The effect of red blood cell transfusion on cerebral oxygenation and metabolism after severe traumatic brain injury*

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Objective: **There is evidence to suggest that anemia after severe traumatic brain injury (sTBI) is detrimental. However, there is a paucity of evidence supporting the use of transfusion of packed red blood cells in patients with sTBI. To understand the acute effect of packed red blood cell transfusion on cerebral oxygenation and metabolism in patients with sTBI.**

Design: **Prospective clinical study.**

Setting: **Addenbrooke's Neurosciences Critical Care Unit, a 21-bed tertiary academic unit.**

Patients: **Thirty patients with sTBI.**

Interventions: **Patients were randomized by computer random number generator to one of three transfusion thresholds: 8, 9, or 10 g/dL. When the patients' hemoglobin concentration fell below their assigned threshold, two units of packed red blood cells were transfused over 2 hours. A 1-hour period of stabilization was observed before final data collection.**

Measurements and Main Results: **The primary outcome was change in brain tissue oxygen ($P_{bt}O_2$). Secondary outcomes included dependence of baseline hemoglobin concentration and baseline $P_{bt}O_2$ on the relationship of transfusion and $P_{bt}O_2$, and the effect of transfusion on lactate pyruvate ratio (LPR) and brain pH as markers of cerebral metabolic state. Fifty-seven percent of patients experienced an increase in $P_{bt}O_2$ during the course of the study, whereas in 43% of patients, $P_{bt}O_2$ either did not change or decreased. Multivariable generalized estimating equation analysis revealed change in hemoglobin concentration to significantly and positively associated with change in $P_{bt}O_2$ [0.10 kPa/(g/dL) 95% confidence interval 0.03–0.17, $p = 0.003$]. Improvement in $P_{bt}O_2$ was not associated with baseline hemoglobin concentration or low $P_{bt}O_2$ (<1 kPa). Fifty-six percent of patients experienced an increase in LPR. No significant relationship between change in LPR or transfusion on pH_{bt} and change in hemoglobin could be demonstrated.**

Conclusions: **Transfusion of packed red blood cells acutely results in improved brain tissue oxygen without appreciable effect on cerebral metabolism.**

Trial Registration: **ISRCTN89085577. (Crit Care Med 2009; 37: 1074–1078)**

KEY WORDS: critical care; transfusion; craniocerebral trauma; anemia; microdialysis

Traumatic brain injury (TBI) remains a critical public health challenge (1). TBI-related deaths are common, occurring in 19.4 of 100,000 persons annually (1). Population-based epidemiologic studies of severe TBI report a case fatality of 30% to 54% (2–5). For survivors of severe TBI, complete recovery to preinjury levels is uncommon; ~60% of survivors have ongoing deficits in the areas of cognitive competency, major activity, and leisure and recreation (6).

There is evidence to suggest that anemia may be injurious to the brain. Anemia during cardiopulmonary bypass has been associated with worsened neurologic status adults both in children (7) and adults (8). In patients undergoing chronic hemodialysis, Pickett et al (9) showed that normalizing hematocrit (40% to 45%) with the use of additional recombinant human erythropoietin results in improvement in neurocognitive function. In patients with TBI, Gopinath et al (10) found that the occurrence of jugular venous desaturation was strongly associated with neurologic outcome, and anemia has been identified as a contributing cause of jugular venous desaturation (11). Importantly, anemia in patients with TBI has been associated with reduced survival (12) and lower hospital discharge Glasgow Coma Scale (GCS) scores, Glasgow Outcome Scale scores, and Ranchos Los Amigos scores (13).

Despite the pathophysiological rationale and associative outcome evidence supporting the detrimental effect of anemia on the brain, there is a paucity of evidence supporting the use of transfusion of packed red blood cells to improve outcome. Furthermore, the optimal hemoglobin level is not known. Gaehtgens

*See also p. 1166.

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Drs. Zygun and Gupta had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Zygun, Gupta, Menon, and Hutchinson designed the study. Drs. Zygun, Nortje, and Timofeev collected the data. All authors participated in the analysis and manuscript preparation.

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and Marx (14) suggested that a hematocrit of 42% to 45% will optimize cerebral oxygen delivery in healthy human volunteers. Animal studies have shown that a hematocrit of 30% to 33% gives an optimal balance of viscosity and oxygen carrying capacity (15). However, randomized controlled trials that define the optimal hemoglobin level in patients with severe TBI do not exist. Thus, no consensus is apparent with respect to transfusion practice in these patients. Furthermore, there is little understanding of the effects of transfusion on cerebral oxygenation and metabolism.

To gain further insight into the optimal transfusion strategy in patients with severe TBI, a prospective clinical study was performed in which the effect of packed red blood cell transfusion on cerebral oxygenation and metabolism was examined.

METHODS

This study was approved by the local research ethics committee, and written informed assent was obtained from the next of kin of all patients.

All patients were admitted to the Neurosciences Critical Care Unit at Addenbrooke's Hospital (Cambridge University Hospitals NHS Foundation Trust), with the diagnosis of severe TBI from January 15, 2003, until July 27, 2005, were screened. The Addenbrooke's Neurosciences Critical Care Unit is a tertiary academic unit comprising 21 adult Neurosciences Critical Care Unit beds serving a referral population of ~2.5 million persons. Approximately 120 patients a year are admitted with severe TBI. The study inclusion criteria were as follows: >16 years; severe TBI (defined as a TBI resulting in a resuscitated GCS score ≤8, intracranial hypertension >20 mm Hg for greater than 10 minutes, or requiring neurosurgical intervention), and informed assent from the next of kin. The exclusion criteria were active hemorrhage, active coronary ischemia as judged by dynamic ischemic electrocardiogram changes or positive troponin levels not due to myocardial contusion, inability to place cerebral oxygenation monitors, failure to fall below allocated transfusion threshold during intracranial pressure, and brain tissue oxygen monitoring and lack of informed assent from next of kin.

Patients were managed according to Addenbrooke's Neurosciences Critical Care Unit protocols (16), which include sedation with propofol and fentanyl, paralysis with atracurium, and support of cerebral perfusion pressure to 70 mm Hg. Monitored variables included electrocardiogram, peripheral oxygen saturation, end-tidal carbon dioxide, jugular venous oxygen saturation, arterial blood pressure, and intracranial pressure. Apart from the transfusion intervention, all other aspects of physiology were kept as stable as possible during the study period.

Patients were randomized by computer random number generator to one of three transfusion thresholds: 8, 9, or 10 g/dL. A tissue oxygen monitor (Neurotrend, Codman, Raynham, MA) and cerebral microdialysis catheter (CMA Microdialysis, Solna, Sweden) were placed through a specially designed cranial access device in the nondominant frontal region. When the patients' hemoglobin concentration fell below their assigned threshold, two units of packed red blood cells were transfused, each over 1 hour regardless of assigned transfusion threshold. A 1-hour period of stabilization was observed before final data collection. Physiologic data were recorded and hemoglobin concentration measured at baseline and at 30, 60, 90, 120, and 180 minutes after initiation of transfusion. Continuous physiologic measurements were collected at a frequency of 50 Hz and averaged over 5 minutes centered on the time point of interest. The primary outcome was change in brain tissue oxygen ($P_{bt}O_2$). Secondary outcomes included dependence of baseline hemoglobin concentration and baseline $P_{bt}O_2$ on the relationship of transfusion and $P_{bt}O_2$, and the effect of transfusion on lactate pyruvate ratio (LPR) and brain pH (pH_{bt}) as markers of cerebral metabolic state.

Statistical Analysis

Analysis of continuous, normally distributed variables within and between groups were undertaken using the appropriate Student's *t* test. Non-normally distributed continuous variables were analyzed using the Mann-Whitney *U* test. Categorical variables were analyzed using Fisher's exact test. A *p* value of <0.05 was considered significant. All statistical tests were two-sided. Given the exploratory nature of this analysis, no correction was made for multiple comparisons.

Primary analysis, change in $P_{bt}O_2$ over change in hemoglobin concentration, was performed using a population-averaged panel-data model developed using a generalized estimating equation variant of the generalized linear method. An exchangeable within-group correlation structure was used. Individual patient regression analysis was used to substantiate the univariable generalized estimating equation analysis. Clinically relevant variables included in the multivariable model were selected *a priori* by the investigators. Stepwise elimination was not used. Similar procedures were repeated for analysis of changes LPR and pH_{bt} over time. All analyses were performed with Stata Version 8.0 (Stata Corporation, College Station, TX).

Table 1. Patient characteristics

Age mean (SD)	39 (15)
Male (%)	70
Median postresuscitation Glasgow coma score (intraquartile range)	7 (6, 10)
Injury severity score mean (SD)	24 (10)
Pupils abnormal	41%
Prehospital hypotension	3%
Prehospital hypoxemia	17%
Acute Physiology and Chronic Health Evaluation II mean (SD)	19 (6)
CT Marshall score[a] (%)	
2a	3
2b	7
2d	7
3	10
5b	7
5c	3
5d	23
6c	13
6d	27
Intracranial hypertension	93%
Intensive care unit length of stay median (intraquartile range)	23 (16, 30)
Intensive care unit mortality	10%
Hospital mortality	15%
Glasgow outcome score[b] At 6 months, number (%)	
1	4 (21)
2	1 (5)
3	7 (37)
4	3 (16)
5	4 (21)

[a]The Marshall score is a classification based on the initial computed tomography (CT) scanutilizing the status of the mesencephalic cisterns, degree of midline shift, and presence or absence of surgical masses. This categorization allows for more accurate categorization of diffuse head injury. (*J Neurosurg* 1991; 75(Suppl):S14–S20.

[b]Available for 19 of 30 patients.

RESULTS

Thirty nonconsecutive patients were studied. The characteristics of the patients are presented in Table 1. Transfusion occurred on median (intraquartile range) day 4 (3, 6) after injury. Patients received a mean (SD) of 551 (58) mL of packed red cells. The systemic and cerebral physiologic measurements during the study period are presented in Table 2.

Change in Brain Tissue Oxygen. Median (intraquartile range) change in $P_{bt}O_2$ was 0.07 (−0.25 to 0.58) kPa. Fifty-seven percent of patients experienced an increase in $P_{bt}O_2$ over the course of the study, whereas in 43% of the patients $P_{bt}O_2$ either did not change or decreased. Before study, cerebral perfusion pressure, Pa_{O_2}, probe location, age, GCS, time of transfusion from injury, pH_{bt}, Pa_{CO_2}, and

Table 2. Systemic and cerebral physiologic measurements

	Time (min)					
	0 Pretransfusion	30	60	90	120	180 Posttransfusion
[Hb] g/dL, mean (SD)	8.2 (1.1)	8.4 (1.0)	8.9 (0.9)	9.5 (1.0)	9.9 (1.3)	10.1 (1.5)
Cerebral perfusion pressure mm Hg mean (SD)	81 (11)	82 (10)	83 (9)	82 (8)	83 (10)	82 (13)
ICP mm Hg mean (SD)	15 (6)	16 (6)	17 (7)	17 (6)	17 (6)	17 (6)
Pa_{O_2} (kPa) mean (SD)	14 (2)	14 (2)	14 (3)	14 (3)	14 (3)	14 (2)
Pa_{CO_2} (kPa) mean (SD)	4.57 (0.55)	4.49 (0.62)	4.61 (0.61)	4.59 (0.61)	4.61 (0.53)	4.62 (5.4)
Cardiac index[a] (L/min/m^2)	4.2 (0.5)	4.3 (0.7)	4.5 (1.0)	4.4 (0.6)	4.2 (0.5)	4.1 (0.7)
Oxygen delivery index[a] (mL/min/m^2)	499 (102)	517 (126)	564 (162)	580 (103)	589 (123)	569 (120)
S_jO_2 % (SD)[b]	77 (7)	78 (7)	77 (7)	75 (7)	76 (7)	75 (8)
Brain tissue oxygen (kPa) mean (SD)	2.5 (1.6)	2.5 (1.7)	2.5 (1.7)	2.5 (1.6)	2.6 (1.7)	2.8 (2.0)
Microdialysate lactate, median (IQR)	2.8 (1.9–4.0)	2.7 (1.8–4.0)	2.7 (1.9–3.8)	2.5 (1.9–3.7)	2.5 (1.9–3.7)	2.8 (1.9–3.9)
Microdialysate pyruvate, median (IQR)	93 (72–166)	93 (69–168)	91 (68–161)	93 (69–165)	91 (71–148)	96 (72–149)
Lactate pyruvate ratio, median (IQR)	26 (21–35)	26 (22–35)	26 (21–33)	26 (22–32)	26 (21–32)	27 (21–30)
Brain pH, median (IQR)	7.23 (7.16–7.28)	7.23 (7.15–7.29)	7.22 (7.13–7.27)	7.23 (7.14–7.27)	7.23 (7.17–7.28)	7.23 (7.17–7.27)

IQR, intraquartile range.
[a]Available for six patients; [b]Available for 15 patients.

temperature were deemed to potentially confound the primary analysis and included in the univariable and multivariable analysis presented in Table 3. Multivariable generalized estimating equation analysis revealed the following variables to be positively associated with an increase in $P_{bt}O_2$: [Hb] 0.10 kPa/(g/dL) 95% confidence interval (CI), 0.03–0.17, $p = 0.003$; Pa_{O_2} 0.10 kPa/kPa 95% CI, 0.04–0.14. $p < 0.001$; and cerebral perfusion pressure 0.02 kPa/mm Hg 95% CI, 0.008–0.031, $p = 0.001$. Probe location, age, GCS, time of transfusion from injury, pH_{bt}, $P_{bt}CO_2$, and temperature were not significantly related to change in $P_{bt}O_2$. Improvement in $P_{bt}O_2$ was not associated with baseline hemoglobin concentration (assigned transfusion threshold group). Low $P_{bt}O_2$ (<1 kPa) was present in three patients before transfusion and there was no obvious effect on the relationship of change in $P_{bt}O_2$ to change in hemoglobin concentration [initial $P_{bt}O_2 < 1$ kPa: 0.12 kPa/(g/dL), 95% CI −0.07 to 0.32; initial $P_{bt}O_2 \geq 1$ kPa: 0.09 kPa/(g/dL), 95% CI 0.01–0.16].

Change in Cerebral Metabolism. Fifty-six percent of patients experienced an increase in LPR during the course of the study, whereas in 44% of patients, LPR remained constant or declined. In generalized estimating equation analysis, no significant relationship between change in LPR and change in hemoglobin could be demonstrated coefficient (95% CI): 0.07/(g/dL) (−0.38 to 0.51, $p = 0.76$). *Post hoc* analysis revealed a significant interaction between the change in hemoglobin concentration and baseline LPR in the prediction of change in $P_{bt}O_2$ ($p = 0.023$ for the interaction term). LPR greater than 25 is a commonly used threshold value indicative of ischemia. For those with a baseline LPR less than 25, the predicted change in $P_{bt}O_2$ per unit change in hemoglobin concentration was −0.001 kPa/(g/dL); 95% CI −0.11 to 0.11. However, for those with a baseline LPR greater than 25, $P_{bt}O_2$ increased significantly [0.18 kPa/(g/dL); 95% CI 0.06–0.31]. Unlike the described modifying effects of baseline LPR on change in $P_{bt}O_2$ with transfusion, baseline LPR did not modify the change in LPR with transfusion. No significant change in pH_{bt} occurred during the study period.

DISCUSSION

These data are the first to prospectively describe the acute effect of red blood cell transfusion on cerebral oxygenation and metabolism in patients with severe TBI. A statistically significant increase in $P_{bt}O_2$ was demonstrated after transfusion of two units of packed red blood cells. Smith et al (17) found similar results on a review of a longitudinal database of patients with TBI and subarachnoid hemorrhage. In both this study and the study by Smith et al, considerable variability in $P_{bt}O_2$ response to transfusion was noted, with 43% and 26% of patients experiencing a decline in $P_{bt}O_2$, respectively. The interpretation of the data by Smith et al limited by the omission of multivariable analytic techniques required to adjust for factors strongly related to $P_{bt}O_2$ such as Pa_{O_2} or cerebral perfusion pressure. Importantly, this study is the first to incorporate measures of cerebral cellular metabolism in the assessment of acute transfusion. No beneficial effect of transfusion could be demonstrated in terms of cerebral microdialysate LPR, purportedly a marker of cellular redox state (18), or pH_{bt}.

The increase in $P_{bt}O_2$ was most prominent in patients with an LPR greater than 25. Classically, increased LPR has been considered a marker of ischemia, but recent literature suggests LPR to be more accurately described as a marker of mitochondrial dysfunction. Vespa et al (19) correlated LPR with positron emission tomography measures of metabolism of oxygen. They found that LPR most tightly corresponds to nonischemic reduction in the cerebral metabolic rate for oxygen, a measure of mitochondrial oxidative function.

$P_{bt}O_2$ needs to be interpreted as a measure of the balance between oxygen supply and demand (20). Increased delivery

Table 3. Change in $P_{bt}O_2$

Variable	Unadjusted			Adjusted		
	Coefficient	95% Confidence Interval	*p*	Coefficient	95% Confidence Interval	*p*
[Hb] (g/dL)	0.09	0.01–0.16	0.016	0.10	0.03–0.17	0.003
Pao_2 (kPa)	0.08	0.02–0.13	0.002	0.10	0.04–0.14	<0.001
Cerebral perfusion pressure (mm Hg)	0.02	0.007–0.033	0.002	0.02	0.008–0.031	0.001
Location[a]	0.13	−1.20 to 1.46	0.85	0.63	−0.70 to 1.97	0.35
Age (yrs)	0.006	−0.032 to 0.045	0.75	0.002	−0.037 to 0.42	0.90
Glasgow Coma Scale score	−0.11	−0.31 to 0.10	0.29	−0.09	−0.30 to 0.11	0.38
Time from injury (days)	−0.05	−0.21 to 0.13	0.59	−0.08	−0.26 to 0.11	0.42
$Paco_2$ (kPa)	0.04	−0.38 to 0.30	0.8	0.01	−0.30 to 0.33	0.95
pH_b	1.21	−0.47 to 2.90	0.16	1.45	0−2.9	0.05
Temperature (°C)	0.17	−0.11 to 0.45	0.25	0.14	−0.14 to 0.43	0.33
Transfusion threshold group (9 vs. 8 g/dL)	−1.21	−2.58 to 0.17	0.09	−1.15	−2.55 to 0.26	0.11
Transfusion threshold group (10 vs. 9 g/dL)	−0.49	−1.86 to 0.89	0.49	−0.62	−2.08 to 0.85	0.41

[a]Location: probe in normal vs. abnormal tissue on computed tomography scan.

of oxygen with impaired mitochondrial function could result in higher levels of $P_{bt}O_2$. In patients with normal LPR, constant $P_{bt}O_2$ could result from increased delivery of oxygen, with an equivalent increased metabolism of oxygen. Importantly, although the absolute increase in $P_{bt}O_2$ per g/dL hemoglobin concentration was statistically significant, it is questionable if this magnitude is clinically significant. Furthermore, no effect of acute transfusion on cerebral metabolism (LPR or pH_{bt}) could be demonstrated regardless of the baseline LPR.

Weiskopf et al (21) demonstrated that a reduction of hemoglobin level to 6 and 5 g/dL produces subtle, reversible increases in reaction time and impaired immediate and delayed memory in healthy volunteers. As previously mentioned, anemia during cardiopulmonary bypass has been associated with unfavorable neurologic outcomes (7, 8). Jonas et al (7) performed a randomized clinical trial demonstrating a reduced psychomotor development index in infants undergoing cardiopulmonary bypass at hematocrit values near 22%, compared with patients maintained at hematocrit values near 28%. Habib et al (8) retrospectively reviewed 5,000 adult patients undergoing cardiopulmonary bypass. Neurologic injury (permanent stroke, coma) was more frequently experienced as lowest hematocrit increased. Experimentally, acute hemodilutional anemia accentuated cerebral tissue hypoxia after fluid percussion injury in rats (22). In pigs after fluid percussion TBI, Gibson (23) found that resuscitation with blood compared with saline was superior in terms of intracranial pressure and survival. In patients with severe TBI, low hematocrit has also been associated with detrimental outcomes. Alvarez et al (12) has described a four-fold increase in the odds of death in patients with severe TBI who experienced a hematocrit <30%. Carlson et al (13) found lowest hematocrit was associated with lower discharge GCS scores and long-term lower Glasgow Outcome Scale scores in 169 patients with severe TBI.

Despite the convincing evidence indicating that anemia is associated with negative neurologic outcome, there is little support for the correction of anemia in these patients with transfusion of packed red blood cells. McIntyre performed a subgroup analysis of 67 patients with moderate to severe TBI in Transfusion Triggers in Critical Care trial (24) that did not reveal a statistically significant difference in 30-day mortality (liberal 13%, 17% restrictive, $p = 0.64$) or multiple organ dysfunction (25). The study by Carlson et al (13) suggested that although low hematocrit was associated with unfavorable neurologic outcome, regression analysis showed that more days with hematocrit <30% were associated with improved neurologic outcomes. Transfusion was significantly associated with all lower outcome scores on discharge. Thus, although anemia may be harmful to the brain, transfusion may be associated with additional risk. Taken in context with the results of this study, these data question the use of transfusion in those stable patients with TBI.

This study has limitations that warrant discussion. The study period was relatively short. After transfusion, ~25% to 30% of prestorage 2,3-diphosphoglycerate may be restored in donor erythrocytes with resultant improvement in oxygen delivery (26). It must also be acknowledged that the $P_{bt}O_2$ and microdialysis monitors sample a relatively small portion of brain (~1.5 cm^2) that may not be representative of whole brain metabolism. Finally, the nonconsecutive nature of patient selection potentially limits generalizability of the results.

CONCLUSIONS

Transfusion of packed red blood cells acutely results in improved brain tissue oxygen without appreciable effect on cerebral metabolism as measured by LPR or pH_{bt}. The improvement in brain tissue oxygenation is primarily seen in those with deranged cerebral metabolic status at baseline. These data suggest that a reevaluation of transfusion practice in patients with severe TBI is warranted.

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REFERENCES

1. Adekoya N, Thurman DJ, White DD, et al: Surveillance for traumatic brain injury deaths—United States, 1989–1998. *MMWR Surveill Summ* 2002; 51:1–14
2. Zygun DA, Laupland KB, Hader WJ, et al: Severe traumatic brain injury in a large Canadian health region. *Can J Neurol Sci* 2005; 32:87–92
3. Kraus JF, Black MA, Hessol N, et al: The

incidence of acute brain injury and serious impairment in a defined population. *Am J Epidemiol* 1984; 119:186–201
4. Masson F, Thicoipe M, Aye P, et al: Epidemiology of severe brain injuries: A prospective population-based study. *J Trauma* 2001; 51: 481–489
5. Tiret L, Hausherr E, Thicoipe M, et al: The epidemiology of head trauma in Aquitaine (France), 1986: A community-based study of hospital admissions and deaths. *Int J Epidemiol* 1990; 19:133–140
6. Dikmen SS, Machamer JE, Powell JM, et al: Outcome 3 to 5 years after moderate to severe traumatic brain injury. *Arch Phys Med Rehabil* 2003; 84:1449–1457
7. Jonas RA, Wypij D, Roth SJ, et al: The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: Results of a randomized trial in infants. *J Thorac Cardiovasc Surg* 2003; 126: 1765–1774
8. Habib RH, Zacharias A, Schwann TA, et al: Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: Should current practice be changed? *J Thorac Cardiovasc Surg* 2003; 125:1438–1450
9. Pickett JL, Theberge DC, Brown WS, et al: Normalizing hematocrit in dialysis patients improves brain function. *Am J Kidney Dis* 1999; 33:1122–1130
10. Gopinath SP, Robertson CS, Contant CF, et al: Jugular venous desaturation and outcome after head injury. *J Neurol Neurosurg Psychiatr* 1994; 57:717–723
11. Robertson CS, Valadka AB, Hannay HJ, et al: Prevention of secondary ischemic insults after severe head injury. *Crit Care Med* 1999; 27:2086–2095
12. Alvarez M, Nava JM, Rue M, et al: Mortality prediction in head trauma patients: Performance of Glasgow Coma Score and general severity systems. *Crit Care Med* 1998; 26: 142–148
13. Carlson AP, Schermer CR, Lu SW: Retrospective evaluation of anemia and transfusion in traumatic brain injury. *J Trauma* 2006; 61:567–571
14. Gaehtgens P, Marx P: Hemorheological aspects of the pathophysiology of cerebral ischemia. *J Cereb Blood Flow Metab* 1987; 7:259–265
15. Pendem S, Rana S, Manno EM, et al: A review of red cell transfusion in the neurological intensive care unit. *Neurocrit Care* 2006; 4:63–67
16. Patel H, Menon D, Tebbs S, et al: Specialist neurocritical care and outcome from head injury. *Intensive Care Med*, 2002; 28: 547–553
17. Smith MJ, Stiefel MF, Magge S, et al: Packed red blood cell transfusion increases local cerebral oxygenation. *Crit Care Med* 2005; 33: 1104–1108
18. Hillered L, Vespa PM, Hovda DA: Translational neurochemical research in acute human brain injury: The current status and potential future for cerebral microdialysis. *J Neurotrauma* 2005; 22:3–41
19. Vespa P, Bergsneider M, Hattori N, et al: Metabolic crisis without brain ischemia is common after traumatic brain injury: A combined microdialysis and positron emission tomography study. *J Cereb Blood Flow Metab* 2005; 25:763–774
20. Vespa PM: Brain tissue oxygen monitoring: A measure of supply and demand. *Crit Care Med* 2006; 34:1850–1852
21. Weiskopf RB, Kramer JH, Viele M, et al: Acute severe isovolemic anemia impairs cognitive function and memory in humans. *Anesthesiology* 2000; 92:1646–1652
22. Hare GMT, Mazer CD, Rassouli AP, et al: Hemodilutional anemia accentuates cerebral hypoxia following traumatic brain injury. *J Neurotrauma* 2003; 20:P421
23. Gibson JB, Maxwell RA, Schweitzer JB, et al: Resuscitation from severe hemorrhagic shock after traumatic brain injury using saline, shed blood, or a blood substitute. *Shock* 2002; 17:234–244
24. Hebert PC, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; 340: 409–417
25. McIntyre LA, Fergusson DA, Hutchison JS, et al: Effect of a liberal versus restrictive transfusion strategy on mortality in patients with moderate to severe head injury. *Neurocrit Care* 2006; 5:4–9
26. Beutler E, Wood L: The in vivo regeneration of red cell 2,3 diphosphoglyceric acid (DPG) after transfusion of stored blood. *J Lab Clin Med* 1969; 74:300–304