

Gender Influences Cerebral Oxygenation After Red Blood Cell Transfusion in Patients with Severe Traumatic Brain Injury

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Published online: 14 September 2010
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Abstract

Background Important differences with respect to gender exist in the prognosis and mortality of traumatic brain injury (TBI) patients. The objective of this study was to assess the role of gender as an independent factor in cerebral oxygenation variations following red blood cell transfusion (RBCT).

Methods This retrospective analysis of a prospective study was conducted on patients with severe TBI. Hemoglobin levels were measured at baseline and 6 h after transfusion. Brain tissue oxygen pressure (PbrO₂), cerebral perfusion pressure (CPP), intracranial pressure (ICP), and mean arterial pressure (MAP) were measured at baseline, at the end of RBCT and at 1, 2, 3, 4, 5, and 6 h after transfusion. After the patients were stratified into two groups according to gender, the effect of RBCT on PbrO₂ (cerebral oxygenation) was analyzed using a multivariate analysis of

variance with repeated measures (MANOVA). The MANOVA was repeated after adjusting for all covariables with baseline differences between groups.

Results At baseline, we found differences in age ($P = 0.01$), weight ($P = 0.03$), MAP ($P = 0.01$), ISS ($P = 0.05$), and CCP ($P = 0.01$) between the groups. After adjusting for these co-variables, we observed that gender and age were related to the increase in PbrO₂ ($P = 0.05$ and $P = 0.04$, respectively).

Conclusions Our results suggest that the effect of RBCT on cerebral oxygenation, as measured by PbrO₂, is greater in women than in men.

Keywords Brain tissue oxygen pressure · Cerebral oxygenation · Gender · Severe traumatic brain injury and transfusion

Abbreviations

CPP	Cerebral perfusion pressure
EtCO ₂	End-tidal CO ₂
FiO ₂	Oxygen inspired fraction
GCS	Glasgow Coma Scale
ICP	Intracranial pressure
MAP	Mean arterial pressure
PaO ₂	Oxygen arterial pressure
PbrO ₂	Brain tissue oxygen pressure
TCDB	Traumatic Coma Data Bank
TBI	Traumatic brain injury

Introduction

Severe traumatic brain injury (TBI) is a major cause of death and disability, particularly in those aged 15–30 years.

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The severity scoring Acute Physiology and Chronic Health Evaluation II score (APACHE), Glasgow Coma Scale, age, and blood transfusion, among other factors, have been consistently used as risk factors that influence the clinical outcome of these patients. Although there is no disagreement that these risk factors are strongly and negatively related to poor prognoses, controversy exists regarding the influence of gender on early and late clinical outcome in TBI patients.

There is emerging evidence suggesting that males and females respond differently to head injuries. In an early study [1], female TBI patients had a better work capacity during the rehabilitation period. These results were corroborated in a large cohort of 72,294 patients with moderate to severe TBI, where females showed a significantly lower risk in both mortality and developing any complications [2].

Conversely, in a large retrospective study of 1,830 TBI patients, no differences were observed between men and women with respect to mortality or development of acute respiratory distress syndrome, pneumonia, or systemic sepsis [3]. Moreover, clinical outcome has been shown to be worse in TBI female patients when evaluated by randomized controlled [4], observational [5], and large meta-analysis [6] studies.

Differences in the susceptibility to cerebral edema, neuronal death via apoptotic mechanisms [7], and gender-related hormones [8–11] are suspected explanations of how gender influences clinical outcome in TBI patients, even though no definitive evidence seems to exist.

Cerebral hypo-oxygenation is the leading cause of preventable death and disability in patients sustaining severe TBI. Whether males and females have different levels of baseline post-traumatic cerebral hypoxia and whether gender influences a patient's response to goal-directed therapy to relieve cerebral hypoxia remains largely unknown. In healthy volunteers [12], no gender-related differences appear to exist with respect to cerebral oxygenation when evaluated using near-infrared spectroscopy. Most patients with severe TBI are monitored through a brain tissue oxygen pressure intracranial probe (PbrO₂), which allows continuous assessment of cerebral oxygenation. We and others [13, 14] have previously demonstrated that transfusion of red blood cells (RBCs) increases cerebral oxygenation in most (but not all) anemic TBI patients.

We hypothesized that men and women behave differently with respect to red blood cell transfusion (RBCT)-mediated increases in cerebral oxygenation, assessed by PbrO₂. Therefore, this study aimed to assess the role of gender as an independent factor modifying PbrO₂ variations after transfusion.

Methods

Setting and Patients

We performed a retrospective analysis of a database of prospectively followed patients with severe TBI. All the patients were admitted to the neurotrauma intensive care unit (22 beds) at the public University Hospital Virgen del Rocío, Seville, Spain (a level I trauma center with a capacity for 2,000 beds) from March 2004 to March 2007. The Institutional Review Board approved this study and waived the need for patient's informed consent.

The inclusion and exclusion criteria for this study have been extensively described elsewhere [13, 15]. In brief, stable anemic patients with severe TBI (Glasgow Coma Score ≤ 8) and fulfilling all of the following criteria were included: (1) had an intraparenchymal intracranial pressure (ICP) and PbrO₂ catheter previously inserted; (2) had passed the initial resuscitation phase; (3) had no evidence of bleeding; (4) had pre-transfusion hemoglobin levels ≤ 95 g/l; (5) that were hemodynamically stable (mean arterial pressure > 75 mm Hg with no or low-dose vasoactive drugs); (6) were under controlled mechanical ventilation (patients sedated and fully adapted to the ventilator); (7) had an oxygen arterial pressure (PaO₂)/oxygen inspired fraction (FiO₂) ratio > 250 ; and (8) had a body temperature $< 38^\circ\text{C}$. Unstable patients (frequent changes in arterial pressure, inspired oxygen concentration, or ventilatory regimen) or those requiring urgent surgery within the following few hours of admission were excluded.

Study Strategy

Cerebral oxygen pressure was monitored using the LICOX IMC System (GMS, Kiel-Mielkendorf, Germany). Whenever possible, the probe was placed in normal brain tissue rather than in pericontusional or contused tissue. Blood pressure recordings were obtained with a radial artery fluid-coupled system. End-tidal carbon dioxide (ETCO₂) and peripheral oxygen saturation (SaO₂) were continuously monitored by capnography and pulse-oximetry. All the methods have been previously described in detail [15].

All the patients were sedated with a midazolam and morphine infusion. In addition, a vecuronium infusion was used when proper synchronization with the ventilator was not possible. During the study time, ventilation was adjusted to maintain normal ETCO₂ values and oxygen saturation $> 96\%$. During the first 6 h of monitoring, all the physiologic variables were closely observed, and changes in ventilatory setting, ETCO₂, FIO₂, levels of sedation and analgesia, and infusion of fluids and vasoactive drugs were minimized.

Criteria for transfusing to neurocritical patients have been published elsewhere [16]. However, the transfusion decision was made by the physician responsible for the patient in each case, and the decision was independent of the purposes of this study. Informed consent was obtained from the patient's relative prior to RBCT, and all the patients received prestorage leukodepleted packed RBCs stored in additive solution (saline, adenine, glucose, and mannitol) and anticoagulant preservative (citrate–phosphate–dextrose). After baseline measurements, one unit of packed RBCs (approximately 270 ml) was transfused along a 120-min period depending on the baseline hemoglobin level and the patient's clinical status.

Study Measurements

Eight sets of data were prospectively collected for each transfusion episode: one pre-transfusion set (at baseline) and seven post-transfusion sets (at the end of transfusion and at post-transfusion hours 1, 2, 3, 4, 5, and 6). PbrO₂, cerebral perfusion pressure (CPP), intracranial pressure (ICP), and mean arterial pressure (MAP) were measured in each period. Arterial blood lactate level, FiO₂ and PaO₂, and hemoglobin were only measured at baseline and 6 h after transfusion.

Other Recorded Variables

Age (years), weight (kg), length of storage of transfused erythrocytes (days), RBCT (units/patient), Injury Severity Score (ISS), Glasgow Coma Score, APACHE II score, 6-month mortality, and Traumatic Coma Data Bank based on Computerized Tomography (TCDB CT) were also recorded.

Statistical Analysis

The Kolmogorov–Smirnov test was used to assess the normality of the distribution of continuous variables. Continuous variables are presented as means \pm standard deviation (SD), and qualitative variables are presented as number of cases and percentages. Parametric unpaired Student's *t* tests were used for comparison of non-repeated quantitative variables such as the values of PbrO₂ over the dependent variable time. A MANOVA test was used with PbrO₂ as the within-subject variable and gender as the between-subject variable. Age, weight, CPP, ISS, and hemoglobin were included as covariables because there were baseline differences between the groups. Pre-transfusional hemoglobin was included because it was an important variable related to transfusion. All the analyses were performed using statistical software (SPSS 17.0; SPSS, Chicago, IL).

Results

Eighty-eight patients were evaluated over the 3-year study period. Data were analyzed after the patients were stratified into two groups according to gender, resulting in seventy men (79.5%) and eighteen women (20.5%). Baseline characteristics of patients are reported in Table 1, which shows between-group differences regarding age, weight, MAP, ISS, and CCP. After RBCT, the hemoglobin level increased from 88.4 ± 7.6 to 102 ± 10 g/l ($P = 0.02$) in men and from 86.2 ± 10 to 106 ± 12 g/l ($P = 0.01$) in women. No significant differences between the groups were observed with respect to pre transfusion ($P = 0.31$) and post-transfusion ($P = 0.07$) hemoglobin levels.

As shown in Table 2, both groups of patients had homogeneous baseline PbrO₂ levels and experienced an increment in PbrO₂ levels following RBCT. However, this increment was higher in women than in men throughout the observation period ($P = 0.04$), particularly during the first 4 post-transfusion hours (Table 2 and Fig. 1). The maximum increment, with respect to baseline, was at 3 h after RBCT (31.9% in women vs. 17.2% in men; $P < 0.05$).

To further investigate the relationship between the post-RBCT PbrO₂ increase and gender, we repeated the MANOVA analysis after adjusting for all covariables with baseline differences between groups (i.e., weight, CPP, age, and ISS) (Table 1). The MAP was not included because of its relationship to the CPP. Hemoglobin levels were included because of their relation to the transfusion. In this adjusted model, it was observed that both patient gender ($P = 0.05$) and age ($P = 0.04$) were related to the increase in PbrO₂. Age was inversely related to the PbrO₂ increment in both groups. Interestingly, despite the fact that women in our study were older (Table 1), they always experienced higher PbrO₂ increments than men.

Discussion

This retrospective study investigated whether gender influences the short-term response to RBCT on cerebral oxygenation. Cerebral oxygenation was measured using an intracerebral PbrO₂ probe and evaluated over a 6-hr post-transfusion observation period. Eighty-eight patients with severe TBI included in the study were divided into two groups according to gender. Although both groups had similar baseline PbrO₂ values before RBCT, women had greater cerebral oxygenation after RBCT throughout the entire observation period ($P = 0.04$), with the largest differences observed at post-transfusion hours 1, 2, and 3 (Table 2).

Cerebral hypo-oxygenation is the leading cause of preventable death and disability in patients sustaining severe

Table 1 Baseline characteristics of patients according to gender

	Whole sample (n = 88)	Male (n = 70)	Female (n = 18)	P
Age (years)	35.4 ± 15.9	32.8 ± 13.9	45.5 ± 19.4	0.01
Weight (kg)	73.7 ± 10.3	74.9 ± 10.5	69.1 ± 7.7	0.03
Length of storage of transfused erythrocytes (days)	15.3 ± 8.9	16.1 ± 8.9	12.3 ± 8.6	0.12
Hemoglobin (g/l)	87.9 ± 8.2	88.4 ± 7.7	86.2 ± 10.3	0.31
RBCT (units/patient)	1.6 ± 0.5	1.6 ± 0.5	1.5 ± 0.5	0.90
ISS	28.6 ± 5.7	29.2 ± 5.7	26.3 ± 5.5	0.04
TCDB CT				
II	31 (35)	24 (34)	7 (39)	0.10
III	17 (19)	16 (23)	1 (6)	
IV	8 (9)	4 (6)	4 (22)	
V	26 (30)	22 (31)	4 (22)	
VI	6 (7)	4 (6)	2 (11)	
GCS	5.8 ± 1.8	5.8 ± 1.9	6.2 ± 1.6	0.47
APACHE	15.3 ± 4.6	14.9 ± 4.5	16.5 ± 5.0	0.23
PbrO ₂ (mm Hg)	24.1 ± 9.4	23.9 ± 9.6	24.8 ± 9.0	0.74
StO ₂ (%)	99.6 ± 0.9	99.5 ± 1.0	99.7 ± 0.7	0.54
MAP (mm Hg)	90.9 ± 11.3	92.5 ± 10.9	84.4 ± 10.5	0.01
ICP (mm Hg)	14.9 ± 5.9	14.9 ± 6.2	14.6 ± 4.7	0.81
CCP (mm Hg)	75.8 ± 11.6	77.4 ± 11.1	69.8 ± 11.9	0.01
PaO ₂ /FiO ₂	297.9 ± 133.2	294.8 ± 120.1	309.9 ± 179.3	0.97
Lactate (mmol/l)	1.0 ± 0.4	1.0 ± 0.4	1.0 ± 0.5	0.96
Mortality at 6 months	14 (19.9)	11 (15.7)	3 (16.4)	0.96

APACHE Acute Physiology and Chronic Health Evaluation, ISS Injury Severity Score, GCS Glasgow Coma Scale, TCDB Trauma Coma Data Bank, TCDB CT categorization (Traumatic Coma Data Bank based on computerized tomography) as number (percentage) of patients for each categorization, MAP mean arterial pressure, ICP intracranial pressure, CPP cerebral perfusion pressure, PbrO₂, brain tissue oxygen pressure, StO₂, peripheral arterial oxygen saturation assessed by pulse-oxymetry

Table 2 Time-course of brain tissue oxygen pressure (PbrO₂) from baseline to 6 h after transfusion, according to gender

PbrO ₂ (mm Hg)	Male (n = 70)	Female (n = 18)	P value
Baseline	23.9 ± 9.6	24.8 ± 9.0	0.748
End of transfusion	26.4 ± 9.1	29.8 ± 11.3	0.185
Post-transfusion hour 1	26.4 ± 9.6	32.1 ± 12.2	0.036
Post-transfusion hour 2	26.3 ± 9.0	32.3 ± 13.1	0.024
Post-transfusion hour 3	27.2 ± 9.8	32.6 ± 13.1	0.050
Post-transfusion hour 4	26.2 ± 9.5	30.8 ± 11.0	0.077
Post-transfusion hour 5	26.4 ± 9.5	30.0 ± 10.2	0.159
Post-transfusion hour 6	26.2 ± 9.5	29.6 ± 11.8	0.198

Values expressed as mean ± SD

P male versus female

TBI. Thus, goal-directed therapy for maintaining PbrO₂ values in the normal range has been demonstrated to reduce mortality and to improve the clinical outcome of patients with TBI following major trauma [17]. Our group and others have previously documented that PbrO₂ is increased after RBCT [13, 14]. However, whether gender plays a role

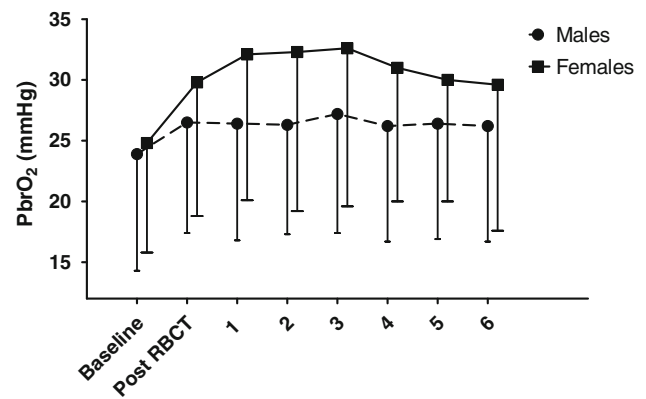


Fig. 1 Variations of PbrO₂ after RBCT in men versus women (P = 0.04). Data are plotted as means ± SD

in the effect of RBCT on cerebral oxygenation remains to be elucidated.

There are several reasons that may account for the observed gender-related differences in PbrO₂ after RBCT. First, women have higher levels of circulating estrogens and progesterone, which could exert a neuroprotective

effect due to their anti-inflammatory properties [11, 18, 19]. Estrogen has been shown to improve vasodilatation via an enhancement in nitric oxide (NO) production by the endothelial isoform of NO synthase (eNOS) due to increases in both endothelial eNOS expression and level of activation [20]. However, higher cerebral flow velocities have been shown in both pre-pubertal girls [21] and elderly women [22], so it is unlikely that gender differences in the increment of PbrO₂ after RBCT can be explained solely on the basis of differences in estrogen levels. In this regard, data from experimental TBI models in animals have suggested that progesterone may be associated with decreased cerebral edema following brain injury [18, 23], which might contribute to better cerebral perfusion in women. However, despite the apparent protective effect of female steroid hormones in animal models, studies in humans sustaining TBI, specifically designed to detect gender-related differences, suggest that women actually have a poorer outcome than men [4–6, 24].

Second, although both women and men received the same volume of RBCT in our study, the body weight of women was significantly lower than in men. Thus, women had a lower intravascular volume and, consequently, the effect of RBCT on hemoglobin levels might have been proportionately greater, thus leading to a greater increase in PbrO₂.

Greater mortality and poorer functional outcome have been shown to occur in the elderly following TBI [25]. Kirkness et al. [24] examined the interaction of gender and age in relation to post-injury outcome in a population of 157 individuals with TBI, and they concluded that females aged 30 years or older had a significantly poorer outcome than either males or younger females, suggesting that both gender and age were the main factors influencing clinical outcome. In fact, our data show that the increase of PbrO₂ was inversely proportional to the age of the patients. In our study population, the women were significantly older than the men, yet the increase in PbrO₂ was higher, suggesting that gender had a greater influence on cerebral oxygenation than age. Nevertheless, to our knowledge, no study has investigated the relationship between aging and increases of cerebral oxygenation after transfusion. Given that we did not find any differences in 6-month mortality between men and women, the opposite effects of age and gender on brain oxygenation and outcome might have cancelled each other.

This study has limitations. First, its observational design precludes the establishment of any causal relationship. Second, the male-to-female ratio was unbalanced. This limitation is difficult to avoid because at our institution, as well as others, there are more male than female TBI patients admitted to the ICU. Third, PbrO₂ might not be an accurate tool to demonstrate the effect of RBCT on tissue oxygen

uptake. However, previous studies have consistently shown an increase in PbrO₂ after RBCT in patients with severe TBI [13, 14, 26]. Finally, in our study, the effect of RBCT on cerebral oxygenation was only measured during the initial 6 post-transfusion hours. This was because previous studies have failed to demonstrate an advantage to increasing the follow-up period from 6 to 24 h [13, 26].

In summary, the main finding of this study was that women and men with severe TBI have differential cerebral oxygenation following RBCT. Women experienced a greater increase in cerebral oxygenation after RBCT than men, at least during the first 6 h after transfusion. Given the possible implications, these preliminary results should be corroborated by future studies with larger cohorts.

Acknowledgments This study is supported by Spanish Government funds (Fondo de Investigación Sanitaria—FIS—Proyecto de Investigación: PI 081069), by Consejería de Salud de la Junta de Andalucía (Proyecto de Investigación: PI 0157/2006) and by Fundación MAPFRE 2008.

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