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Anemia and red blood cell transfusion in neurocritical careAndreas H Kramer¹ and David A Zygun²¹Departments of Critical Care Medicine & Clinical Neurosciences, University of Calgary, Foothills Medical Center, 1403 29thSt. N.W., Calgary, AB, Canada, T2N 2T9²Departments of Critical Care Medicine, Clinical Neurosciences, & Community Health Sciences, University of Calgary, Foothills Medical Center, 1403 29thSt. N.W., Calgary, AB, Canada, T2N 2T9Corresponding author: Andreas H Kramer, andreas.kramer@albertahealthservices.ca

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This is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**Abstract**

Introduction Anemia is one of the most common medical complications to be encountered in critically ill patients. Based on the results of clinical trials, transfusion practices across the world have generally become more restrictive. However, because reduced oxygen delivery contributes to 'secondary' cerebral injury, anemia may not be as well tolerated among neurocritical care patients.

Methods The first portion of this paper is a narrative review of the physiologic implications of anemia, hemodilution, and transfusion in the setting of brain-injury and stroke. The second portion is a systematic review to identify studies assessing the association between anemia or the use of red blood cell transfusions and relevant clinical outcomes in various neurocritical care populations.

Results There have been no randomized controlled trials that have adequately assessed optimal transfusion thresholds specifically among brain-injured patients. The importance of

ischemia and the implications of anemia are not necessarily the same for all neurocritical care conditions. Nevertheless, there exists an extensive body of experimental work, as well as human observational and physiologic studies, which have advanced knowledge in this area and provide some guidance to clinicians. Lower hemoglobin concentrations are consistently associated with worse physiologic parameters and clinical outcomes; however, this relationship may not be altered by more aggressive use of red blood cell transfusions.

Conclusions Although hemoglobin concentrations as low as 7 g/dl are well tolerated in most critical care patients, such a severe degree of anemia could be harmful in brain-injured patients. Randomized controlled trials of different transfusion thresholds, specifically in neurocritical care settings, are required. The impact of the duration of blood storage on the neurologic implications of transfusion also requires further investigation.

Introduction

A key paradigm in the management of neurocritical care patients is the avoidance of 'secondary' cerebral insults [1-3]. The acutely injured brain is vulnerable to systemic derangements, such as hypotension, hypoxemia, or fever, which may further exacerbate neuronal damage [4-7]. Thus, critical care practitioners attempt to maintain a physiologic milieu that minimizes secondary injury, thereby maximizing the chance of a favorable functional and neurocognitive recovery.

Anemia is defined by the World Health Organization as a hemoglobin (Hb) concentration less than 12 g/dl in women and 13 g/dl in men [8]. It is one of the most common medical complications encountered in critically ill patients, including those with neurologic disorders. About two-thirds of patients have Hb concentrations less than 12 g/dl at the time of intensive care unit (ICU) admission, with a subsequent decrement of about 0.5 g/dl per day [9-12]. The etiology of ICU-acquired anemia is multifactorial. Systemic inflammation reduces red

CBF: cerebral blood flow; C_aO_2 : arterial oxygen content; $CMRO_2$: cerebral metabolic rate; CO: cardiac output; CO_2 : carbon dioxide; CPP: cerebral perfusion pressure; DO_2 : oxygen delivery; Hb: hemoglobin; HBBS: hemoglobin-based blood substitutes; ICH: intracerebral hemorrhage; ICU: intensive care unit; LPR: lactate to pyruvate ratio; MRI: magnetic resonance imaging; NO: nitric oxide; O_2 : oxygen; OEF: oxygen extraction fraction; $P_{bt}O_2$: brain tissue oxygen tension; PCO_2 : partial pressure of carbon dioxide; PET: positron emission tomography; PO_2 : partial pressure of oxygen; RBC: red blood cell; RCT: randomized controlled trial; SAH: subarachnoid hemorrhage; SO_2 : oxygen saturation; $S_{jv}O_2$: jugular venous oxygen saturation; TBI: traumatic brain injury.

blood cell (RBC) development by blunting the production of erythropoietin and interfering with the ability of erythroblasts to incorporate iron [13-17]. RBC loss is accelerated by frequent phlebotomy, reduced RBC survival, and occasional hemorrhage. Large volumes of fluid used during resuscitation, with resultant hemodilution, may also contribute to early reductions in Hb levels [18-22].

Anemia can easily be corrected with the use of allogeneic RBC transfusions. The proportion of patients receiving blood during their ICU stay varies from 20 to 44%, and those who are transfused receive an average of as many as five units [10,11,23,24]. However, two multi-center, randomized controlled trials (RCTs) and two large observational studies have shown the liberal use of blood transfusions, with the goal of maintaining relatively arbitrary Hb concentrations (e.g. 10 g/dl), to not only be ineffective at improving outcomes, but also potentially harmful [10,11,25,26]. Still, because impaired oxygen (O₂) delivery is thought to be an important factor in secondary brain injury, it remains uncertain whether these findings can be broadly applied to neurocritical care patients. Accordingly, it remains common practice for clinicians to set target Hb levels at a minimum of 9 to 10 g/dl in this setting [27-29].

Materials and methods

To describe the physiologic and clinical implications of anemia and transfusion in neurocritical care patients, we used the OVID interface to search MEDLINE from its inception until March 9, 2009. We combined the following MESH headings: (anemia OR blood transfusion OR hemodilution OR hematocrit OR hemoglobins) AND (stroke OR craniocerebral trauma OR subarachnoid hemorrhage OR cerebral hemorrhage OR cerebrovascular circulation OR cardiac surgical procedures OR coronary artery bypass). This search yielded 2137 English language publications dealing primarily with adults (>18 years old). Each abstract was reviewed, and both human and animal studies assessing the impact of anemia, hemodilution, or the use of RBC transfusions on a physiologic or clinical outcome were chosen for more detailed review. Relevant review articles and case reports were also included, and the references of selected papers were screened for additional publications. Clinical studies involving specific groups of neurocritical care patients were selected for inclusion in evidentiary tables.

Results and discussion

Physiologic implications of anemia

Cerebral blood flow and oxygen delivery

The amount of oxygen reaching specific organs is the product of local blood flow and the arterial oxygen content (C_aO₂). The latter is dependent on the Hb concentration and the degree to which it is saturated with O₂ (S_aO₂), with a small amount of O₂ also dissolved in blood. Thus, global systemic O₂ delivery can be expressed by the following equation:

$$DO_2(\text{ml O}_2 / \text{min}) = \text{cardiac output}(\text{L} / \text{min}) \times (\text{Hb}(\text{g} / \text{L}) \times (\text{S}_a\text{O}_2(\%) \times 1.39(\text{ml O}_2 / \text{g Hb})) + (0.003 \times \text{PO}_2))$$

O₂ delivery to the brain can be conceptualized using the same equation, but by substituting cerebral blood flow (CBF) for cardiac output (CO). Flow through the cerebral vasculature is determined by the cerebral perfusion pressure (CPP), the length and caliber of the vessels, and the viscosity of blood, as described by the Hagen-Poiseuille equation:

$$\text{Flow} = (\pi r^4 \Delta P) / 8 \eta L (\text{where } r = \text{radius}, P = \text{pressure}, L = \text{length}, \text{ and } \eta = \text{viscosity})$$

Regulation of CBF and cerebral O₂ delivery in response to physiologic stressors is achieved largely by homeostatic variations in the caliber of cerebral vessels (the 'r' in the above equation; Figure 1).

CPP is the difference between mean arterial pressure and cerebral venous pressure; intracranial pressure is widely used as a surrogate for the latter. The response of the cerebral vasculature to changes in CPP is referred to as CBF autoregulation ('pressure-reactivity'). Cerebral arterioles vasoconstrict in response to raised CPP and vasodilate when there are reductions, thereby maintaining constant CBF (Figure 1a). Autoregulation is sometimes impaired in neurocritical care patients, such that CBF becomes directly dependent on CPP, making the brain more vulnerable to both hypo- and hyperperfusion [30-32].

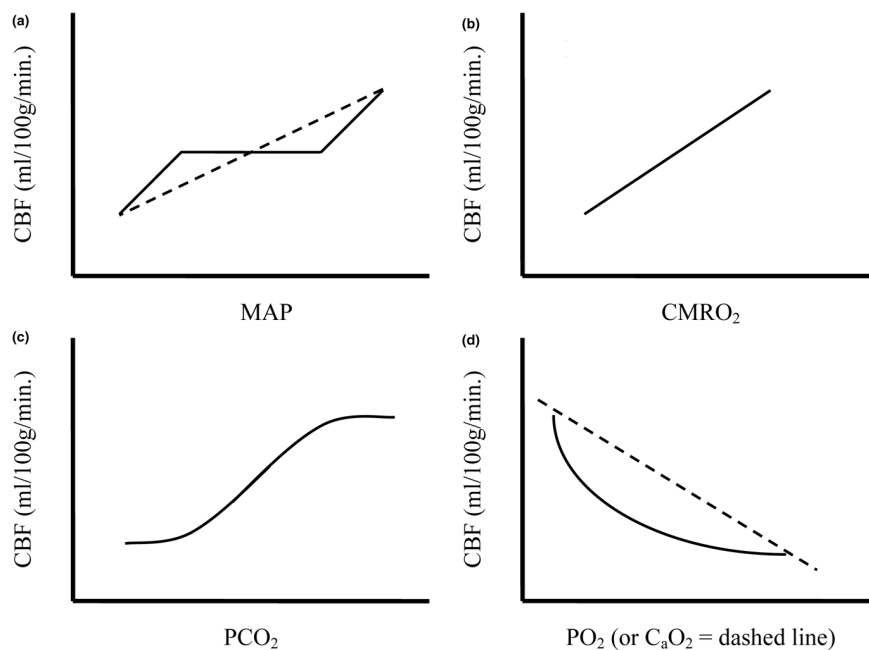
There are numerous other stimuli that may modify cerebral vascular resistance and CBF. Both global and regional CBF are tightly coupled to metabolism. Thus, physiologic changes that lead to a reduction in cerebral metabolic rate (CMRO₂) (e.g. hypothermia or sedation) will also proportionally reduce CBF (Figure 1b). In addition, CBF is influenced by variations in the partial pressures of carbon dioxide (PCO₂; 'CO₂-reactivity'), and to a lesser degree, O₂ (PO₂) (Figures 1c, d). CBF increases in response to a decrease in PO₂, although this effect is probably minimal until the level approaches 60 mmHg [30].

In response to worsening anemia, neuronal O₂ delivery is initially preserved both by the systemic cardiovascular response and mechanisms that are more specifically neuroprotective.

Cardiovascular response to anemia

A falling Hb concentration is sensed by aortic and carotid chemoreceptors, resulting in stimulation of the sympathetic nervous system, which in turn raises heart rate and contractility, thereby augmenting CO [33-35]. The reduction in blood viscosity results in a corresponding reduction in afterload, as well as enhanced flow through post-capillary venules, greater venous return, and increased preload [36-38]. Thus, stroke volume, CO, and blood pressure (as well as CPP) increase in response to isovolemic anemia. Tissues are further protected from falling O₂ delivery because of their capacity to increase O₂ extraction and maintain constant O₂ consumption. In the brain, irreversible ischemia may not occur until the O₂ extrac-

Figure 1



Physiologic parameters influencing cerebral blood flow (a) The effects of mean arterial blood pressure (MAP) (solid line = normal autoregulation; dashed line = deranged autoregulation), (b) cerebral metabolic rate ($CMRO_2$), (c) partial pressure of carbon dioxide (PCO_2), (d) partial pressure of oxygen (PO_2) and arterial oxygen content (C_aO_2) (solid curved line = PO_2 ; dashed line = C_aO_2) are shown. CBF = cerebral blood flow.

tion fraction (OEF) exceeds 75% [39-43]. Systemic anaerobic metabolism does not develop until the Hb concentration falls well below 5 g/dl in otherwise healthy individuals [44]. On the other hand, many neurocritical care patients have concomitant cardiac disease and left ventricular dysfunction which may prevent an appropriate increase in CO in response to sympathetic stimulation. This is commonly the case even in the absence of pre-existing heart disease; for example, among patients with acute 'high-grade' aneurysmal subarachnoid hemorrhage (SAH) (Hunt-Hess grades 3 to 5), more than one-third have regional left ventricular wall motion abnormalities detectable by echocardiography [45].

Cerebrovascular response to anemia

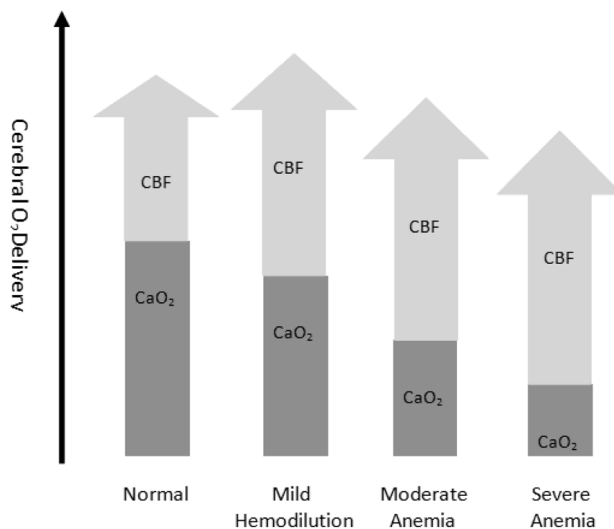
Apart from the increased flow produced by higher CPP and lower blood viscosity, anemia also induces cerebral vasodilatation [46-48]. When Hb (and therefore C_aO_2) falls, there appears to be a disproportionate increase in CBF in relation to other organs (Figure 1d) [49]. The mechanisms underlying this increase in vessel caliber are still being clarified, but include some of the same factors involved in CBF pressure-autoregulation; these have recently been reviewed in detail [46]. Importantly, anemia results in upregulation of nitric oxide (NO) production by perivascular neurons and vascular smooth muscle surrounding cerebral blood vessels. The importance of these pathways is supported by the observation that inhibition of NO synthase blunts hypoxia- and anemia-induced cerebral

vasodilatation [50-52]. However, additional factors are undoubtedly involved [53-55]. Sympathetic β_2 receptor stimulation is an example of one such mechanism that contributes to vasodilatation and maintenance of CBF [56]. Other biochemical mediators that are upregulated in the brain in response to anemia include vascular endothelial growth factor, hypoxia inducible factor 1α , and erythropoietin [46,57]. Although it seems likely that these mediators are neuroprotective, it remains possible that they could also have harmful pathophysiologic effects [46].

Compensatory mechanisms eventually fail

As anemia worsens, the resultant increases in CBF and OEF eventually become insufficient to overcome the reduced C_aO_2 produced by a low Hb concentration (Figure 2). The point at which this threshold is reached is not clear and probably varies somewhat between patients. A sophisticated mathematical model based on animal data suggested that $CMRO_2$ is well preserved in normal brain, even with severe reductions in Hb concentration. In contrast, penumbral brain appears to be much more vulnerable, with O_2 delivery and $CMRO_2$ progressively declining as Hb falls below 10 to 12 g/dl [58-62]. As with cerebral ischemia, impairment of the usual protective mechanisms induced by anemia has also been demonstrated as a result of brain trauma [63].

Figure 2



Effects of falling hemoglobin concentration on cerebral oxygen delivery. With mild hemodilution, it is theoretically possible that the resultant increase in cerebral blood flow (CBF) can raise overall O_2 delivery. However, with further decrements in hemoglobin, the increment in CBF is insufficient to overcome the reduction in arterial oxygen content (C_aO_2).

A study of euvoletic hemodilution in healthy human volunteers confirmed that even profound anemia (Hb about 5 g/dl) was relatively well tolerated; however, subtle abnormalities in neurocognitive testing began to emerge when Hb concentrations fell below 7 g/dl [64,65]. The co-existence of other physiologic stressors may also make anemia less tolerable; for example, experimental studies have found that cerebral O_2 delivery is preserved in the presence of both severe anemia and hypotension individually, but not when they are both present [66,67]. Additionally, anemia-induced cerebral vasodilatation appears to interfere with the usual response to variations in PCO_2 [47,68-70]. These observations raise concerns that relatively inadequate O_2 delivery could occur at Hb levels well above 7 g/dl in critical care patients with cerebrovascular disease, pre-existing central nervous system pathology (e.g. an ischemic or 'traumatic' penumbra) or deranged regulation of CBF. Thus, there is strong physiologic rationale for believing that a restrictive transfusion threshold of 7 g/dl, although clearly safe in many critical care patients [25,26], may not be without risk in neurocritical care patients.

Risks of red blood cell transfusion

Even if anemia is harmful, this does not necessarily prove that liberal use of allogeneic RBCs to normalize Hb concentrations is justified. Emerging data indicates that stored blood has important differences from patients' own blood. A number of changes occur over time as RBCs are being stored; some of these alterations could have important implications after transfusion, and they are collectively referred to as the 'storage lesion'. Biochemical changes include reductions in ATP, loss of membrane phospholipids, and oxidative damage to proteins. The consequence is a gradual change in RBC appear-

ance from the usual biconcave discs to irreversibly deformed and stellate-shaped spherocytocytes [71,72]. Loss of RBC membrane function, as well as an increased tendency to adhere to endothelium, may interfere with microcirculatory flow [72,73]. RBC 2-3-diphosphoglycerate levels become depleted to the point of being essentially undetectable after one week of storage. Although levels are usually restored within 24 to 72 hours after transfusion, the transiently increased binding affinity of Hb interferes with the release of O_2 for use by tissues [74].

Thus, although blood transfusions are generally given with the intention of raising O_2 delivery, the storage-induced changes may prevent RBCs from achieving their intended purpose. For example, studies using gastric tonometry parameters as a surrogate for mesenteric perfusion have not shown improvements following transfusion [75,76]. Similarly, RBCs also appear to have little effect on skeletal muscle O_2 tension in postoperative patients or on global O_2 consumption in the critically ill [77,78].

Transfusion-related acute lung injury is now the most common cause of transfusion-related mortality reported to the Food and Drugs Administration [79]. Transfusion may have immunosuppressive effects, which are thought to be due to concomitant white blood cell transmission. Several studies have suggested a link between the use of allogeneic RBCs and both nosocomial infections and acute respiratory distress syndrome [80-83]. Alternatively, RCTs, where well-matched groups were transfused with differing intensities, have not yet convincingly confirmed these associations [25,26]. Furthermore, the risk of

complications may be less since the implementation of universal leukoreduction in many jurisdictions [84].

It has been suggested that the use of fresher blood might further minimize the risks of transfusion, while also maximizing their physiologic effect. Results have been conflicting, and there is little data specifically in neurocritical care patients [71,75,76]. A recent animal study found fresh blood to be more effective at raising brain tissue oxygen tension ($P_{bt}O_2$) and preserving CBF in comparison to stored blood [85]. Alternatively, Weiskopf and colleagues performed isovolemic hemodilution to Hb concentrations of 55 to 74 g/L in healthy volunteers and then transfused them with autologous blood stored for either less than five hours or more than 14 days; neurocognitive test performance did not differ between the two groups [86].

Anemia and RBC transfusion in specific neurocritical care settings

The importance of ischemia in causing secondary brain injury appears to vary for different neurocritical care conditions. For example, cerebral vasospasm and delayed infarction are major causes of neurologic deterioration in the two weeks following a ruptured cerebral aneurysm [87,88]. In contrast, the frequency and relevance of cerebral ischemia in the pathophysiology of traumatic brain injury (TBI) or intracerebral hemorrhage (ICH) continue to be debated [40,89-91]. Accordingly, the significance of anemia and optimal transfusion thresholds may not be consistent from one condition to the next.

Lessons from cardiac surgery

A great deal of what is known about the neurologic effects of anemia has been reported in the cardiac surgical literature. A substantial proportion of patients undergoing cardiac surgery receive blood transfusions, even though large volume hemorrhage is comparatively less common [92]. Perioperative stroke occurs in 1 to 6% of patients and is strongly associated with greater morbidity and mortality [93,94]. An even larger proportion ($\geq 50\%$) develops at least transient neurocognitive dysfunction that is likely to be, at least in part, due to cerebral ischemia [95,96]. Thus, the prevention and treatment of cerebral ischemia is of major concern in the perioperative period.

We identified 12 studies assessing the association between perioperative Hb concentrations and subsequent neurologic complications (Table 1). When defined as an Hb concentration less than 12.5 g/dl, about one-quarter of patients are anemic preoperatively [97]. Blood loss and hemodilution during cardiopulmonary bypass usually lead to nadir intraoperative Hb concentrations of 7.0 to 8.5 g/dl; levels at ICU admission are typically 8.5 to 9.5 g/dl [98]. Several, but not all, studies have suggested that the degree of Hb reduction is an independent predictor of stroke, delirium, neurocognitive dysfunction, and other adverse outcomes [97-108] (Table 1).

Although it has not been proven with certainty that these relations are causative, it seems prudent to avoid major reductions in Hb as best as possible with relevant blood-conservation strategies [109-113].

A recent RCT involving 121 elderly patients undergoing coronary artery bypass compared two intraoperative hematocrit targets (15 to 18% vs. $\geq 27\%$) [102]. The study was terminated early because of high complication rates in both groups; however, a greater degree of postoperative neurocognitive dysfunction was observed among patients managed with more extreme hemodilution. In addition, although not necessarily directly applicable to adults, further evidence that excessive hemodilution may have harmful neurologic effects comes from the neonatal literature. Combined data from two RCTs suggested that hematocrit levels below 23.5% during cardiopulmonary bypass were associated with impaired psychomotor development at one year of age [114-116].

Whether using RBC transfusions to maintain higher perioperative Hb levels helps avoid neurologic complications remains uncertain. For example, although Karkouti and colleagues found nadir hematocrit levels during cardiopulmonary bypass to be a predictor of stroke in a multivariable analysis, the same was also true for the perioperative use of transfusions [105]. An association between transfusion and focal or global neurologic deficits has been confirmed in numerous other studies (Table 2) [117-125].

One study compared clinical outcomes, including the risk of perioperative stroke, between 49 Jehovah's Witnesses who underwent cardiac surgery without blood products and a matched control group of 196 patients, in whom RBC transfusions were used. No significant differences were observed; however, only nine patients in total experienced a stroke, such that this study lacked statistical power to detect a difference. The severity of anemia in Jehovah's Witness patients was not reported [123].

In a large, single-center, retrospective study, Koch and colleagues explored whether the association between RBCs and worse outcomes could be related to the duration of blood storage. Outcomes were compared among cardiac surgical patients depending on whether they were transfused with exclusively 'newer' (≤ 14 days old; median 11 days) or 'older' (>14 days old; median 20 days) blood during the perioperative period [126]. In-hospital mortality and postoperative complications, including sepsis, renal failure, and need for mechanical ventilation, were greater among patients receiving older blood. However, there was no significant difference in the incidence of stroke and coma.

In summary, there remains uncertainty concerning optimum Hb levels for neuroprotection of patients undergoing cardiac surgery. Many intensivists routinely employ a postoperative

Table 1

Adult studies assessing the association between anemia and the development of perioperative stroke or cognitive dysfunction among patients undergoing cardiac surgery

| Study | Patients | Design and setting | Multivariable analysis | Exposure | Outcome | Main result |
|--------------------------------|---------------------|---|---|--|---|---|
| Karkouti and colleagues [97] | 10,179 | Retrospective (prospective database) Single-center | Logistic regression | Maximum decrease intraoperative Hb compared with baseline | Composite of in-hospital death, stroke (new persistent postoperative neurologic deficit), or dialysis-dependent renal failure | >50% decrement in Hb independently associated with composite outcome |
| Bell and colleagues [98] | 36,658 (CABG) | Retrospective (prospective database) Multi-center | Logistic regression | Preoperative Hb | Postoperative stroke (not further defined) | No significant association between Hb and stroke |
| Karkouti and colleagues [99] | 3286 (CABG) | Retrospective Multi-center | Logistic regression and propensity scores | Preoperative anemia (Hb <12.5 g/dl) | Postoperative stroke (new neurologic deficit) | - Risk of stroke 1.1% in non-anemic pts vs. 2.8% in anemic patients - Trend towards more stroke among anemic patients in propensity-matched analysis |
| Chang and colleagues [100] | 288 | Retrospective Single-center | Logistic regression | Postoperative Hct <30% | Delirium (<i>DSM-IV</i> criteria) | Postoperative hct <30% associated with development of delirium (OR = 2.2, <i>P</i> = 0.02) |
| Kulier and colleagues [101] | 4804 | Retrospective (prospective database) Multi-center | Logistic regression | Preoperative Hb | 'Cerebral outcomes' = stroke or encephalopathy (not further defined) | - Each 10 g/L Hb reduction associated with 15% increase in risk of non-cardiac (renal or CNS) complications - Association stronger for renal complications |
| Matthew and colleagues [102] | 121 (CABG; age >65) | Prospective RCT Single-center | Logistic regression | Comparison of hemodilution to hct of $\geq 27\%$ vs. 15 to 18% | Six-week postoperative neurocognitive function (battery of 5 tests) | - Trial stopped early because of unusually high rate of complications in both groups - Significant interaction between age and hct; more neurocognitive deficits among older patients with low hct |
| Cladellas and colleagues [103] | 201 (VR) | Retrospective (prospective database) Single-center | None | Preoperative anemia (Hb <12 g/dl) | New permanent stroke or transient ischemic attack (not further defined) | - Risk of TIA or stroke 9.5% in anemic patients vs. 4.4% in non-anemic |
| Giltay and colleagues [104] | 8139 (CABG) | Retrospective Single-center | Logistic regression | Lowest hematocrit first 24 hours ICU | Psychotic symptoms (hallucinations and/or delusions) | Hct <25% associated with psychosis (OR = 2.5 vs. hct >30%, CI 1.2 to 5.3) |

Table 1 (Continued)**Adult studies assessing the association between anemia and the development of perioperative stroke or cognitive dysfunction among patients undergoing cardiac surgery**

| | | | | | | |
|---------------------------------------|-------------|---|---------------------|--------------------------|---|--|
| Karkouti and colleagues [105] | 10,949 | Retrospective (prospective database) Single-center | Logistic regression | Nadir intraoperative hct | Postoperative stroke (new persistent postoperative neurologic deficit) that was present on emergence from anesthesia | Each 1% hct reduction associated with OR = 1.1 for stroke ($P = 0.002$) |
| Habib and colleagues [106] | 5000 | Retrospective (prospective database) Single-center | None | Nadir intraoperative hct | Transient or permanent postoperative stroke (not further defined) | Risk of TIA or stroke 5.4% in quintile with lowest hct vs. 1.3% in quintile with highest hct ($P < 0.001$) |
| DeFoe and colleagues [107] | 6980 (CABG) | Retrospective (prospective database) Multi-center | Logistic regression | Nadir intraoperative hct | Intra- or postoperative stroke (new focal neurologic deficit which appears and is still at least partially evident more than 24 hours after onset; occurs during or following CABG) | No statistically significant association between hct and stroke |
| Van Wermeskerken and colleagues [108] | 2804 (CABG) | Retrospective Single-center | Logistic regression | Nadir intraoperative hct | Adverse neurologic outcomes: stroke, coma, or TIA; verified retrospectively by neurologist | No significant association between hct and outcome |

CABG = coronary artery bypass grafting; CI = confidence interval; CNS = central nervous system; Hb = hemoglobin; hct = hematocrit; ICU = intensive care unit; OR = odds ratio; RCT = randomized controlled trial; TIA = transient ischemic attack; VR = valve replacement

transfusion threshold of 7 g/dl, although this may not be the optimum Hb level for the avoidance of neurologic complications. By necessity, the recommendations of published consensus guidelines are relatively non-specific, and state that it is "not unreasonable to transfuse red cells in certain patients with critical noncardiac end-organ ischemia whose Hb levels are as high as 10 g/dl" [111]. Funding was recently secured in the UK for a multi-center RCT comparing transfusion triggers of 7.5 vs. 9 g/dl [92].

Traumatic brain injury

The majority of patients dying from severe TBI have histologic evidence of ischemic damage [127]. Early global CBF reductions occur in many patients, often to levels that are considered to be in the ischemic range [128,129]. Reductions in both jugular venous O₂ saturation (S_vO₂) and P_{bt}O₂ are not only common, but their frequency and depth are predictive of worse outcomes [130-133]. However, the fall in CBF may be appropriate for a corresponding drop in metabolic rate [134,135]. Recent studies using positron emission tomography (PET) have suggested that although ischemia does occur, it is less common than previously thought. Furthermore, much of the 'metabolic distress' detected by multimodal monitoring

(S_vO₂, P_{bt}O₂, and microdialysis parameters) is not necessarily attributable to classical ischemia [39,134,135].

On the other hand, there appears to be a great deal of regional heterogeneity in CBF and CMRO₂ [136]. Even if the overall ischemic brain volume is relatively small, certain vulnerable regions may still benefit from enhanced O₂ delivery [137]. As with cardiac surgical patients, relatively extreme reductions in Hb are likely to be deleterious. A recent animal model found that although isovolemic hemodilution to Hb concentrations of 5 to 7 g/dl resulted in an overall increase in CBF, it produced larger contusion volumes, more apoptosis, and lower P_{bt}O₂ [138].

Potentially beneficial physiologic effects of transfusion have been shown in four studies of patients with severe TBI [139-142], each of which demonstrated that P_{bt}O₂ increases following the administration of RBCs (Table 3) [139]. However, this increment was inconsistent, relatively small and often of questionable clinical importance. Of concern, in some cases there was even a reduction in P_{bt}O₂. It is possible that some of the variation in the cerebral effects of transfusion could be, in part, attributable to the variable age of transfused blood. Leal-

Table 2**Adult studies assessing the association between transfusion and the development of perioperative stroke or cognitive dysfunction among patients undergoing cardiac surgery**

| Study | Patients | Design and setting | Multivariable analysis | Exposure | Outcome | Main result |
|-------------------------------|---------------------|---|---|--|--|--|
| Brevig and colleagues [117] | 2531 | Retrospective (prospective database) Single-center | None | Any blood product transfusion | Postoperative CVA (not further defined) | Despite reduction in proportion of patients transfused over time (43% in 2003 vs. 18% in 2007), no change in proportion of patients with CVA (0.8 to 1.5%) |
| Ngaage and colleagues [118] | 383 (≥80 years old) | Retrospective (prospective database) Single-center | Logistic regression | Any blood product transfusion | Neurologic complications (confusion/agitation, seizures, TIA, RIND, stroke, or coma) | Transfusion associated with neurologic complications (OR = 3.6 vs. no transfusion, $P = 0.003$) |
| Murphy and colleagues [119] | 8518 | Retrospective Single-center | Logistic regression and propensity scores | Any perioperative RBC transfusion | Composite of MI, stroke (permanent or transient), or renal failure | RBC transfusion was associated with composite outcome (OR = 3.35 for transfusion vs. no transfusion; $P < 0.0001$) |
| Whitson and colleagues [120] | 2691 | Retrospective (prospective database) Single-center | Logistic regression | Any RBC transfusion | CVA (not further defined) | RBC transfusion was associated with CVA (OR = 1.7, $P = 0.01$) |
| Norkiene and colleagues [121] | 1367 | Retrospective Single-center | Logistic regression | Any RBC transfusion | Delirium (<i>DSM-IV</i> criteria) | Postoperative RBC transfusion was associated with delirium (OR = 4.6, $P < 0.001$) |
| Koch and colleagues [122] | 11,963 (CABG) | Retrospective (prospective database) Single-center | Logistic regression | Total number of units of RBCs transfused | Focal or global neurologic deficits or death without awakening | RBC transfusion was associated with stroke (OR = 1.73 for each unit RBCs; $P < 0.0001$) |
| Stamou and colleagues [123] | 49 JW patients | Retrospective Single-center | 196 controls Logistic regression and propensity scores | Any RBC transfusion Nadir Hb not reported | Perioperative stroke | No statistically significant difference in risk of stroke between JWs refusing RBCs and transfused control patients |
| Karkouti and colleagues [105] | 10,949 | Retrospective (prospective database) Single-center | Logistic regression | Total number of units of blood product | New perioperative persistent postoperative neurological deficit | Transfusion was associated with stroke (OR = 1.02 for each unit RBCs; $P = 0.01$) |
| Bucerius and colleagues [124] | 16,184 | Retrospective (prospective database) Single-center | Logistic regression | Any perioperative RBC transfusion | Temporary or permanent focal or global neurologic deficit | 'High transfusion requirement' (≥1000 ml) was associated with stroke (OR = 6.04; $P < 0.0001$) |

Table 2 (Continued)

Adult studies assessing the association between transfusion and the development of perioperative stroke or cognitive dysfunction among patients undergoing cardiac surgery

| | | | | | | |
|-------------------------------|-------------|---|---------------------|-------------------------------|--|---|
| D'Ancona and colleagues [125] | 9916 (CABG) | Retrospective (prospective database) Single-center | Logistic regression | Any blood product transfusion | New temporary or permanent, focal or global neurologic deficit | Transfusion was associated with stroke (OR = 1.59 vs. no transfusion; $P = 0.002$) |
|-------------------------------|-------------|---|---------------------|-------------------------------|--|---|

CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; Hb = hemoglobin; JW = Jehovah's Witness; MI = myocardial infarction; OR = odds ratio; RBC = red blood cell; RIND = reversible ischemic neurologic deficit; TIA = transient ischemic attack.

Noval and colleagues recently found that only those patients having received RBCs less than 14 days old had a statistically significant improvement in $P_{bt}O_2$ one hour after transfusion [141]. Although these results are intriguing, they are too premature to influence clinical practice and require confirmation in larger studies. Just because $P_{bt}O_2$ rises, does not necessarily mean that $CMRO_2$ has increased. On the contrary, Zygun and colleagues found no improvement in cerebral lactate to pyruvate ratio (LPR – a marker of ischemia and 'metabolic distress') in response to transfusion, despite an increment in $P_{bt}O_2$ [142].

In a retrospective study of 169 patients with TBI, Carlson and colleagues found nadir hematocrit levels to be associated with a worse Glasgow Outcome Scale at hospital discharge. However, the association between RBC transfusion and poor outcome was even stronger [143]. Other observational studies have reached similar conclusions (Table 4) [144-151]. Unfortunately, there are no large RCTs to guide practice at this time. The TRICC trial enrolled only 67 patients with severe TBI [150]. Although no statistically significant benefit from a liberal transfusion strategy was observed, this subgroup was too small to reach meaningful conclusions. Thus, the optimal use of RBCs in patients with severe TBI remains unclear. A recent survey found that practice across the USA is variable, and that the majority of clinicians believe a threshold of 7 g/dl to be too restrictive, especially in the presence of intracranial hypertension [27].

Subarachnoid hemorrhage

Narrowing of the cerebral vasculature (angiographic vasospasm) complicates about two-thirds of cases of SAH. Vasospasm most often emerges between days 3 and 14 after SAH and is the most important cause of secondary brain injury [87]. Evidence of cerebral infarction that was not present initially is observed in as many as 50 to 70% of survivors using magnetic resonance imaging (MRI) [152,153]. Unlike other forms of stroke, the predictable risk of vasospasm and cerebral ischemia provides a unique opportunity for the provision of neuroprotection prior to the insult.

Three studies have assessed the association between daily Hb concentrations and eventual neurologic outcome [154-156]. Each of these demonstrated that patients with an unfavorable outcome consistently have lower Hb levels throughout

much of the first two weeks in hospital (Table 5). The degree of decrement in Hb levels over time was also highly predictive of outcome [154]. Despite the use of multivariable analyses, there were numerous potentially confounding variables that could not be adjusted for. For example, patients who are 'sicker' tend to have more blood drawn for laboratory tests, have more invasive procedures performed, and tend to receive more intravenous fluids, all of which could contribute to lower Hb concentrations. Thus, the association between lower Hb and poor outcome has not conclusively been proven to be causative.

As in other settings, several studies have also shown a strong association between transfusion and unfavorable outcomes following SAH (Table 5) [28,157-160]. One unconfirmed report suggested that the use of RBCs could contribute to the development of cerebral vasospasm, perhaps by promoting inflammation or depleting endogenous NO supplies [160]. A recent observational study found no difference in complications based on the transfusion of older (>21 days) compared with newer (≤ 21 days) units of blood, although this assessment was based on only 85 transfused patients [28].

Hemodilution, together with hypervolemia and hypertension, has been used as part of 'triple H therapy', a therapeutic strategy to improve CBF in patients with vasospasm [161]. One study used $^{133}\text{Xenon}$ injections to assess global CBF in eight patients with SAH. As expected, isovolemic hemodilution from a mean Hb of 11.9 to 9.2 g/dl produced an increase in global CBF and a reduction in cerebral vascular resistance. However, the increase in CBF was not sufficient to overcome the reduction in C_aO_2 , such that global O_2 delivery fell and ischemic brain volume actually increased [162]. Complimentary findings were subsequently reported by Muench and colleagues, who used aggressive volume expansion on days 1, 3, and 7, which produced a concomitant reduction in Hb concentration ranging from 1.3 to 2.0 g/dl. Although this intervention consistently produced a small increment in CBF, it actually caused a proportionally larger decline in $P_{bt}O_2$ (Table 3) [163].

More recently, Dhar and colleagues assessed the effects of transfusion in patients with SAH using PET [164]. PET scans were performed before and after the administration of one unit of RBCs to patients with pre-transfusion Hb concentrations less than 10 g/dl. Although no change in $CMRO_2$ was

Table 3**Clinical studies assessing the impact of anemia or RBC transfusions on $P_{bt}O_2$ and other physiologic parameters in brain-injured patients**

| Study | Patients | Design | Baseline | Intervention | Main findings |
|---------------------------------|------------------------|--------------------------------------|--|---|---|
| Smith and colleagues [139] | 23 TBI 12 SAH | Retrospective (prospective database) | Hb = 8.7 g/dl $P_{bt}O_2$ = 24.4 mmHg | Any RBC transfusion (number of units not specified <i>a priori</i> ; 80% received ≥ 1 unit; mean Hb increased to 10.2 g/dl) General transfusion threshold Hb <10 g/dl or hct <30% (no protocol) | - Mean increment in $P_{bt}O_2$ 3.2 mmHg (15%) - Increment not related to baseline $P_{bt}O_2$ - $P_{bt}O_2$ decreased in 9/35 patients (26%) |
| Leal-Noval and colleagues [140] | 51 TBI | Prospective observational | Hb = 9.0 g/dl $P_{bt}O_2$ = 24.4 mmHg | 1 or 2 units RBCs (number of units not specified <i>a priori</i> ; 52% received 2 units; mean Hb increased to 10.6 g/dl) General transfusion threshold Hb <10 g/dl (no protocol) | - Mean increment in $P_{bt}O_2$ 3.8 mmHg (16%) - Increment larger at lower baseline $P_{bt}O_2$ - $P_{bt}O_2$ decreased in 13/51 patients (25%) |
| Leal-Noval and colleagues [141] | 66 TBI (males) | Prospective observational | Hb = 8.9 g/dl $P_{bt}O_2$ = 21.3 to 26.2 mmHg | 1 or 2 units RBCs (number of units not specified <i>a priori</i> ; 59% received 2 units; mean Hb increased to 10.2 g/dl) General transfusion threshold Hb <9.5 g/dl (no protocol) | - Newer units of blood (≤ 14 days) resulted in greater mean increment in $P_{bt}O_2$ (3.3 mmHg (16%) vs. 2.1 mmHg (8%)) - $P_{bt}O_2$ decreased only in patients receiving older blood (>19 days) |
| Zygun and colleagues [142] | 30 TBI | Prospective RCT | Hb = 8.2 g/dl $P_{bt}O_2$ = 18.8 mmHg | Randomized to transfusion thresholds of 8, 9, or 10 g/dl; 2 units RBCs administered over 2 hours (mean Hb increased to 10.1 g/dl) | - Mean increment in $P_{bt}O_2$ 2.2 mmHg (12%) - Increment in $P_{bt}O_2$ most prominent when LPR >25 - $P_{bt}O_2$ decreased in 13/30 patients (43%) - No effect on $S_{iv}O_2$ or microdialysis parameters |
| Ekelund and colleagues [162] | 8 SAH (TCD-vaso-spasm) | Prospective interventional | Hb = 11.9 g/dl | Isovolemic hemodilution (venesection with infusion of dextran 70 and 4% albumin) to mean Hb of 9.2 g/dl | - Outcomes (using $^{133}Xenon$ and SPECT): - Increased global CBF (52.3 to 58.6 ml/100 g/min) - Reduced cerebral vascular resistance - Reduced oxygen delivery - Increased ischemic brain volume |
| Muench and colleagues [163] | 10 SAH | Prospective interventional | Hb = 10.6 g/dl $P_{bt}O_2$ = 24.8 mmHg | Volume expansion with HES \pm crystalloid to achieve ITBVI >1000 ml/m ² ; this produced a decline in Hb of 1.3 to 2.0 g/dl (on various days) | - Although hypervolemia/hemodilution produced a slight increment in CBF, $P_{bt}O_2$ decreased by an average of 0 to 5 mmHg - Only induced hypertension was consistently effective at raising $P_{bt}O_2$ |

Table 3 (Continued)**Clinical studies assessing the impact of anemia or RBC transfusions on $P_{bt}O_2$ and other physiologic parameters in brain-injured patients**

| | | | | | |
|---------------------------------|--------|--------------------------------------|----------------|---|--|
| * Dhar and colleagues [164] | 8 SAH | Prospective interventional | Hb = 8.7 g/dl | One unit RBCs (mean Hb increased to 9.9 g/dl) | - Outcomes assessed using PET: - No significant change in CBF - Reduced O_2 extraction ratio (49 to 41%; $P = 0.06$) - No significant change in $CMRO_2$ - Reduction in oxygen extraction ratio observed also in territories with vasospasm and low oxygen delivery |
| Oddo and colleagues [165] | 20 SAH | Retrospective (prospective database) | Not applicable | None | - Hb <9 g/dl associated with higher risk of $P_{bt}O_2$ <20 mmHg (OR 7.2, $P < 0.01$) and LPR >40 (OR 4.2, $P = 0.02$) |
| Chang and colleagues [237] | 27 TBI | Retrospective | Not applicable | None | - 13.7% of $P_{bt}O_2$ readings <20 mmHg - No significant association between $P_{bt}O_2$ and Hb |
| Naidech and colleagues [238] | 6 SAH | Prospective observational | Not reported | 14 RBC transfusions (no protocol) | - Hb correlated with cerebral oximetry (rO_2) - rO_2 increased following 11/14 transfusions, but not statistically significant |
| Sahuquillo and colleagues [239] | 28 TBI | Prospective | Not applicable | None | - Critical LOI (suggestive of ischemia/infarction) associated with lower Hb (11.7 g/dl vs. 13.1 g/dl) |
| Cruz and colleagues [240] | 62 TBI | Retrospective (prospective data) | Not applicable | None | - Cerebral extraction of oxygen was highest when Hb <10 g/dl |

* published only as abstract.

CBF = cerebral blood flow; $CMRO_2$ = cerebral metabolic rate; Hb = hemoglobin; HES = hydroxyethyl starch; ITBVI = intrathoracic blood volume index; LOI = jugular venous lactate: oxygen index; LPR = lactate: pyruvate ratio; $P_{bt}O_2$ = brain tissue oxygen tension; PET = positron emission tomography; RBC = red blood cell; RCT = randomized controlled trial; rO_2 = cerebral oximetry; SAH = subarachnoid hemorrhage; $S_{jv}O_2$ = jugular venous oxygen saturation; SPECT = single photon emission computed tomography; TBI = traumatic brain injury; TCD = transcranial Doppler.

observed, OEF dropped from 49 to 41%. Thus, it is possible that in vulnerable regions of the brain with relatively high OEF, RBC transfusions could help avoid irreversible infarction. Another recent study of 20 SAH patients found Hb concentrations less than 9 g/dl to be associated with lower $P_{bt}O_2$ and higher LPR [165].

In summary, there is now extensive data to suggest that even moderate degrees of anemia are associated with worse physiologic parameters and clinical outcomes in patients with SAH. However, it is not clear that the use of RBC transfusions can modify these associations. An adequately powered, RCT com-

paring different transfusion thresholds is urgently required, especially in light of the vulnerability of these patients to delayed cerebral ischemia and the frequency with which they develop anemia.

Ischemic stroke

Because of the known inverse relation between hematocrit and CBF, there has long been interest in the clinical use of hemodilution in the management of acute ischemic stroke [166]. Some studies have suggested that relatively high Hb concentrations may predispose to the development of strokes [167-173], as well as contribute to worse outcomes when cer-

Table 4

Clinical studies assessing the association between hemoglobin concentrations, anemia, or transfusion and subsequent outcomes among patients with traumatic brain injury

| Study | Patients | Design and setting | Exposure | Pre-transfusion Hb or Hct | Analysis (variables) | Main result |
|----------------------------------|-----------------------------|--|--|---------------------------|--|--|
| Carlson and colleagues [143] | 169 | Retrospective Single-center | - Number of days hct <30% - Nadir hct - RBC transfusion | Not reported | Linear regression assessing GOS as continuous variable | - Number of RBC units, lowest hct associated with worse discharge outcome - Number of days hct <30% associated with better outcome |
| #Steyerberg and colleagues [144] | 3554 | <i>Post hoc</i> analysis of several RCTs Multi-center | Admission Hb (median 12.7 g/dl) | Not relevant | Logistic regression (10 covariates) | - Lower Hb associated with poor 3 to 6 month outcome (OR for 14.3 g/dl vs. 10.8 g/dl = 0.78, 0.70 to 0.87) - Laboratory variables (Hb and glucose) improved prognostic models |
| Duane and colleagues [145] | 788 | Retrospective Single-center | Hb in first 72 hours RBC transfusion | Not reported | Logistic regression (age, ISS, total blood products) | - Minimum hemoglobin in first 72 hours associated with hospital mortality (OR = 0.86, 0.73 to 1.0 per g/dl increment) - RBC transfusions not associated with mortality, but with nosocomial infection |
| Salim and colleagues [146] | 1150 | Retrospective (prospective database) Single-center | Anemia (Hb <9 g/dl; occurred in 46%) and RBC transfusion (46%) | Not reported | Logistic regression (10 covariates) | - RBC transfusion associated with hospital mortality (OR = 2.2, $P = 0.004$) and complications (OR = 3.7, $P < 0.0001$) - Anemia associated with adverse outcomes only when transfusion not included in model |
| George and colleagues [147] | 82 (Hb 8.0 to 10.0 g/dl) | Retrospective Single-center | RBC transfusion (52%) | 8.6 g/dl | Cox proportional hazard regression (age, motor GCS, blood ethanol, lowest Na ⁺ , complications) | RBC transfusion predicted mortality ($P < 0.05$) |
| #Van Beek and colleagues [148] | 3872 | <i>Post hoc</i> analysis of several RCTs Multi-center | Admission Hb | Not relevant | Logistic regression (age, motor score, pupil reactivity) | - Lower Hb associated with higher risk of death/vegetative state at 3 to 6 months (OR = 0.69, 0.60 to 0.81, for 75 th percentile vs. 25 th percentile) |

Table 4 (Continued)

Clinical studies assessing the association between hemoglobin concentrations, anemia, or transfusion and subsequent outcomes among patients with traumatic brain injury

| | | | | | | |
|--|-----|---|--|--------------|--|--|
| Schirmer-Makalsen and colleagues [149] | 133 | Retrospective Single-center | Hb ever <8 g/dl (22%) | Not reported | Logistic regression (10 covariates) | A single Hb <8 g/dl did not predict adverse outcome |
| McIntyre and colleagues [150] | 67 | <i>Post hoc</i> analysis of RCT Multi-center | Comparison of transfusion thresholds of 7.0 g/dl vs. 10.0 g/dl | Not reported | Logistic regression (age, APACHE II, PAC use) | - 30-day mortality 17% in restrictive group vs. 13% in liberal group ($P = 0.64$) - Development of MOD and ICU LOS similar in both groups |
| Robertson and colleagues [151] | 102 | Prospective Single-center | Hb at time of CBF determination | Not reported | Logistic regression (age, CBF, GCS, CPP, CMRO ₂) | - Lower Hb associated with unfavorable GOS after 3 months |

‡ Based, in part, on same datasets

APACHE = Acute Physiology and Chronic Health Evaluation; CBF = cerebral blood flow; CMRO₂ = cerebral metabolic rate; CPP = cerebral perfusion pressure; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; Hb = hemoglobin; hct = hematocrit; ICU = intensive care unit; ISS = injury severity score; LOS = length of stay; MOD = multiple organ dysfunction; OR = odds ratio; PAC = pulmonary artery catheter; RBC = red blood cell; RCT = randomized controlled trial.

bral ischemia occurs [174-177]. It is conceivable that increased viscosity could have a particularly deleterious effect on microvascular flow through the ischemic penumbra. Consistent with this notion, Allport and colleagues performed serial MRI scans in 64 stroke patients and found that a higher baseline hematocrit was independently associated with infarct growth and less chance of successful reperfusion [178].

The deleterious association with a higher hematocrit has, however, been inconsistent and largely observed at levels in excess of 45% (Table 6). Indeed, several studies have shown a U-shaped relation where low hematocrit levels are also associated with larger infarct size and worse outcomes [175,177,179-184]. The lowest risk of stroke and the best outcomes have generally been observed with mid-range hematocrit levels of about 42 to 45% [172,175]. This range was also supported by a study using ¹³³Xe to assess CBF in stroke patients, with the finding that cerebral O₂ delivery was optimized at a hematocrit level of 40 to 45% [185]. Conversely, several animal studies have suggested that cerebral O₂ delivery and neuroprotection are optimized at slightly lower hematocrit or Hb values, in the range of 30 to 36% and 10 to 12 g/dl, respectively [58,186,187]. Greater degrees of hemodilution consistently appear to be deleterious [188]. Some case reports have even described patients with relatively stenotic cerebral vessels who may have developed ischemic strokes directly attributable to anemia [189-191].

Several RCTs and a meta-analysis have not shown any clear benefit to using hemodilution as a therapeutic strategy in acute ischemic stroke [192]. However, there was a great deal of heterogeneity in the methodology of these studies (timing of treatment, specific type and dose of plasma expander, target hematocrit). Although each study deliberately produced

reductions in hematocrit with the use of colloids and/or phlebotomy, the reductions were relatively modest, generally not beyond 37 to 38% [192-196].

More recently, several animal studies and phase II human trials have suggested that hemodilution with relatively high doses of albumin may reduce infarct size and enhance the efficacy of thrombolytic therapy [197-200]. It is likely that this effect was observed, in part, because of the unique properties of albumin, rather than only hemodilution. In a phase II dose-finding study, the reduction in hematocrit induced by the highest doses of albumin averaged 6 to 10% [198,199].

In summary, there is currently no routine role for hemodilution in the management of acute ischemic stroke. Whether transfusing anemic stroke patients with Hb concentrations lower than 9 to 11 g/dl is beneficial has not been well evaluated.

Intracerebral hemorrhage

There has been controversy regarding the importance of cerebral ischemia in causing secondary brain injury after ICH. Early studies had suggested that an expanding intracerebral hematoma could cause mechanical compression and vasoconstriction of the surrounding vasculature, thereby producing a 'perihematomal penumbra' [201-203]. Imaging with PET, CT perfusion scans, and MRI have confirmed that the majority of patients with ICH have a surrounding rim of hypoperfusion [91,204-206]. The biochemistry of this region appears to be similar to that of traumatic cerebral contusions [207]. However, OEF is not increased in the perihematomal tissues, suggesting that this hypoperfusion is due to reduced cerebral metabolism, rather than true ischemia [91]. Thus, mild reductions in Hb concentration are unlikely to have a major impact in contributing to neuronal death. Nevertheless, it remains

Table 5

Clinical studies assessing the association between hemoglobin concentrations, anemia, or transfusion and subsequent outcomes among patients with aneurysmal subarachnoid hemorrhage

| Study | Patients | Design and setting | Exposure | Mean pre-transfusion Hb/Hct | Analysis (variables) | Main result |
|----------------------------------|----------|--|---|--|--|--|
| #Kramer and colleagues [28] | 245 | Retrospective Single-center | - Anemia (nadir Hb <10 g/dl) - RBC transfusion (35%) | 9.5 g/dl No transfusion protocol | Logistic regression (WFNS score, age, vasospasm, modified Fisher score) | - Anemia and transfusion associated with poor 6 week outcome (association stronger for transfusion) - RBCs associated with nosocomial infection - Age of blood not associated with complications |
| #Kramer and colleagues [154] | 245 | Retrospective Single-center | Daily nadir Hb over 2 weeks | 9.5 g/dl No transfusion protocol | GEE to account for correlated data (WFNS score, age, vasospasm, modified Fisher score) | - Hb and decline in Hb over time predict poor outcome - Association between Hb and outcome stronger among high grade patients |
| †Naidech and colleagues [155] | 611 | Retrospective (prospective database) Single-center | - Mean and nadir Hb over 2 weeks - 35% transfused | Not reported No transfusion protocol | Multinomial regression (Hunt-Hess, age, cerebral infarction) | Higher nadir (but not mean) Hb associated with better outcome after 3 months (OR = 0.83 per 10 g/dl increase; <i>P</i> = 0.04) |
| Naidech and colleagues [156] | 103 | Retrospective (prospective database) Single-center | - Mean Hb over 2 weeks - 47% transfused | 9.2 g/dl No transfusion protocol | Logistic regression (Hunt-Hess, age, 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) |
| Tseng and colleagues [157] | 160 | <i>Post hoc</i> analysis 2 RCTs) Single-center | RBC transfusion (19%) | Not reported | Logistic regression (age, WFNS, IVH, postoperative deficits, sepsis, DIDs) | - Transfusion associated with poor outcome at discharge (OR = 4.5, <i>P</i> = 0.04) but not 6 months - More colloid use predicted lower hct and need for transfusion |
| †Wartenberg and colleagues [158] | 576 | Retrospective (prospective database) Single-center | Anemia (Hb <9 g/dl treated with transfusion; 36% of cohort) | Not reported No transfusion protocol | Logistic regression (Hunt-Hess, age, cerebral infarction, re-bleeding, aneurysm size >10 mm) | Anemia associated with worse 3 month outcome (OR = 1.8; <i>P</i> = 0.02) |
| * DeGeorgia and colleagues [159] | 166 | Retrospective Single-center | RBC Transfusion (49%) | Not reported No transfusion protocol | Logistic regression (Hunt-Hess, APACHE II) | Transfusion associated with worse outcome at discharge among patients with vasospasm, not without (OR = 2.9, CI = 1.1 to 7.8) |
| Smith and colleagues [160] | 441 | Retrospective (prospective database) Single-center | RBC transfusion (61%) | Intra-operative: 39.6% Post-operative: 32.0% No transfusion protocol | Logistic regression (Hunt-Hess, Fisher, smoking, intra-operative rupture, delay to surgery) | - Intraoperative transfusion associated with poor 6 month outcome (OR = 2.4, CI = 1.3 to 4.5) - Postoperative transfusion associated with angiographic vasospasm (OR = 1.7, CI = 1.0 to 2.8)) |

& †: studies used same datasets; *: published only as abstract
 APACHE = Acute Physiology and Chronic Health Evaluation; CI = 95% confidence intervals; DID = delayed ischemic deficit; GEE = generalized estimating equation; Hb = hemoglobin; hct = hematocrit; IVH = intraventricular hemorrhage; OR = odds ratio; RBC = red blood cell; RCT = randomized controlled trial; WFNS = World Federation of Neurological Surgeons score.

Table 6

Studies assessing the association between hemoglobin concentrations or anemia and subsequent clinical outcomes among patients with acute ischemic stroke

| Study | Patients | Design and setting | Exposure | Outcome | Main result | Comment |
|------------------------------|---|--|---|---|---|--|
| Sacco and colleagues [174] | 3481 ischemic stroke | Retrospective (prospective database) Multi-center | Baseline hct (patients divided into quartiles) | Death at 28 days | Hct >46% associated with death, but only among women | Hct ≤40% represented lowest quartile; effects of more extreme anemia not reported |
| Diamond and colleagues [175] | 1012 ischemic stroke | Retrospective Single-center | Baseline hct Median 41%; inter-quartile range 38 to 44% | Discharge home (rather than nursing facility) | High and low hct associated with worse outcome (U shaped curve) Optimal hct 45% | Only 2% of patients had hct <30% at time of their stroke |
| Lowe and colleagues [177] | 270 ischemic stroke | Retrospective Single-center | Baseline hct | Death in hospital | Patients with high hct (≥50%) had higher mortality (66 to 71%) | Elderly (≥75) with hct <40% also had higher mortality (65%) |
| Allport and colleagues [178] | 64 hemispheric ischemic stroke | Prospective Single-center | Baseline hct Median 42%; range 33 to 48% | Reperfusion, infarct growth on serial MRI | Higher hct associated with less reperfusion (OR = 0.53, $P < 0.0001$) and more infarct growth (OR = 1.26, $P < 0.05$) | This was a study of the effects of high hct; few patients were anemic |
| †Huang and colleagues [179] | 774 ischemic stroke | Prospective Single-center | Anemia (Hb <13 g/dl for men, <12 g/dl for women) (21%) | Death and mRS ≥3 at 3 years | Anemic patients more likely to die (OR = 2.2, $P = 0.02$) and to have a poor neurological outcome (67% vs. 60%, $P = 0.07$) | Numerous potential confounders not adjusted for; severity of anemia not well characterized |
| †Huang and colleagues [180] | 66 ischemic stroke (complicating ICA occlusion) | Prospective Single center | Anemia (Hb <13 for men, <12 for women) | Death or recurrent stroke at 2 years | Anemia associated with death or recurrent stroke at 2 years (OR = 5.1, $P = 0.012$) | Numerous potential confounders not adjusted for; severity of anemia not well characterized |
| Nybo and colleagues [181] | 250 ischemic stroke | Retrospective Single-center | Anemia (Hb <13 g/dl for men, <12 g/dl for women) (15%) | Death at 6 months | Anemia associated with greater risk of death (OR = 3.6, CI = 1.4 to 9.3) | Numerous potential confounders not adjusted for; severity of anemia not well characterized |
| Bhatia and colleagues [182] | 116 ischemic or hemorrhagic stroke | Retrospective Single-center | Baseline Hb | Death at 30 days | Hb not associated with risk of death | Degree of anemia relatively mild |
| Wade and colleagues [183] | 1377 symptomatic cerebrovascular disease | Retrospective (<i>post hoc</i> review of prospective RCT) Multi-center | Hb >15 g/dl vs. ≥15 g/dl at study entry | Stroke | Patients with Hb ≥15 had similar outcomes to patients with Hb <15 g/dl | This was a study of the effects of high Hb; few patients were anemic |
| LaRue and colleagues [184] | 2077 ischemic or hemorrhagic stroke | Retrospective (prospective database) Multi-center | Baseline hct (patients divided into quartiles) | Death in hospital | Hct not predictive of death (neither when high nor low) | Neurologic outcomes (other than death) not reported |

CI = confidence interval; Hb = hemoglobin; hct = hematocrit; ICA = internal carotid artery; MRI = magnetic resonance imaging; mRS = modified Rankin scale; OR = odds ratio; RCT = randomized controlled trial

uncertain whether perihematoma tissues tolerate anemia as well as healthy brain.

Use of hemoglobin-based blood substitutes

Hb-based blood substitutes (HBBS) have theoretical advantages over other fluids in the resuscitation of neurocritical care patients, because they have the potential to achieve the CBF-enhancing effects of hemodilution, while concomitantly maintaining, or even raising, C_aO_2 . Several animal studies performed in the setting of experimental ischemic stroke, TBI, and SAH-induced vasospasm have supported this concept [208-221]. Alternatively, free Hb may also have numerous deleterious effects, probably mediated, in large part, by scavenging of NO [222]. Although not all products are identical, a recent meta-analysis of RCTs suggested that their use is associated with an increased risk of death and myocardial infarction [223]. One phase II RCT involving 85 patients with ischemic stroke reported worse neurological outcomes with the use of diaspirin cross-linked Hb [224]. Of the five RCTs involving trauma patients, none specifically assessed the subgroup of patients with TBI, although the largest study reported no statistically significant interaction between HBBS and admission Glasgow coma scale on mortality [225-229]. Two of the three RCTs in the setting of cardiac surgery reported the occurrence of perioperative stroke; there were no differences between HBBS-treated and control patients [230,231]. Thus, although the use of HBBS in neurocritical care should be further investigated, there is currently no role for the routine use of these products.

Conclusions

Anemia is common in neurocritical care patients, is associated with worse outcomes, and should be avoided as much as possible with blood conservation strategies. Although Hb concentrations as low as 7 g/dl are well tolerated by most critically ill patients [25], there is ample data from animal studies, as well as human physiologic and observational studies to suggest that such a severe degree of anemia could be harmful in the brain-injured patient. Thus, in our practice, we frequently transfuse selected patients with Hb concentrations less than 8 to 9 g/dl. However, because allogeneic RBCs have multiple potentially deleterious effects, it cannot be assumed that the use of transfusions to 'correct' Hb levels alters the association between anemia and adverse outcomes. The impact of the duration of blood storage on the neurologic implications of transfusion requires further investigation. Unfortunately, existing guidelines provide little guidance to clinicians in deciding when to transfuse anemic stroke and neurocritical care patients [232-236]; clearly, RCTs are needed.

Competing interests

The authors declare that they have no competing interests.

Key messages

- Despite an increment in cerebral blood flow, even moderate reductions in Hb concentration lead to less overall cerebral oxygen delivery, resulting in lower $P_{bt}O_2$ and 'metabolic distress' (higher OEF and LPR).
- Although the relation has not been proven with certainty to be causative, anemia is consistently associated with worse outcomes among neurocritical care patients.
- Despite some beneficial physiologic effects (increased $P_{bt}O_2$ and reduced OEF), it remains uncertain whether transfusion can improve cerebral metabolism and help salvage tenuous 'penumbral' brain tissue, thereby improving neurologic recovery.
- Although a transfusion threshold of 7 g/dl is safe in many general critical care patients, it remains unclear if this is also true in neurocritical care patients.
- The duration of red blood cell storage may have implications on the cerebral consequences of transfusion.

Authors' contributions

AHK was responsible for the conception and design of the study, the analysis and interpretation of the data, and the drafting and revision of the manuscript. DAZ was responsible for the analysis and interpretation of data, and the revision of the manuscript. Both authors approved the final version of the manuscript.

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