidence to support a particular transfusion strategy or Hb level in patients with SAH. Twenty-seven articles were selected for detailed review (Tables 1, 2, 3, 4) [27, 29–31, 44–66]. These studies addressed brain physiology related to transfusion or Hb (11 articles—5 in traumatic brain injury and 6 in SAH; Table 1), anemia in SAH (5 articles; Table 2), RBCT management in SAH (8 articles; Table 3), and erythropoietin after aneurysm rupture (4 articles; Table 4). Most studies describe retrospective analyses of clinical series. Overall, the quality of evidence is very low according to the GRADE criteria. One small, randomized pilot study evaluated two transfusion strategies in SAH [58]; however, this study was underpowered, and no conclusions about a particular strategy could be made. The study, however, suggests that a randomized trial is safe and feasible.

The data summarized in the tables support that anemia affects about half of patients with SAH and is linked with worsened outcome. While RBCT has been shown to have beneficial effects on brain physiology, RBCT is associated with medical complications, infection, vasospasm, and poor outcome after SAH. It remains unclear whether RBCTs are simply a marker of disease severity or an independent cause of worse outcome. Erythropoietin data are very limited.

In addition to those articles meeting criteria for detailed review, additional publications provide clinically useful information on the potential role of RBCT in SAH. These studies are summarized below.

### Anemia After SAH

Anemia is common after SAH. Depending on the definition applied, anemia has been identified in 40–50% of SAH patients and only 16% maintain Hb > 11 g/dL [27, 54, 55, 67]. The mean drop in Hb after SAH is 3 g/dL, and anemia develops after a mean of 3.5 days [27]. Anemia may exacerbate the reduction in oxygen delivery that underlies DCI. Observational studies have linked anemia or a larger Hb reduction with infarction, dependency, and death after SAH [19, 29, 55, 68]. In addition, patients with an unfavorable outcome consistently have lower Hb levels, especially between days 6 and 11, following SAH (i.e., during the greatest risk period for DCI) [55].

**Table 1** Summary of published literature that examines the effect of RBCT on brain oxygen and metabolism

References	Patient number	Designs	Intervention	Baseline laboratory values	Main results
Smith et al. (2005) [44]	23 TBI 12 SAH	Retrospective (prospective database)	Any RBCT (number of units not specified a priori; 80% received 1 unit; mean Hb increased to 10.2 g/dL). General transfusion threshold Hb < 10 g/dL or hematocrit < 30% (no protocol)	Hb = 8.7 g/dL PbtO <sub>2</sub> = 24.4 mm Hg	Overall mean increase in PbtO <sub>2</sub> 3.2 mmHg (15%) Increase not related to baseline PbtO <sub>2</sub> In 26 pts, whose PbtO <sub>2</sub> increased mean increase was 5.1 ± 9.4 mmHg (49%) PbtO <sub>2</sub> decreased in 9/35 patients (26%)
Leal-Naval et al. (2008) [45]	51 TBI	Prospective observational	1 or 2 units of packed red blood cells (# of units not specified a priori; 52% received 2 units; mean Hb increased to 10.6 g/dL) RBCT threshold Hb < 10 g/dL	Hb = 9.0 g/dL PbtO <sub>2</sub> = 24.4 mm Hg	Mean increase in PbtO <sub>2</sub> 3.8 mm Hg (16%) Increase greater at lower baseline PbtO <sub>2</sub>
Leal-Naval et al. (2008) [46]	66 TBI (all males)	Prospective observational	1 or 2 units transfused Number of units not specified a priori; 59% received 2 units; mean Hb increased to 10.2 g/dL) RBCT threshold Hb < 9.5	Hb = 8.9 g/dL PbtO <sub>2</sub> = 21.3 to 26.2 mm Hg	PbtO <sub>2</sub> decreased in 13 of 51 patients (25%) Units of blood < 14 days associated with greater mean PbtO <sub>2</sub> increase (3.3 mmHg [16%] vs. 2.1 mmHg [8%])
Zygun et al. (2009) [47]	30 TBI	Prospective RCT	Randomized to RBCT thresholds of 8, 9, or 10 g/dL 2 Units packed red blood cells administered over 2 h (mean Hb increased to 10.1 g/dL) Cerebral microdialysis and PbtO <sub>2</sub> monitored	Hb = 8.2 g/dL PbtO <sub>2</sub> = 18.8 mm Hg	PbtO <sub>2</sub> decreased only in patients who received blood stored > 19 days Mean increase in PbtO <sub>2</sub> 2.2 mmHg (12%) Increase in PbtO <sub>2</sub> greatest when LPR > 25 PbtO <sub>2</sub> decreased in 13/30 patients (43%)
Figaji et al. (2010) [48]	17 TBI (children)	Retrospective (prospective database)	19 transfusions if Hb < 7–10 g/dL Mean change Hb 2.8 ± 1.1 g/dL	Mean Hb 8.4 ± 0.8 g/dL Mean PbtO <sub>2</sub> 29.9 ± 8.4	No effect on jugular venous O <sub>2</sub> saturation or microdialysis parameters PbtO <sub>2</sub> increased in 79% of RBCT Effects of RBCT on PbtO <sub>2</sub> observed at 4 but not 24 h. Mean PbtO <sub>2</sub> change at 4 h 17% Increase greater with higher baseline Hb and PbtO <sub>2</sub> . Effect associated with CPP change
Ekelund et al. (2002) [49]	8 SAH (TCD-vaso-spasm)	Prospective interventional	Isovolemic hemodilution (venesection with infusion of dextran 70 and 4% albumin) to mean Hb of 9.2 g/dL Outcome assessed using 133Xenon and SPECT	Hb = 11.9 g/dL	Increased global CBF (52.3 to 58.6 ml/100 g/min) Reduced cerebral vascular resistance Reduced oxygen delivery Increased ischemic brain volume

Table 1 continued

References	Patient number	Designs	Intervention	Baseline laboratory values	Main results
Muench et al. (2007) [50]	10 SAH	Prospective interventional	Volume expansion with HES ± crystalloid to achieve ITBVI > 1,000 ml/m <sup>2</sup> produced decline in Hb of 1.3–2.0 g/dL	Hb = 10.6 g/dL PbtO <sub>2</sub> = 24.8 mm Hg	Although hypovolemia/hemodilution produced a slight CBF increase, PbtO <sub>2</sub> decreased by an average of 0–5 mm Hg Only induced hypertension increased PbtO <sub>2</sub>
Dhar et al. (2009) [51]	8 SAH (female)	Prospective interventional	One unit RBCs transfused when Hb < 10 g/dL (mean Hb increased to 9.9 g/dL). Outcomes assessed using PET	Hb = 8.7 g/dL	No significant change in CBF RBCT increased cerebral O <sub>2</sub> delivery (18%) without decreasing global CBF Increase O <sub>2</sub> delivery greater in oligemic regions (28 vs. 15%, <i>P</i> < 0.001) Reduced O <sub>2</sub> extraction ratio (49–41%; <i>P</i> = 0.06) No significant change in cerebral metabolic rate of O <sub>2</sub> Reduction in O <sub>2</sub> extraction ratio observed also in territories with vasospasm and low O <sub>2</sub> delivery
Naidech et al. (2008) [52]	6 SAH	Prospective observational	14 RBCTs (no protocol)	Not reported	Hb correlated with cerebral oximetry that increased numerically but not statistically significantly in 11/14 RBCTs
Oddo et al. (2009) [53]	20 SAH	Retrospective (prospective database)	206 matched Hb, PbtO <sub>2</sub> , and LPR	Hb = 10.0 g/dL (range, 7.1–15.8)	Hb < 9 g/dL associated with higher risk of PbtO <sub>2</sub> < 20 mm Hg (OR 7.2, 95% CI 2.3–27.1, <i>P</i> < 0.01) and LPR > 40 (OR 4.2, CI 1.33–13.55; <i>P</i> = 0.02) Adjusted for CPP, CVP, PaO <sub>2</sub> /FiO <sub>2</sub> ratio and vasospasm
Kurtz et al. (2010) [54]	34 SAH	Retrospective	359 matched Hb, PbtO <sub>2</sub> , and LPR	Median Hb 9.7 g/dl (IQR 8.8–10.5)	Decrease in Hb associated with increased risk of PbtO <sub>2</sub> < 15 (OR 1.7, 95% CI 1.1–2.4, <i>P</i> = 0.01 for every unit decrease) Hb < 9 (OR 3.7 [1.5–9.4]) and 9.1–10 (OR 1.9 [1.1–3.3]) associated with risk of metabolic distress (LPR > 40)

CBF, cerebral blood flow; CI, confidence interval; CPP, cerebral perfusion pressure; CVP, central venous pressure; Hb, hemoglobin; HES, hydroxyethyl-starch; IQR, interquartile range; ITBVI, intrathoracic blood volume index; LPR, lactate pyruvate ratio; OR, odds ratio; PbtO<sub>2</sub>, brain tissue oxygen; PET, positron emission tomography; RBC, red blood cells; RBCT, red blood cell transfusion; RCT, randomized controlled trial; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; TCD, transcranial Doppler

**Table 2** Summary of published literature that examines anemia and SAH

References	Designs	RBCT	Mean Hb or Hct	Measures	Main outcome
Sampson et al. (2010) [27]	Retrospective, single center <i>N</i> = 243 (survived > 3 days)	19% received RBCT; 39% of anemic patients	Mean admission Hct 39.8%	Logistic regression Baseline factors with <i>P</i> < 0.10 entered into backward stepwise analysis using multivariate logistic regression	Anemia in 47% Symptomatic vasospasm more frequent with anemia (OR, 5.14; 95% CI, 2.7–9.76) Mortality greater with anemia (OR, 5.88; 95% CI, 1.64–21) Anemia more common with female sex (OR, 3.7; 95% CI, 1.8–7.6), baseline Hct < 36% (OR 3.9, 95% CI 1.5–10.1), hypertension (OR, 2.1; 95% CI, 1.1–4.2), and poor clinical grade (OR, 5.9; 95% CI, 2.3–15.0) Hct decrease linked with surgery (OR, 13.5; 95% CI, 6.0–30.3) and admission SIRS score (OR, 5.7; 95% CI, 1.7–19.2) and associated with RBCT
Kramer et al. (2009) [55]	Retrospective, single center <i>N</i> = 245	Daily nadir Hb over 2 weeks. 35% transfused	Hb 9.5 g/dL No transfusion protocol	Generalized estimating equation to account for correlated data (WFNS score, age, vasospasm, and modified Fisher score)	Hb and decline in Hb over time predict poor outcome. Association between Hb and outcome stronger among poor-grade patients
Naidech et al. (2007) [30]	Retrospective review of prospective database, single center. <i>N</i> = 611	Mean Hb over 2 weeks. 35% transfused	Not reported No transfusion protocol	Multinomial regression (Hunt-Hess, age, and cerebral infarction)	Higher nadir (but not mean) Hb associated with better outcome after 3 months (OR, 0.83; 95% CI, 0.74–0.93, per g/dL increase; <i>P</i> = 0.04)
Naidech et al. (2006) [31]	Retrospective review of prospective database, single center. <i>N</i> = 103	Mean Hb over 2 weeks. 47% transfused	Hb 9.2 mg/dL No RBCT protocol	Logistic regression (Hunt-Hess, age, and angiographic vasospasm)	Higher 2-week mean Hb associated with better outcome at discharge (OR = 0.57 per 10 g/dL increase; <i>P</i> = 0.04)
Wartenberg et al. (2006) [56]	Retrospective review of prospective database, single center. <i>N</i> = 576	Anemia (Hb < 9 g/dl treated with RBCT; 36% of cohort)	Not reported No RBCT protocol	Logistic regression (Hunt-Hess, age, cerebral infarction, re-bleeding, and aneurysm size > 10 mm)	Anemia associated with worse 3-month outcome (OR 1.8, 95% CI 1.1–2.9, <i>P</i> = 0.02)

CI, confidence interval; Hb, hemoglobin; Hct, hematocrit; RBCT, red blood cell transfusion; SIRS, systemic inflammatory response score; WFNS, world federation of neurological surgeons score

Publications by Naidech et al. (2006, 2007) and Wartenberg et al. (2006) [30, 31, 56] contain many of the same patients recruited at the same single center

**Table 3** Summary of published literature that examines the clinical effects of RBCT in SAH

References	Designs	Mean pre-RBCT Hb or Hct	Analysis	Main outcome
Levine et al. (2010) [57]	Retrospective review of prospective database  N = 421 Hb < 10 g/dL threshold for RBCT. 214 (50.8%) received RBCT	Not reported  Mean admission Hb 13.8 g/dL no RBCT and 13.1 g/dL RBCT	Logistic regression: age, admission clinical grade and Hb, average ICU Hb, symptomatic vasospasm and other admission variables associated with outcome	RBCT associated with medical complications (OR, 1.8; 95% CI, 1.1–3.0), major medical  Complications (OR, 2.1; 95% CI, 1.2–3.7), any infection (OR, 2.8; 95% CI, 1.7–4.5), pneumonia (OR, 2.6; 95% CI, 1.5–4.7), septicemia (OR, 2.9; 95% CI, 1.2–6.8), and need for mechanical ventilation (OR, 2.8; 95% CI, 1.5–5.1)
Naidech et al. (2010) [58]	Randomized, single-blinded, single-center study  N = 44 (high-risk for spasm) Goal Hb 10 (N = 23) or 11.5 (N = 21) mg/dL	9.5 g/dL (goal 10 g/dL)	Intention to treat analysis	Number infarcts on imaging, NIHSS at 14 days, modified Rankin score at 14 and 28 days similar but all favored higher Hb  Safety end points same  3 Protocol violations
Kramer et al. (2008) [29]	Retrospective, single-center study  N = 245 Anemia (nadir Hb < 10 g/dL) RBCT (35%)	9.5 g/dL  No RBCT protocol	Logistic regression:  WFNS score, age, vasospasm, modified Fisher score	Nadir Hb < 10 mg/dL (OR 2.7, 95% CI 1.5–5) and RBCT (OR 4.8, 95% CI 2.5–9.1) associated with death, disability and delayed infarct  Only RBCT associated with outcome if both anemia and RBCT in model (OR, 4.3; 95% CI 1.,5–9.3)  RBCT associated with nosocomial infection (OR, 3.2; 95% CI, 1.7–5.5)
Broessner et al. (2009) [59]	Observational cohort, single-center study  N = 292 27% Received RBCT No protocol described	First measured Hb 13.2 g/dL At time of RBCT, 60% with Hb 8-9 g/dL and 27% 7–8 g/dL	Logistic regression: age, Hunt and Hess grade, length of stay, surgery or coil, sex, and aneurysm	Transfusion not associated with ICU mortality or long-term outcome
Springer et al. (2009) [60]	Prospective, single-center study  N = 232 alive at 3 months Number of RBCT not reported	Not reported	Logistic regression age, education, and race/ethnicity	27% with cognitive impairment at 3 months; associated with anemia (Hb < 9 g/dL) and RBCT (OR, 3.4; 95% CI, 1.4–9.6)
Kramer et al. (2009) [55]	Retrospective, single-center study  N = 245 Daily nadir Hb over 2 weeks	9.5 g/dL  No RBCT protocol	Generalized estimating equation to account for correlated data (WFNS score, age, vasospasm, and modified Fisher score)	Hb and decline in Hb over time predict poor outcome  Association between Hb and outcome stronger among poor-grade patients RBCT in 72% of patients with vasospasm versus 25% without vasospasm



Table 3 continued

References	Designs	Mean pre-RBCT Hb or Hct	Hb or Analysis	Main outcome
Tseng et al. (2008) [61]	Post hoc analysis of 2, single-center RCTs N = 160	Not reported	Logistic regression (age, WFNS, IVH, postoperative deficits, sepsis, and DIDs)	RBCT associated with poor outcome at discharge (OR 4.5, $P = 0.04$ ) but not at 6 months
Smith et al. (2004) [62]	Exposure not reported Retrospective review of prospective database from single center	Intraoperative RBCT: 39.6% Postoperative RBCT: 32.0%	Logistic regression (smoking history, Hunt and Hess, Fisher, intraoperative aneurysm rupture, and delay to surgery)	More colloid use predicted lower Hct and need for RBCT Intraoperative RBCT associated with poor 6-month outcome (OR 2.4, 95% CI 1.3–4.5)
	N = 441 RBCT (61%)	No RBCT protocol		Postoperative RBCT associated with angiographic vasospasm (OR 1.7, 95% CI 1.0–2.8)

CI, confidence interval; DID, delayed ischemic deficit; Hb, hemoglobin; Hct, hematocrit; ICU, intensive care unit; NIHSS, national institutes of health stroke scale; OR, odds ratio; RBCT, red blood cell transfusion; RCT, randomized clinical trial; WFNS, world federation of neurological surgeons score

Experimental evidence links anemia with reduced PbtO<sub>2</sub> and increased neuron injury after acute brain injury [69–71]. In the normal brain, compensatory vasodilation occurs with Hb < 10 g/dL [72], so brain hypoxia usually is manifest only at lower Hb levels (e.g., <6 g/dL) [73]. When cerebrovascular reserve is impaired, e.g., in patients with SAH, tissue hypoxia and cell injury may develop at a higher Hb. For example, using cerebral microdialysis in 20 poor-grade SAH patients, Hb ≤ 9 g/dL was identified as an independent factor associated with cerebral tissue injury [53]. In a similar study in which patients requiring FiO<sub>2</sub> > 60% were excluded, Kurtz et al. linked Hb < 10 g/dL with cell energy dysfunction [54]. Consistent with this, mathematical modeling based on animal experiments of brain ischemia suggests that Hb < 10 g/dL is associated with brain hypoxia [71].

Correction of anemia with RBCT may, therefore, improve PbtO<sub>2</sub> and attenuate cell damage. In SAH patients, anemia can be associated with poor outcome, and avoidance of low Hb may, therefore, be warranted [56]. The optimal Hb threshold for RBCT in SAH patients remains unclear although a recent clinical study suggests that Hb > 11 g/dL is associated with less cerebral infarction and improved outcome after SAH [30].

#### RBCT in General Medical and Surgical Critical Care

In most cases, RBCT is used in critical care for the treatment of anemia [74, 75], with a commonly used Hb cutoff of 10 g/dL to augment oxygen delivery and avoid oxygen debt [76]. This practice is now challenged by evidence that suggests RBCT may exacerbate outcome and increase medical complications in general critical care [32–34]. Consequently, a restrictive RBCT policy (Hb ~ 7 g/dl) may be preferred.

In general critical care patients, RBCT is associated with complications such as immunosuppression, transmission of infectious agents, postoperative infections, and pneumonia [77–83]. RBCT also is an independent risk factor for impaired pulmonary function and prolonged ventilator support, acute lung injury, acute respiratory distress syndrome (ARDS) [84, 85], systemic inflammatory response syndrome [83, 86], renal dysfunction [87], multiple organ failure or dysfunction [34, 88, 89], transfusion reactions [39], and increased length of stay [33]. In SAH patients, RBCT has also been associated with medical complications and infection [29, 57].

Recent observational data suggest that many intensive care patients can tolerate Hb of 7 g/dL, “restrictive” RBCT is safe, or that RBCT may exacerbate outcome or increase complications [35, 74, 80, 89]. These studies, however, included few if any patients with neurological disorders or SAH. There is a dose effect, but as little as one unit of

**Table 4** Summary of published literature that examines EPO and SAH

References	Designs	Main outcome
Tseng et al. (2010) [63]	Post hoc analysis of randomized clinical trial	Younger patients (<60 years old) and patients without sepsis benefit from EPO by a reduction in vasospasm, impaired autoregulation, and unfavorable outcome at discharge
	EPO (30,000 U) or placebo every 48 h for a total of 90,000 U <i>N</i> = 80	Statins may potentiate EPO effect
Tseng et al. (2009) [64]	Single-center, randomized clinical trial	Fewer patients taking EPO had RBCT (4 EPO vs. 12 placebo, Fisher exact <i>P</i> = 0.048)
	EPO (30,000 U) or placebo every 48 h for a total of 90,000 U	EPO group was older Decreased incidence of severe vasospasm from 27.5 to 7.5% ( <i>P</i> = 0.037), reduced DIDs with new cerebral infarcts from 40.0 to 7.5% ( <i>P</i> = 0.001)
	RBCT when Hb < 8 g/dL	Shortened duration of impaired autoregulation (ipsilateral side, <i>P</i> < 0.001)
	<i>N</i> = 80	More favorable outcome at discharge (GOS score, <i>P</i> = 0.039) No difference in 6-month outcome
Springborg et al. (2007) [65]	Single-center, randomized clinical trial	Trial terminated early
	EPO (500 IU/kg/day for three days) or Placebo <i>N</i> = 73	No differences in any end points
Springborg et al. (2003) [66]	Prospective, single-center study 83 corresponding serum and CSF samples <i>N</i> = 18	CSF/serum ratio suggests that EPO in the CSF of SAH patients originates mainly from central nervous system

CSF, cerebrospinal fluid; DID, delayed ischemic deficit; EPO, erythropoietin; GOS, glasgow outcome scale; RBCT, red blood cell transfusion; SAH, subarachnoid hemorrhage

blood may be deleterious [90]. Two randomized trials, one in adults [32] and one in children [91], have addressed RBCT in critical care. The Transfusion Requirements in Critical Care Trial (TRICC) compared a “liberal (10 g/dL)” and “restricted (7 g/dL)” RBCT trigger in 838 ICU patients [32]. Overall 30-day mortality was similar, with lower mortality in the restrictive RBCT group among younger (<55 years) and less ill (APACHE II < 20) patients. Concern remains, however, that restrictive RBCT may not be tolerated in patients with some conditions, e.g., reduced cerebrovascular or cardiac reserve. Consequently, patients with ARDS, sepsis, myocardial ischemia, or traumatic brain injury may require higher Hb levels [92–94]. For example, there may be a benefit to liberal RBCT in elderly patients, with acute coronary syndrome and admission Hb < 8 g/dL [93, 94]. The CRUSADE initiative data from 44,242 patients with non-ST segment elevation acute coronary syndrome suggest that the association between RBCT and outcomes was a function of nadir hematocrit [95]. RBCT tended to have a beneficial impact with hematocrit < 25%, with increased mortality when nadir hematocrit was > 27%. Conversely, liberal RBCT does not appear to benefit patients who require prolonged mechanical

ventilation, where theoretically the oxygen carrying benefit of RBCT might hasten recovery [96, 97]. Together, these various data suggest the effect of RBCT on outcome may depend on the need for oxygen delivery and on the individual patient and his or her pathology.

#### RBCT in SAH

Retrospective studies report that about one-quarter of patients with SAH receive RBCT during surgery and up to two-thirds during their intensive care stay [31, 98–100]. The first RBCT during intensive care is generally administered a mean of 4.6 days after SAH [31], i.e., just as vasospasm becomes maximal.

There are good theoretical reasons to maintain a higher Hb after brain injury, since the brain has stringent O<sub>2</sub> requirements. Most neurosurgeons prefer Hb > 10 g/dL for patients with acute brain injury to maintain optimal oxygen carrying capacity; however, there is variability in the response of brain tissue O<sub>2</sub> (PbtO<sub>2</sub>) to RBCT [44]. Even when RBCT improves PbtO<sub>2</sub>, it is unclear whether this improves brain metabolism [47]. Few studies have investigated RBCT effects on outcome after brain injury. Subset



analysis of 67 traumatic brain injury patients enrolled in the TRICC trial [101] suggests TBI patients can have a similar RBCT threshold to other intensive care patients, while observational data suggest RBCT is associated with worse outcome in this population [102–104]. Many SAH patients, unlike traumatic injury patients, have associated cardiac dysfunction [105], a relative contraindication to restrictive RBCT suggesting that RBCT in SAH needs specific study. PET studies, for example, show that RBCT can improve  $\text{CaO}_2$  and  $\text{DO}_2$  without a detrimental effect on CBF in SAH patients with anemia [51].

Data evaluating an effect of RBCT in patients with SAH are limited, despite fluid status and oxygenation being critical to patient care. Not all studies demonstrate an association between RBCT and poor outcome after SAH [59, 61]. However, recent observational studies and post hoc analysis of other trials link liberal use of RBCT with medical complications, infection, vasospasm, poor cognitive performance, and poor outcome [29, 44, 55–57, 60, 68]. It is conceivable that avoiding hypoxia, rather than anemia alone, may prevent neuron damage [106]. RBCT, however, does not always increase  $\text{PbtO}_2$ , and in 20–25% of patients,  $\text{PbtO}_2$  may decrease [44, 46]. A plausible biologic explanation for the deleterious effects of RBCT is that stored red blood cells have been associated with immunomodulation, impaired vasoregulation, hypercoagulation, altered nitric oxide metabolism, reduced red blood cell deformability, altered red blood cell adhesiveness and aggregability, reduced 2,3-diphosphoglycerate, and impaired microvascular perfusion [36–39]. Some of these factors appear integral to vasospasm [21, 107, 108].

#### Clinical Management Strategies for Anemia in SAH

A recent international survey queried intensive care physicians about SAH care [109]. Among the 626 respondents, recommendations for optimal Hb ranged from  $\sim 8$  g/dL (25%) to  $\sim 12$ – $13$  g/dL (40%). Two-thirds advocated a target Hb  $> 10$  g/dL. There is also widespread variation in the use of RBCT in treating SAH patients, although practices differ from those used in general surgical and medical conditions [110]. Discrepancies identified in clinical practice highlight the need for more research to specifically identify the role of anemia and anemia management in patients with SAH. In addition, there remain many unanswered questions about transfusion after SAH including the role of the following: (1) plasma and platelet component therapies, (2) leukocyte reduction, (3) age of transfused cells, (4) blood product substitutes, and (5) the clinical or biological end point for RBCT. There has been limited study of erythropoietin use, and no firm recommendations about its use can be made.

#### Conclusions

Anemia develops in about 50% of SAH patients and often within 3 days of aneurysm rupture. Risk factors for anemia after SAH include female sex, advanced age, worse clinical grade, lower admission Hb, and surgery. Anemia has also been identified as a risk factor for poor outcome after SAH. It is not clear whether anemia is an independent factor associated with outcome or a marker of disease severity. However, patients in worse clinical grade or those who develop vasospasm are more likely to have a worse outcome if they develop anemia.

There is limited information about how often SAH patients require RBCT, but recent retrospective studies demonstrate that about one-quarter receive RBCT during surgery and up to two-thirds during their intensive care stay. Physiological studies show increases in brain oxygen in 75% of transfusions and increases of brain  $\text{DO}_2$ . RBCT, however, have been associated with vasospasm, medical complications, infections, worse outcome, and cognitive impairment. When both anemia and RBCT are entered into outcome models, transfusion has a greater effect. Again, it is not clear whether RBCT is a marker of disease severity or an independent risk factor for worse outcome. While the overall quality of literature that examines transfusion in SAH is low, it is clear that the results of the TRICC trial and subsequent observational studies of transfusion in general critical care do not and should not apply to SAH patients. For now, clinicians will need to base transfusion decisions for SAH patients in the context of conflicting information and so should focus on an individualized assessment of anemia tolerance, consider blood conservation strategies, and understand the potential risks and benefits of blood transfusion. Further prospective investigations to address the role of anemia, the optimal Hb threshold, and the use of RBCT in SAH are desperately needed.

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