Commentary on:
Effect of Red Blood Cell Transfusion on Unfavorable Neurologic Outcome and Symptomatic Vasospasm in Patients with Cerebral Aneurysmal Rupture: Old versus Fresh Blood
by Kim et al. World Neurosurg 84:1877-1886, 2015

The Rheology of Subarachnoid Hemorrhage

Robert D. Ecker

In 1976, Kosnick and Hunt[1] published an initial series of 7 patients with subarachnoid hemorrhage and symptomatic ischemia treated with albumin, blood transfusion, and norepinephrine to increase systemic blood pressure. Six of 7 patients greatly improved, and so started the paradigm of hypertension, hypervolemia, and hemodilution ("triple-H therapy") for the treatment of patients with symptomatic vasospasm. In the next 4 decades, there were significant improvements in the surgical and endovascular treatment of aneurysmal subarachnoid hemorrhage, development of neurocritical care, and greater understanding of the pathophysiology of cerebral vasospasm and delayed ischemic deficit, all of which have improved outcomes.[2-5] However, subarachnoid hemorrhage continues to have a 17% case fatality, and only 50% of patients have a good outcome as defined by modified Rankin Scale score 0—1.[6]

Delayed cerebral ischemia remains the leading cause of secondary brain injury after subarachnoid hemorrhage; however, treatments remain limited and non—biologically targeted.[4] Since the initial work of Kostick and Hunt, a conundrum has been described that anemia is associated with worse outcomes and excess mortality in patients with subarachnoid hemorrhage.[7-10] However, transfusion is not the solution, as numerous studies have associated transfusion with excess morbidity and mortality, including infection, stroke, systemic complication, and cerebral vasospasm.[8,10-12] This paradox has called into question the tenets of "triple-H" therapy and specifically that hypervolemic hypertension may be injuring patients in part by contributing to the anemia that is associated with poor outcomes.[13]

Anemia is defined by the World Health Organization at sea level as hemoglobin <13.0 g/dL in men and <12.0 g/dL in nonpregnant women.[14] Of patients with subarachnoid hemorrhage, 50% get anemia in the first 3 days.[15] Female sex, worse clinical grade, lower admission hemoglobin, and surgery predict anemia.[15] Causes of anemia include phlebotomy, surgical bleeding, gastrointestinal bleeding, reduced erythropoiesis, reduced red blood cell life span, and fluid overload.[16] When anemia is present, the heart and brain are protected by compensatory mechanisms that increase cardiac output and oxygen extraction. At some threshold, these mechanisms will fail. Critical hemoglobin concentration (critical oxygen delivery) was studied in healthy human volunteers, with levels of 5 g/dL leading to no evidence of decreased oxygenation; however, 3 of 55 subjects had elevated ST segments in the 5—7 g/dL range.[17-19] At 6 g/dL, cognitive deficits can be detected that can be reversed at 7 g/dL.[18] It is likely that these data in healthy volunteers cannot be extrapolated to patients in higher risk

Key words
- Blood transfusion
- Cerebral vasospasm
- Neurologic outcome
- Storage duration

Abbreviations and Acronyms
ABLE: Age of Blood Evaluation
FOCUS: Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair
RECESS: Red Cell Storage Duration Study
TRACS: Transfusion Requirements After Cardiac Surgery
TRICC: Transfusion Requirements in Critical Care

From the Cerebrovascular and Endovascular Neurosurgery, Neuroscience Maine Medical Center, Portland, Maine; and Department of Neurosurgery, Tuft University Medical Center, Boston, Massachusetts, USA

To whom correspondence should be addressed: Robert D. Ecker, M.D. [E-mail: robertecker@me.com]

Citation: World Neurosurg. (2016) 87:494-497.
http://dx.doi.org/10.1016/j.wneu.2015.09.023

groups, such as patients with ischemic heart disease and subarachnoid hemorrhage.

There are 4 randomized trials that support restrictive transfusion strategies in critically ill patients with medical disease, cardiac disease, and traumatic brain injury. The first trial, Transfusion Requirements in Critical Care (TRICC), was published in 1999. This multicenter, randomized, controlled clinical trial demonstrated that a restrictive transfusion strategy using <9.0g/dL as the initial trigger with a goal of 7–9.0 g/dL was not inferior to a liberal transfusion strategy with 10–12 g/dL as a goal in 838 critically ill patients.[20] In the 2 predefined endpoints in patients <55 years old and with Acute Physiology and Chronic Health Evaluation scores ≤20, there was a survival benefit to the restrictive strategy. Of the patients, <10% had a neurologic diagnosis, and most of those patients were in the restrictive group, calling into question the applicability of the restricted transfusion strategy to patients with neurologic injury. The Transfusion Requirements After Cardiac Surgery (TRACS) study found no difference in a composite endpoint of 30-day mortality and severe comorbidity in patients with cardiac disease prospectively randomly assigned to a liberal or restrictive transfusion strategy.[21] The liberal arm had a maintenance goal of 9.1 g/dL. The Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS), a study of liberal or restrictive transfusion in patients with high cardiac risk after hip surgery, showed no difference in mortality or mobility in the group assigned to the restrictive transfusion strategy.[22] The mean hemoglobin in the restrictive arm was 8.0 g/dL. In 2014, a randomized trial in 200 patients with traumatic brain injury of restrictive (7 g/dL) versus liberal (10 g/dL) transfusion thresholds in concert with erythropoietin failed to demonstrate any benefit, and the liberal transfusion group had more thrombotic complications.[23] This was the first meaningful randomized trial of transfusion thresholds in brain-injured patients. These studies together strongly favor a restrictive transfusion strategy, but the restrictive ranges of 7.0 to 9.1 g/dL in these 4 studies are inconsistent.

It is uncertain what transfusion threshold is appropriate for patients with subarachnoid hemorrhage. Large cohort studies in Japan with >1 million person-years of follow-up and nearly 10,000 patients found red cell transfusion to be a long-term risk factor for mortality.[11] Expert opinion surveys found thresholds for transfusion to be on average 8.19 g/dL ranging from 7.85 g/dL for good-grade patients and 8.85 g/dL for patients viewed at risk for delayed cerebral ischemia.[24] Large retrospective reviews, including Naidech et al.[10] and Stein et al.,[8] found poor outcomes at hemoglobin thresholds of 11.7 g/dL and 11.1 g/dL, respectively, but transfusion led to much higher pulmonary and cerebrospinal fluid infection rates.[8,10] The 1 published randomized study included 44 patients with thresholds of 11.5 g/dL and 10 g/dL for transfusion and showed no statistical difference between the groups for stroke, independence, and stroke scale.[25] Physiologic studies included positron emission tomography cerebral blood flow and oxygen delivery studies, brain tissue oxygenation, and microdialysis. Positron emission tomography studies found that transfusion in patients with hemoglobin <10 g/dL led to improved oxygen delivery; however, in regions of oligemia near known regions of vasospasm, the benefit was attenuated by a decrease in cerebral blood flow.[26] In brain tissue oxygen studies, after transfusion in patients with subarachnoid hemorrhage, a clear increase in brain tissue partial pressure of oxygen was demonstrated, but there was no change in the lactate/pyruvate ratio in microdialysis, suggesting that intracellular dysfunction is not leading to increased oxygen use and metabolism.[27]

One of the hypotheses for why transfusion has not benefited patients with subarachnoid hemorrhage is that old stored blood that is subject to "storage lesion" is adversely affecting outcome. Early studies of transfused blood stored in citrate and glucose established 24-hour survival of 70% as the acceptable threshold for posttransfusion 24-hour survival.[28] Blood banks generally distribute the oldest blood first so as not to waste this scarce resource. Smaller hospitals with smaller storage capacity tend to get the newer units, meaning that the sickest patients at the large referral centers tend to get the oldest blood. The addition of acid-citrate-dextrose, phosphate, adenine, and nutrient solutions has progressively increased storage time from 21 days to 45 days.[28] With this increase in survival, red blood cells are known to become depleted of adenosine diphosphate, 2,3-disphosphoglycerate, and nitric oxide and undergo membrane phospholipid vesiculation and loss, protein oxidation, lipid peroxidation, and eventually progression from reversible loss of shape to irreversible formation of spheroecinocytes. All of these changes have been postulated potentially to affect red blood cell oxygen carrying capacity and constitute "storage lesion." The lesion is thought to be worse after 14 days. Naidech et al.[25] performed the 1 previous prospective cohort study in transfusion in subarachnoid hemorrhage and found that the age of the transfused blood did not matter, but only 19% of the patients received packed red blood cells before 14 days. Kramer et al.[29] in a retrospective study of 245 patients found no difference in the outcomes in patients with subarachnoid hemorrhage based on the age of blood.

In April 2015, 2 prospective randomized trials looking at the age of blood transfusion were published: ABLE (Age of Blood Evaluation) and RECESS (Red Cell Storage Duration Study).[30,31] In the ABLE trial, 1219 critically ill patients in 64 centers in Canada and Europe were randomly assigned to receive either early (6.1 days of storage) or standard (22.0 days of storage) packed red blood cells. There was no decrease in mortality for patients receiving early units or any difference in secondary outcomes, including major illnesses; duration of respiratory, hemodynamic, or renal support; length of stay in the hospital; and transfusion reactions. In RECESS, 1481 patients >12 years old undergoing major complex cardiac surgery were randomly assigned to transfused units that were 7 days versus 28 days in storage. There were no differences in mortality with 7-day units versus 28-day units.

Kim et al. add to the literature on blood age and risk of transfusion in subarachnoid hemorrhage. In their retrospective cohort study, 211 consecutive patients with subarachnoid hemorrhage were split into 3 groups: no transfusion, transfusion with blood that was <14 days old, and transfusion with blood >14 days old. There were 136 patients in the no transfusion group, 39 patients in the <14 days transfusion group, and 36 patients in the >14 days transfusion group; the average age of the packed red blood cells was 10 days and 17.5 days. Statistical significance was