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ORIGINAL ARTICLE

The Effect of Packed Red Blood Cell Transfusion on Cerebral Oxygenation and Metabolism After Subarachnoid Hemorrhage

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Abstract

Background Anemia adversely affects cerebral oxygenation and metabolism after subarachnoid hemorrhage (SAH) and is also associated with poor outcome. There is limited evidence to support the use of packed red blood cell (PRBC) transfusion to optimize brain homeostasis after SAH. The aim of this study was to investigate the effect of transfusion on cerebral oxygenation and metabolism in patients with SAH.

Methods This was a prospective observational study in a neurological intensive care unit of a university hospital. Nineteen transfusions were studied in 15 consecutive patients with SAH that underwent multimodality monitoring (intracranial pressure, brain tissue oxygen, and cerebral microdialysis). Data were collected at baseline and for 12 h after transfusion. The relationship between hemoglobin (Hb) change and lactate/pyruvate ratio (LPR) orbrain tissue oxygen ($PbtO_2$) was tested using univariate and multivariable analyses.

Results PRBC transfusion was administered on the median post-bleed day 8. The average Hb concentration at baseline was 8.1 g/dL and increased by 2.2 g/dL after

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transfusion. $PbtO_2$ increased between hours 2 and 4 post-transfusion and this increase was maintained until hour 10. LPR did not change significantly during the 12-h monitoring period. After adjusting for SpO_2, cerebral perfusion pressure, and LPR, the change in Hb concentration was independently and positively associated with a change in $PbtO_2$ (adjusted b estimate = 1.39 [95 % confidence interval 0.09–2.69]; $P = 0.04$). No relationship between the change in Hb concentration and LPR was found.
Conclusions PRBC transfusion resulted in $PbtO_2$ improvement without a clear effect on cerebral metabolism prior to SAH.

Keywords Subarachnoid hemorrhage · Stroke · Cerebral metabolism · Brain oxygen

Introduction

In patients with subarachnoid hemorrhage (SAH), anemia is a common complication and an independent predictor of poor outcome [1]. Although observational studies have shown that a Hb concentration >11 g/dL is associated with improved outcome, the optimal Hb concentration after SAH is still unclear [2–4]. Moreover, a low Hb concentration adversely affects cerebral metabolism and oxygenation after SAH [5, 6].

PRBC transfusion has also been associated with unfavorable outcomes after SAH, independent of the degree of anemia, and with higher rates of vasospasm and infections [1, 3, 4, 7–9].

There is limited evidence of the effects of increasing Hb concentration after transfusion on cerebral physiology after SAH [10, 11]. We hypothesized that increased Hb concentration after transfusion is associated with an improvement of brain oxygen and the reduction of LPR. The aim of this study was to investigate the effects of PRBC transfusion on cerebral oxygenation and metabolism in patients with poor-grade SAH.

Methods

This prospective observational study was conducted in the neurological ICU at Columbia University Medical Center between January 2008 and June 2009, under Institutional Review Board approval. We studied 19 PRBC transfusions given to 15 consecutive comatose patients who were admitted with poor-grade (Hunt and Hess grades 3–5) aneurysmal SAH and underwent multimodality neuromonitoring with combined $PbtO_2$ and cerebral microdialysis (CMD). The inclusion criterion was (1) the transfusion of PRBC. The exclusion criteria were (1) active hemorrhage and (2) the malfunction of $PbtO_2$ and CMD.

Patients were managed according to SAH guidelines established by the American Heart Association [12]. PRBC transfusion was left to the discretion of the clinical team, targeting Hb concentrations >8 g/dL unless there was evidence of symptomatic vasospasm or myocardial ischemia.

ICP catheters, CMD catheters (CMA 70; Mdialysis AB; flow rate, 0.3 mL/min; North Chelmsford, Massachusetts, USA), and $PbtO_2$ probes (Licox; Integra Neurosciences; Plainsboro, New Jersey, USA) were inserted via a triple-lumen bolt at the bedside into visually normal white matter of the hemisphere deemed at greatest risk for secondary injury or of the right frontal lobe.

Physiological variables were collected at baseline and every 120 min for 12 h after the after initiation of transfusion. To best reflect the mean physiological variables every 2 h after transfusion, we averaged 5 min of continuous measurement of each parameter. Hb was measured at baseline and post-transfusion. In the exploratory analyses, we plotted the average values of LPR and $PbtO_2$ over time after PRBC transfusion. Changes in $PbtO_2$ and LPR from baseline to post-transfusion were studied using multivariate models.

Statistical Analysis

We performed univariate and multivariate analyses using generalized estimating equations (GEE) to study whether changes in Hb are associated with changes in $PbtO_2$ or LPR. Adjusted b estimates and 95 % confidence intervals (CI) were reported in the final models. Statistical analyses were performed using SPSS 16 software (SPSS Inc., Chicago, IL, USA). A P value <0.05 was considered significant.

Results

All 15 patients included in the study were mechanically ventilated and had a GCS score less than or equal to 8. The median patient age was 52 years old (IQR 41–66). The median APACHE II score was 23 (IQR 22–28), the Hunt and Hess scores were 4 or 5 in 80 % of patients and 53 % of patients had a modified Fisher grade of 4. Transfusion was administered on median post-bleed day 8, and 4 patients received transfusions on 2 different occasions that were at least 1 day apart (Supplemental Table 1).

We plotted $PbtO_2$ and LPR over time for the 12-h monitoring period. $PbtO_2$ showed an increase between hours 2 and 4 after the initiation of transfusion. LPR did

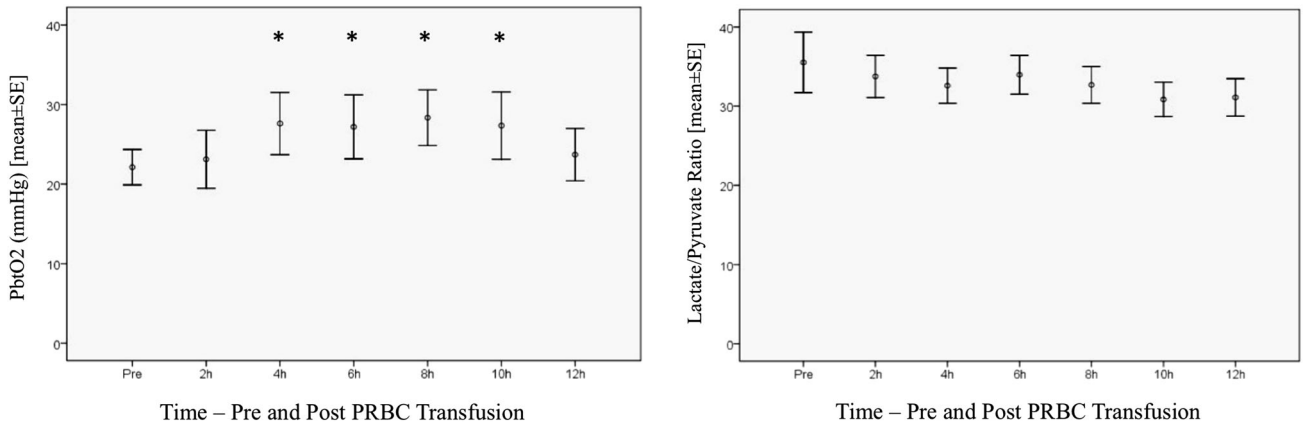

Fig. 1 Evolution of $PbtO_2$ and LPR, at baseline and for 12 h post-transfusion. The data are presented as the mean ± the standard error of the mean (SEM); $*P < 0.05$

not show a clear change during the 12-h monitoring period (Fig. 1).

The average Hb concentration at baseline was 8.1 g/dL and increased by 2.2 g/dL after transfusion. Mean baseline LPR values were below the critical threshold of 40. Mean baseline $PbtO_2$ was normal, and both $PbtO_2$ and CPP increased after transfusion compared to baseline (Table 1).

We studied the relationship between changes in $PbtO_2$ or LPR and other physiologic variables in two separate models. After adjusting for SO_2 and LPR, every 1 g/dL increase in Hb concentration was associated with a 0.11 mmHg increase in CPP and a 1.39 mmHg increase in $PbtO_2$ (Table 2). There was no significant relationship observed between changes in Hb concentration and changes in LPR (Supplemental Table 2). We tested for significant interactions between pre-specified variables and none were found.

Discussion

In this small prospective study, we found a significant and positive association between changes in hemoglobin concentration after PRBC transfusion and improvement of $PbtO_2$ in comatose and mechanically ventilated patients with poor-grade SAH.

Recent studies demonstrated improvements in oxygenation after transfusion in patients with SAH [10, 11, 13]. These data suggest that transfusions are associated with an improvement in oxygen delivery to the brain without measurable metabolic impact. The effects on oxygen delivery are most likely explained by improved cerebral blood flow and improved oxygen carrying capacity. This is corroborated in our study because the effect of Hb concentration remains after adjusting for CPP increase. Again, this did not result in improved metabolism.

Table 1 Physiological parameters

Variable	Baseline	Post-transfusion	*P* value
Hemoglobin (g/dL)	8.1 (1.1)	10.3 (0.9)	<0.001
Cerebral perfusion pressure (mmHg)	85.9 (17.3)	98.4 (19.6)	0.01
Systemic glucose (mg/dL)	131.2 (40.4)	145.8 (32.8)	0.23
End-tidal CO_2 (mmHg)	30.6 (5.6)	30.2 (4.9)	0.31
Oxygen saturation (%)	99.2 (1.2)	99.4 (1.2)	0.38
$PbtO_2$ (mmHg)	20.1 (13.7)	24.9 (15.2)	0.001
LPR	36.6 (15.9)	35.5 (16.4)	0.62
Lactate (mmol/L)	3.8 (1.9)	4.1 (2.2)	0.43
Pyruvate (mmol/L)	119.0 (65.9)	123.8 (56.0)	0.48
Glucose (mmol/L)	1.3 (1.3)	1.2 (0.7)	0.40

Mean (SD). Post-transfusion parameters were collected at the time of hemoglobin measurement, which was conducted 4 h (IQR 2–6) after initiating transfusion

Table 2 Changes in $PbtO_2$

Variables	Univariate			Multiivariate		
	Coefficient	95 % CI	*P*	Coefficient	95 % CI	*P*
Δ Hemoglobin (g/dL)	2.20	0.91–3.49	0.001	1.39	0.09–2.69	0.036
Δ Cerebral perfusion pressure (mmHg)	0.11	0.11–0.12	<0.001	0.11	0.05–0.17	<0.001
Δ LPR	−0.31	−0.53–(−0.09)	0.006	−0.201	−0.36–(−0.04)	0.014
Δ End-tidal CO_2 (mmHg)	0.64	−0.76–2.04	0.37			
Δ SO_2 (%)	2.13	2.13–2.13	<0.001	0.128	−1.07–1.33	0.84
Baseline PO_2 (mmHg)	−0.12	−0.44–0.02	0.447			
Baseline FiO_2 (%)	−3.77	−15.55–8.01	0.53			
Baseline PCO_2 (mmHg)	−0.21	−0.54–0.12	0.21			

Univariate and multivariate linear regression models using GEE

Potential explanations of this result include a lack of ischemia at baseline and metabolic distress caused by mitochondrial dysfunction.

Our study has some limitations. First, we did not assess clinical outcomes and complications. Second, we were not able to evaluate the effects of transfusion with low baseline Hb and $PbtO_2$ or high LPR. Third, our sample size was small. This may explain why we found no changes in metabolism. Fourth, although we ran multivariate models using repeated measurement analyses to study the physiological associations between variables, we acknowledge that the small sample size may warrant caution when interpreting our results.

Our findings are hypothesis-generating but may also have important clinical implications. With increasing evidence that anemia affects cerebral physiology and that a liberal blood transfusion strategy may worsen the outcome, using brain oxygen as a target for goal-directed therapy, may allow for an individualized approach to PRBC transfusion. Further studies are needed to determine the effect of transfusions in patients with disrupted tissue metabolism caused by low oxygen delivery. Randomized clinical trials are needed to assess the effect of a goal-directed PRBC transfusion strategy.

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