Effect of Red Blood Cell Transfusion on Unfavorable Neurologic Outcome and Symptomatic Vasospasm in Patients with Cerebral Aneurysmal Rupture: Old versus Fresh Blood

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■ BACKGROUND: **Red blood cell (RBC) transfusion, especially with "old" blood, is associated with adverse clinical outcomes. We compared the effects of fresh blood versus old blood transfusion on poor neurologic outcomes and symptomatic vasospasm in patients with ruptured cerebral aneurysms.**

■ METHODS: **In this retrospective study, 211 patients with aneurysmal rupture were divided into 3 groups: nontransfusion (n = 136), fresh blood (RBC storage ≤14 days) transfusion (n = 39), and old blood (RBC storage >14 days) transfusion (n = 36). Unfavorable neurologic outcomes (modified Rankin Scale score ≥3) and symptomatic cerebral vasospasm were assessed.**

■ RESULTS: **The incidence of unfavorable neurologic outcomes was significantly higher in the fresh blood and old blood transfusion groups compared with the nontransfused group (71.8% and 58.3% vs. 21.3%; P < 0.01); the incidence of symptomatic vasospasm was significantly higher in the old blood group compared with the fresh blood and nontransfusion groups (57.1% vs. 26.7% and 22.2%; P < 0.05). On binary logistic regression, old age, Hunt and Hess grade 3–4, high postoperative C-reactive protein level, RBC transfusion, delayed infarction, and hydrocephalus were independent predictors of unfavorable neurologic outcomes. Young age, Fisher grade 3–4, old RBC transfusion, and surgical clipping were independent predictors of postoperative symptomatic vasospasm.**

■ CONCLUSIONS: **RBC transfusion itself, regardless of the duration of RBC storage, was associated with unfavorable neurologic outcomes in patients with ruptured cerebral aneurysms. Also, old blood transfusion, but not fresh blood transfusion, was associated with increased symptomatic cerebral vasospasm.**

INTRODUCTION

Packed red blood cells (RBCs) undergo various morphologic and biochemical changes during ex vivo storage, such as loss of deformability, altered adhesiveness and aggregation, a reduction in 2,3-diphosphoglycerate and nitric oxide (NO), and an increase in the fragmentation of RBCs and adenosine diphosphate.[1,2] These changes, referred to as "storage lesions," diminish the oxygen-carrying capacity of RBCs and impair their passage through capillaries. Several studies found that transfusion of "old" blood increases postoperative mortality and postoperative complications, such as infection, multiorgan failure, and vascular thrombosis.[3–7]

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

Abbreviations and Acronyms
CI: Confidence interval
CRP: C-reactive protein
CRP POD 1–3: C-reactive protein level measured from the first to the third day after surgery
Hb: Hemoglobin
ICU: Intensive care unit
IQR: Interquartile range
NO: Nitric oxide
OR: Odds ratio
POD: Postoperative day
RBC: Red blood cell
SAH: Subarachnoid hemorrhage

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RBC transfusion is frequently performed in patients with subarachnoid hemorrhage (SAH) to improve cerebral oxygen delivery.[8] In a previous study in patients undergoing neurosurgical clipping for cerebral aneurysms, 24.5% of patients received RBC transfusions intraoperatively, and 44.6% of patients received RBC transfusions postoperatively.[9] Although RBC transfusion to treat anemia in patients with SAH caused by aneurysmal rupture may seem reasonable, the optimal hemoglobin (Hb) level is unknown.[10] Moreover, several previous studies demonstrated that perioperative blood transfusion is associated with an increased risk of poor outcome or vasospasm, or both, after SAH.[11–14] In particular, reduced NO production and NO availability is associated closely with the development of cerebral vasospasm and delayed cerebral infarction in patients with SAH.[15] However, the effect of the duration of RBC storage on poor neurologic outcomes and cerebral vasospasm has not been investigated extensively in patients with SAH. Although 2 previous studies showed no relationship between the duration of RBC storage and vasospasm or adverse neurologic outcomes in patients with SAH,[12,16] the results in these studies should be reconsidered because the temporal relationship, which is needed to establish causality between blood transfusion and the development of vasospasm, was not evident in these studies.

We hypothesized that transfusion of old rather than fresh blood could be associated with vasospasm and poor neurologic outcomes after SAH because of RBC storage lesions. In this study, we assessed whether perioperative RBC transfusion was related to poor neurologic outcomes and cerebral vasospasm in patients with SAH caused by ruptured cerebral aneurysms. Additionally, we compared the effects of fresh blood versus old blood transfusion on poor neurologic outcomes and cerebral vasospasm.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Seoul National University (No. 1409-048-608). The need for informed consent was waived. All patients with ruptured cerebral aneurysms who were treated with endovascular coiling or surgical clipping within 24 hours after hospital admission between July 2007 and June 2014 were identified, and their electronic medical records, including operative records, anesthetic records, and nursing records, were reviewed retrospectively. Poor-grade patients with aneurysmal SAH, who received only external ventricular drains for intracranial pressure control without securing cerebral aneurysm, were excluded.

Patient Management

In all patients, ruptured cerebral aneurysms were confirmed by cerebral angiography with three-dimensional digital subtraction. To secure ruptured intracranial aneurysms, surgical clipping was generally indicated in patients who had cerebral aneurysms located in the middle cerebral artery, aneurysms with a broad neck or vessels emitting from the aneurysm dome, or massive intracranial hemorrhage associated with the aneurysmal rupture. Postoperative cerebral computed tomography was performed within 24 hours after endovascular coiling or surgical clipping to rule out or confirm an ischemic lesion secondary to direct procedural or surgical manipulation. All patients underwent daily serial neurologic evaluations for vasospasm detection in the surgical intensive care unit (ICU). Symptomatic vasospasm was defined as the presence of a focal neurologic deficit or altered consciousness level with confirmation of vasospasm on brain computed tomography angiography or cerebral angiography. Patients with symptomatic vasospasm were treated with induced hypertension, intravenous nimodipine and magnesium continuous infusion, intra-arterial nimodipine injection in a neuroangiographic room, and blood transfusion if serum Hb was <10 g/dL. Neurologic outcome was estimated at hospital discharge using the modified Rankin Scale.[17] Poor neurologic outcome was defined as a modified Rankin Scale score of ≥3.

Patient Categorization

Patients were divided into 2 groups according to the presence or absence of RBC transfusion during hospital admission, and patients with blood transfusion were further divided into 2 groups based on the duration of RBC storage. Patients were categorized into 3 groups: nontransfusion, fresh blood transfusion, and old blood transfusion. Fresh blood was defined as a blood storage duration ≤14 days, and old blood was defined as a blood storage duration >14 days.[18] The selection of fresh or old blood was based on the decision of a clerk working in the blood bank in our hospital. Neither the anesthesiologists nor neurosurgeons participated in the selection of the transfused blood. A mixed transfusion (2 old RBC units and 1 fresh RBC unit) was given in 3 patients. They were assigned to the old blood group because more old RBCs were transfused than fresh RBCs. All RBC units transfused in this study were buffy coat–depleted RBCs and were stored in citrate phosphate dextrose adenine-1 at 2°C–6°C.

The decision to transfuse RBCs was made by anesthesiologists intraoperatively or by neurosurgeons postoperatively. No particular blood transfusion protocol for patients with aneurysmal rupture was used. Generally, RBC transfusion was always indicated when Hb was <9.0 g/dL, and RBC transfusion was indicated extremely rarely when Hb was ≥10.0 g/dL. When Hb was 9.0–9.9 g/dL, the decision was based on the patient's clinical status and the rate and extent of ongoing blood loss. Target Hb was 10 g/dL.

Data Classification

Patient data were classified into 5 categories: 1) preoperative variables, including demographic data, comorbidities, location and size of aneurysm, neurologic status on admission, and preoperative Hb level; 2) intraoperative variables, including surgery time and surgical technique; 3) postoperative variables, including immediate postoperative Hb level, the presence of mechanical ventilation, Acute Physiology and Chronic Health Evaluation II score on admission to the surgical ICU, C-reactive protein (CRP) level measured from the first to the third day after surgery (CRP POD 1–3), and perioperative transfusion; 4) postoperative complications, including decompression, symptomatic vasospasm, delayed cerebral infarction (late fixed ischemic lesions on brain computed tomography), hydrocephalus, and infection at various sites; and 5) clinical outcome data, including hospital mortality, length of stay in the ICU and hospital, and the modified Rankin Scale score at hospital discharge. The primary endpoints were the incidences of unfavorable neurologic outcomes by the modified Rankin Scale and symptomatic vasospasm. The secondary