Effect of Hemoglobin Transfusion Threshold on Cerebral Hemodynamics and Oxygenation

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Abstract

Cerebral dysfunction caused by traumatic brain injury may adversely affect cerebral hemodynamics and oxygenation leading to worse outcomes if oxygen capacity is decreased due to anemia. In a randomized clinical trial of 200 patients comparing transfusion thresholds <7 g/dl versus 10 g/dl, where transfusion of leukoreduced packed red blood cells was used to maintain the assigned hemoglobin threshold, no long-term neurological difference was detected. The current study examines secondary outcome measures of intracranial pressure (ICP), cerebral perfusion pressure (CPP), and brain tissue oxygenation (PbtO₂) in patients enrolled in this randomized clinical trial. We observed a lower hazard for death (hazard ratio [HR]=0.12, 95% confidence interval [CI]=0.02–0.99) during the first 3 days post-injury, and a higher hazard for death after three days (HR=2.55, 95% CI=1.00–6.53) in the 10 g/dl threshold group as compared to the 7 g/dL threshold group. No significant differences were observed for ICP and CPP but MAP was slightly lower in the 7 g/dL group, although the decreased MAP did not result in increased hypotension. Overall brain tissue hypoxia events were not significantly different in the two transfusion threshold groups. When the PbtO₂ catheter was placed in normal brain, however, tissue hypoxia occurred in 25% of patients in the 7 g/dL threshold group, compared to 10.2% of patients in the 10 g/dL threshold group ($p=0.04$). Although we observed a few differences in hemodynamic outcomes between the transfusion threshold groups, none were of major clinical significance and did not affect long-term neurological outcome and mortality.

Key words: blood flow; clinical trial; intracranial pressure; prospective study; traumatic brain injury

Introduction

ANEMIA IS COMMON in the acute period after traumatic brain injury (TBI), affecting up to 50% of patients.¹ Normal cerebral autoregulation compensates for the reduced oxygen carrying capacity caused by anemia by increasing cerebral blood flow (CBF) to maintain cerebral oxygenation.^{2–7} Dysfunction of cerebrovascular autoregulation caused by the trauma, however, could prevent an adequate increase in CBF. Alternatively, CBF could be increased sufficiently, but the resulting cerebral vasodilatation needed to achieve the increase in CBF may result in an increased intracranial pressure (ICP).⁸ In addition, impaired cerebral autoregulation can result in regional areas of hypoperfusion.⁹ Therefore, patients with TBI may have impaired oxygen delivery in the setting of anemia that is typically well-tolerated in normal subjects.

Because anemia impairs cerebral oxygen delivery, could increase intracranial pressure, and because the decrease in intravascular blood volume could make it more difficult to maintain an adequate blood pressure, anemia is thought to be detrimental to recovery from TBI. Thus, patients are commonly treated to maintain a hemoglobin concentration of at least 10 g/dL.

A recently completed randomized clinical trial comparing transfusion thresholds <7 g/dL versus 10 g/dL showed no long-term neurological benefit of this practice.¹⁰ In a *post hoc* analysis of mortality, we observed possible differences between the transfusion threshold groups in the first few days after injury. A possible explanation for early difference in mortality might be that a lower hemoglobin concentration may contribute toward early cerebral ischemia.

The purpose of this study was to examine the secondary outcome measures of intracranial pressure, cerebral perfusion pressure, and

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brain tissue oxygenation in the patients enrolled in this randomized clinical trial. The hypothesis of these secondary analyses was that the 7 g/dL would have detrimental effects on cerebral hemodynamics. Specifically, we hypothesized that a hemoglobin threshold of 7 g/dL, compared with a threshold of 10 g/dL, would result in a lower mean arterial pressure (MAP) as a result of lower blood volume, would result in higher ICP and higher middle cerebral artery flow velocity (mcaFV) because a higher CBF would be needed to maintain cerebral oxygen delivery, and a lower brain tissue pO_2 (PbtO₂) would occur as a consequence of the lower oxygen content of the blood.

Methods

Study design

The study aims are pre-specified secondary analyses of a randomized clinical trial. Details of the design and the results of the primary analysis have been reported previously.¹⁰ Briefly, participants were randomly assigned to administration of erythropoietin or placebo and to hemoglobin transfusion thresholds of 7 or 10 g/dL in a 2×2 factorial design. An interaction between erythropoietin and transfusion threshold on 6-month neurological outcome was not detected, allowing analysis of all patients in the trial regardless of randomization.

Participants with a closed head injury who were not able to follow commands after resuscitation and could be enrolled within 6 h of injury were recruited from two level 1 trauma centers. Patients were excluded if their Glasgow Coma Scale (GCS) score was three with fixed and dilated pupils, had penetrating trauma, pregnancy, life-threatening systemic injuries, or severe pre-existing disease. Transfusion of leukoreduced packed red blood cells was used to maintain the assigned hemoglobin threshold.

A standard management protocol that included control of ICP to less than 20 mm Hg, maintenance of MAP at least 80 mm Hg, and CPP at least 60 mm Hg was followed throughout the study (details in Appendix 1, Robertson and associates¹⁰). The PbtO₂ probe was placed when possible in an area of injured brain, or in the right frontal white matter when the injury was diffuse. The goal for PbtO₂ was at least 10 mm Hg, and a standard algorithm was followed to treat episodes of brain tissue hypoxia.¹¹

Data analysis

Statistical analyses were conducted on an intent-to-treat basis (two patients who were assigned to the 7 g/dL transfusion threshold were mistakenly treated as if they were in the 10 g/dL group, and there were no crossovers between the randomized groups), and statistical significance was determined by a two-sided *p* value of <0.05 for all analyses with the exception of interaction terms (<0.15). The Wilcoxon rank-sum test was used to compare continuous measures that were not normally distributed among the transfusion threshold groups. Chi-square or Fisher exact test was used to compare categorical variables, when appropriate. The effect of the transfusion threshold group on dichotomous and continuous outcomes among subgroups was tested by including the subgroup×threshold group term in a logistic and linear regression model, respectively.

The generalized estimating equations (GEE) approach was used to compare continuous hemodynamic measures over time until 250 h after admission to the intensive care unit (ICU) among the transfusion threshold groups, adjusting for death. This method is an extension of generalized linear models for analyzing longitudinal data. The threshold group coefficient term can be interpreted as a measure of the difference in the hemodynamic measure between the threshold groups at ICU admission. The threshold-by-time (hour after ICU admission) coefficient can be interpreted as a measure of the difference in slope over time in the hemodynamic measure among the transfusion threshold groups.

Because of the nonlinearity of the data, we fit a restricted cubic spline function (Supplementary Appendix 1; see online supplementary material at <http://www.liebertpub.com>) to the hour after ICU admission with 5 degrees of freedom: two boundary knots at 0 and 250 h, and four internal knots at the 20th, 40th, 60th, and 80th quantiles of hour for ICP and CPP outcomes. The test for nonlinearity was conducted by comparing the Quasi-likelihood Information Criterion (QIC) for models with and without the spline parameters.¹² Similarly, QIC was used to choose the working correlation structure.

Because monitoring was invasive, hemodynamic data were not usually collected if the patient went to the operating room or after the ICP had stabilized. Ignoring the missing values or assuming that they are missing at random can potentially bias the results. Therefore, we multiply imputed missing ICP and MAP values and used the Rubin formula¹³ to combine the GEE coefficient estimates. CPP was calculated from the imputed ICP and MAP values. A single multivariate Wald *p* value was calculated for the spline terms, and the confidence intervals (CIs) were omitted for the spline coefficients because of the uninterpretability of the individual spline components.

When hourly monitoring was being conducted but a single hour had a missing value, the value was linearly interpolated using the adjacent hour's values. For patients who were removed from monitoring because of their values being stabilized, missing values were imputed from a normal distribution with the mean and standard deviation of the patients' nonmissing values in the last 12 h of monitoring. If the patient had fewer than five nonmissing values in the preceding period, we took a random sample of patients who also had monitoring removed because of stabilized ICP, pooled their values 12 h before their last observation, and computed the mean and standard deviation (SD) from this sample to impute values from a normal distribution with this mean and SD. Similarly, the mean and SD of values just before a patient went to the operating room for elevated ICP was used to sample missing values for similar patients.

Cox regression analyses were performed to determine whether or not transfusion threshold assignment increased the risk of death adjusted for enrollment motor Glasgow Coma Scale score. Censoring time was defined as date of withdrawal, death, or patient status at 6 months after injury, whichever occurred first. The proportional hazards assumption was examined using Schoenfeld residual plots, and we tested for a treatment by time (time-dependent) interaction. Because the proportional hazards assumption of the Cox model for mortality was violated, we fit a piecewise proportional hazards model in two separate time intervals, dichotomized at day 3, adjusting for enrollment motor GCS score. Day 3 was not a pre-specified hypothesis but was chosen as the time separating the two intervals based on maximizing the log partial likelihood. All analyses were conducted using R version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Mortality

Survival to 6 months was known for 190 (95%) of the 200 patients enrolled in the study. Fourteen patients in the 7 g/dL transfusion threshold group and 17 patients in the 10 g/dL transfusion threshold group died during the 6 months of follow-up. As previously reported,¹⁰ the overall Kaplan-Meier survival curves were not significantly different for the two transfusion threshold groups (log rank test, *p*=0.72). To adjust for injury severity, Cox regression analyses were performed as a secondary analysis.

There was a lower hazard for death (hazard ratio [HR]=0.12, 95% CI=0.02–0.99) during the first 3 days post-injury, and a higher hazard for death after 3 days (HR=2.55, 95% CI=1.00–6.53) in the 10 g/dL threshold group (Table 1, Fig. 1). Because the

TABLE 1. PIECEWISE COX PROPORTIONAL HAZARDS MODEL ESTIMATES FOR MORTALITY ADJUSTED FOR ENROLLMENT GLASGOW COMA SCALE*

	Hazard ratio	95% Confidence interval	p value
Transfusion threshold 10 g/dL if time ≤ 3 days	0.12	0.02–0.99	0.049
Transfusion threshold 10 g/dL if time > 3 days	2.55	1.00–6.53	0.050
Enrollment motor GCS 4–5	0.20	0.09–0.44	$<.001$

GCS, Glasgow Coma Scale.

*Because the proportional hazards assumption was violated, the transfusion threshold variable was fit in two separate time intervals.

mortality analysis suggested possible early benefit for the 10 g/dL transfusion threshold group, we next examined early cerebral hemodynamic and oxygenation measures.

ICP

Of the 200 patients enrolled in the study, 199 underwent ICP monitoring. The monitors were a ventriculostomy catheter in 193

patients and a parenchymal monitor in 6 patients. One patient woke up quickly and did not need ICP monitoring, and two additional patients withdrew from the study before recording any ICP data, leaving 197 patients with ICP data for analysis (97 in the 7 g/dL threshold group and 100 in the 10 g/dL threshold group). The median number of hours that ICP was monitored was 108 (interquartile range [IQR] = 126, range = 548) hours and was not different in the two transfusion threshold groups (Table 2). Eighty-six (43%) patients underwent prolonged monitoring, defined as having been monitored for more than 5 total days. In the first 48, 120, and 250 h after ICU admission, 12%, 25%, and 48% of ICP values were missing, respectively.

Figure 2 (row 1) shows the trend plot of ICP over the first 10 days after ICU admission in the two transfusion threshold groups using all available data and for available data plus one set of imputed values. Based on the available data, ICP was lowest during the first 24 h after ICU admission and gradually increased over time in both treatment groups, perhaps as the patients who had less severe intracranial hypertension were no longer monitored. Hence, the increase in ICP over time is likely because of the increasing omission of patients with normal ICP over time. This was confirmed in the plots of including imputed data where ICP increased over the first 50 h and then decreased again.

The GEE model using the imputed data failed to detect any differences between the two transfusion threshold groups at baseline (Fig. 4, Supplementary Table S1, $p=0.49$ for intercept term, see online supplementary material at <http://www.liebertpub.com>) or over time (Fig. 4, Supplementary Table S1, $p=0.15$ for overall slope term, see online supplementary material at <http://www.liebertpub.com>). The GEE model using the available, nonimputed data also failed to detect a difference.

The median ICP was 15.63 (IQR=4.7) mm Hg in the 7 g/dL threshold group, and 15.60 (IQR=5.6) mm Hg in the 10 g/dL threshold group. The number of patients whose ICP never exceeded 25 mm Hg was 37/97 (38.1%) in the 7 g/dL threshold group, compared with 22/100 (22.0%) in the 10 g/dL threshold group ($p=0.01$). The pre-specified summary variables for intracranial hypertension, including the time the ICP was greater than 30 mm Hg, the highest ICP recorded, and the highest ICP Treatment Score, were not significantly different in the two transfusion threshold groups (Table 2). There was also no difference detected in the need for individual therapies, including mannitol, barbiturate coma, or decompressive craniectomy, to control ICP in the two treatment groups (Table 2).

The occurrence of intracranial hypertension was recorded as an adverse event during the study. The event was considered serious if it necessitated surgical intervention or barbiturate coma or if it resulted in neurological deterioration or death. Refractory intracranial hypertension defined in this way developed in 52 patients, 23 in the 7 g/dL threshold group compared with 29 in the 10 g/dL threshold group ($p=0.40$). Nine patients died of intracranial hypertension, six in the 7 g/dL threshold group and three in the 10 g/dL threshold group ($p=0.33$).

MAP and CPP

All 200 patients enrolled in the study had monitoring of MAP. Two of the patients withdrew from the study before any MAP data was recorded, leaving 198 sets of blood pressure data for analysis (97 in the 7 g/dL threshold group and 101 in the 10 g/dL group). In the first 250 h after ICU admission, 13% of MAP values were missing. Figure 2 (row 2) shows trend plots of MAP over the first 10 days after ICU admission in the two transfusion threshold groups

FIG. 1. Kaplan-Meier survival curves for patients enrolled with motor Glasgow Coma Scale (GCS) score 1–3 (A) and with motor GCS 4–5 (B) by transfusion threshold. TT, transfusion threshold; CI, confidence interval.

TABLE 2. INTRACRANIAL PRESSURE, INTRACRANIAL PRESSURE TREATMENT, AND BLOOD PRESSURE SUMMARY VARIABLES AND COMPLICATIONS

	7 g/dL group n=97	10 g/dL group n=100	p value
<i>ICP and ICP treatment summary variables and complications</i>			
Time ICP was monitored (h), median (IQR)	96 (132)	127.23 (129)	0.07
ICP was never >25 mm Hg, n (%)	37 (38.1)	22 (22.0)	0.01
Time ICP was >30 mm Hg (h), median (IQR)	0 (3)	1 (4)	0.07
Highest ICP recorded (mm Hg), median (IQR)	30 (16)	33 (14)	0.10
Developed serious adverse event of refractory intracranial hypertension, n (%)	22 (22.7)	27 (27.0)	0.48
Highest ICP treatment score recorded, mean (SD)	13.19 (5.0)	14.12 (5.1)	0.20
Patients requiring mannitol, n (%)	56 (57.7)	66 (66.0)	0.23
Patients requiring barbiturate coma, n (%)	9 (9.3)	14 (14.0)	0.30
Patients requiring decompressive craniectomy, n (%)	31 (32.0)	40 (40.0)	0.24
During admission surgery, n (%)	11 (11.3)	18 (18.0)	0.19
After admission, n (%)	20 (20.6)	22 (22.0)	0.81
Died of refractory intracranial hypertension, n (%)	6 (6.2)	3 (3.0)	0.33
Within 3 days of injury	5 (5.2)	1 (1.0)	0.11
After 3 days of injury	1 (1.0)	2 (2.0)	>0.99
<i>Blood pressure summary variables and complications</i>			
MAP never <70, n (%)	36 (37.1)	35 (35.0)	0.76
CPP never <50, n(%)	38 (39.2)	51 (51.0)	0.10
Developed serious adverse event of hypotension necessitating pressors, n (%)	20 (20.6)	24 (24.0)	0.57

ICP, intracranial pressure; IQR, interquartile range; SD, standard deviation; MAP, mean arterial pressure; CPP, cerebral perfusion pressure.

using available data and one of the imputed data sets. MAP was lowest on the first post-ICU admission day. MAP was slightly lower in the 7 g/dL group, compared with the 10 g/dL group, especially between days 2 and 6 post-ICU admission, but values in both groups remained well above the clinical goal of 80 mmHg.

The average MAP was 88.80 (SD=7.2) mm Hg in the 7 g/dL threshold group, and 92.30 (SD=6.4) mm Hg in the 10 g/dL

threshold group ($p=0.001$). The number of patients who never had a MAP less than 70 mm Hg was 36 (37.1%) in the 7 g/dL threshold group and 35 (35.0%) in the 10 g/dL threshold group ($p=0.76$, Table 2). The number of patients with the serious adverse event of hypotension necessitating pressors was similar in the two treatment groups: 21% in the 7 g/dL threshold group compared with 24% in the 10 g/dL threshold group ($p=0.57$). The GEE model using the

FIG. 2. Trend plot of average intracranial pressure (ICP), mean arterial pressure (MAP), and cerebral perfusion pressure (CPP) over time in the two transfusion threshold groups (TT7=7/g/dL threshold group, TT10=10 g/dL threshold group). The vertical bars indicate the standard error of the mean. The first column is available data and the second column is available data plus one set of imputed values for missing observations. ICU, intensive care unit.

FIG. 3. Trend plot of average brain tissue pO_2 (PbtO₂) over time in the two transfusion threshold groups (TT7=7/g/dL threshold group, TT10=10 g/dL threshold group). The vertical bars indicate the standard error of the mean. (Left plot) all patients; (top right) when the probe was placed in normal tissue; (bottom right) when the probe was placed in contused brain. ICU, intensive care unit.

multiply imputed data failed to identify any statistically significant differences between the transfusion threshold groups (Fig. 4, Supplementary Table S2, see online supplementary material at <http://www.liebertpub.com>).

Over the first 48, 120, and 250 h after ICU admission, 13%, 26%, and 48% of CPP values were missing. Figure 2 (row 3) shows trend plots of CPP over the first 10 days after injury in the two transfusion threshold groups using available data and one of the calculated data from imputed ICP and MAP. CPP was well above the goal of 60 mm Hg in both groups. The GEE model using available data failed to detect any differences over time in the two transfusion threshold groups. Figure 2 (middle right graph) suggests that the 10 g/dL threshold group had slightly higher CPP values over time than the 7 g/dL threshold group.

The GEE intercept coefficient for the transfusion threshold group was marginally significant in each individual imputed data set (p between 0.04 and 0.07); however, likely because of the variability caused by the high percentage of missing values, no difference was detected using the combined multiple imputation estimate (Fig. 4,

Supplementary Table S3, $p=0.16$ for intercept coefficient, see online supplementary material at <http://www.liebertpub.com>). The average CPP was 72.39 (SD=11.8) mm Hg in the 7 g/dL threshold group, compared with 75.98 (SD=9.1) mm Hg in the 10 g/dL threshold group. The number of patients who never had a CPP less than 50 mm Hg was 38 (39.2%) in the 7 g/dL threshold group and 51 (51.0%) in the 10 g/dL threshold group ($p=0.1$, Table 2).

PbtO₂

Of the 200 patients enrolled in the study, 193 had a Licox PbtO₂ probe placed for monitoring brain oxygenation. In six of the patients, no valid PbtO₂ data was obtained, leaving a total of 187 patients with data available for analysis (92 in the 7 g/dL threshold group and 95 in the 10 g/dL threshold group). The median duration of PbtO₂ monitoring was 93 h (IQR=97, range=460), and PbtO₂ was monitored for an average of approximately 1 day longer in the 10 g/dL threshold group (Table 3). For all patients, median PbtO₂ was 27.24 (IQR=17.3) mm Hg. Because the PbtO₂ value is a local

TABLE 3. BRAIN OXYGENATION SUMMARY VARIABLES AND COMPLICATIONS

	7 g/dL group n=92	10 g/dL group n=95	p value
Time PbtO ₂ was monitored (h), median (IQR)	76.5 (78.5)	103 (95)	0.04
Developed brain tissue hypoxia, n (%) ^a	31/92 (33.7)	26/95 (27.4)	0.43
When probe was in normal tissue, n (%)	16/64 (25)	6/59 (10.2)	0.04
When probe was in abnormal tissue, n (%)	15/28 (53.6)	20/36 (55.6)	>0.99
Time PbtO ₂ was <10 mm Hg (h), median (IQR) ^b	0 (9.5)	0 (7)	0.59
When probe was in normal tissue (h, n=123), median (IQR)	0 (5)	0 (0)	0.06
When probe was in abnormal tissue (h, n=64), median (IQR)	9 (28.5)	9 (20.5)	0.86

PbtO₂, brain tissue oxygenation; IQR, interquartile range

^a $p=0.11$ for threshold×tissue interaction (logistic regression with outcome brain tissue hypoxia).

^b $p=0.07$ for threshold×tissue interaction (logistic regression with outcome time PbtO₂ <10 mm Hg [0 vs. >0]).

measure of oxygenation, the value depends on where the probe is placed. When the PbtO₂ probe was placed in normal appearing brain (123 patients), the median PbtO₂ was 29.89 (IQR = 18.2) mm Hg compared with 22.07 (IQR = 15.0) mm Hg when the probe was placed in abnormal appearing brain (64 patients).

GEE analysis suggested a significant transfusion threshold slope over the first 250 hours after ICU admission (Fig. 4, Supplementary Table S4, $p=0.02$, see online supplementary material at <http://www.liebertpub.com>), indicating that there is a difference in the brain tissue oxygenation among the transfusion threshold groups over time. Figure 3 suggests that the 10 g/dL group had increased oxygenation, particularly when the probe was located in normal appearing brain. Nevertheless, the PbtO₂ values in both transfusion threshold groups are well above 20 mmHg throughout the period of monitoring.

Brain tissue hypoxia events were prospectively identified as part of the safety monitoring of the study. For all patients with PbtO₂ monitoring, there was no difference in the occurrence of brain tissue hypoxia defined as a PbtO₂ less than 10 mm Hg. At least one brain hypoxia event occurred in 31 (33.7%) patients in the 7 g/dL threshold group and 26 (27.4%) in the 10 g/dL group. When the location of the probe was taken into consideration, however, there were some significant differences (Table 3). When the probe was located in normal appearing brain, brain tissue hypoxia occurred in 25% of patients in the 7 g/dL threshold group, compared with 10.2% of patients in the 10 g/dL threshold group ($p=0.04$). No

FIG. 4. Generalized estimating equations predicted values in the first 250h after intensive care unit (ICU) admission for intracranial pressure (ICP), cerebral perfusion pressure (CPP), mean arterial pressure (MAP), and brain tissue oxygenation (PbtO₂).

FIG. 5. Trend plot of the average middle cerebral artery flow velocity and hemoglobin concentrations over time in the two transfusion threshold groups (TT7=7g/dL threshold group, TT10=10g/dL threshold group). The vertical bars indicate the standard error of the mean. Hgb, hemoglobin.

difference in the incidence of brain tissue hypoxia was observed when the probe was placed in abnormal appearing brain. We failed to detect a statistically significant interaction term between the threshold group and the type of tissue, however ($p=0.11$).

mcaFV

One hundred and eighty patients had measurements of mcaFV, 88 in the 7 g/dL threshold group and 92 in the 10 g/dL threshold group. Figure 5 shows the trend plot of mcaFV over time in the two threshold groups. The lowest values for mcaFV occurred on the first post-injury day, increased over time, and peaked on day 3 or 4 post-injury. The values for mcaFV were higher in the 7 g/dL threshold group during days 3–6 post-injury. The mcaFV mirrored the hemoglobin concentrations, which were highest on day 1 post-injury, decreased over days 2–4, and were lower in the 7 g/dL threshold group after day 2.

Discussion

We observed a possible early mortality benefit in the 10 g/dL threshold group. One explanation for this finding was the possibility of early cerebral ischemia secondary to anemia resulting in increased mortality. Thus, in this study, we focused on hemodynamic differences among the two threshold groups.

We observed a statistically significant higher average MAP in the 10 g/dL threshold group than in the 7 g/dL threshold group. These differences, however, were very small and did not have clinical consequences in terms of number of episodes of hypotension (MAP < 70 mm Hg). Further, there was no difference in the need for treatment with pressors between the two threshold groups.

Tango and associates⁸ found that hemodilution to a low hematocrit level increases ICP in dogs. In this clinical trial, we did find a transiently higher mcaFV in the 7 g/dL transfusion threshold group. Despite this, we did not observe any evidence that a lower hemoglobin concentration threshold causes increased ICP or need for additional management of ICP.

The lower transfusion threshold resulted in slightly lower PbtO₂ over time. This is consistent with other studies that have found an association between blood transfusions and increased brain tissue

oxygenation.^{14–18} We also observed an increased risk of having an episode of brain tissue hypoxia when the PbtO₂ probe is placed in normal appearing brain tissue, but not in contused brain. These results should be interpreted with caution because the interaction term between probe placement and threshold was not statistically significant. Using continuous monitoring of brain oxygenation with prompt management of tissue hypoxia, this increased risk does not seem to worsen long-term neurological outcome.

Our study has several strengths. The study takes advantage of a randomized trial of transfusion threshold in patients with TBI. Collection of detailed physiology and treatment measures during the trial allowed these secondary analyses. The limitations of this study are primarily because of having to impute missing values of the hemodynamic outcomes. The invasive nature of the ventriculostomy catheter and Licox probe prohibited us from obtaining measurements other than when medically necessary. Therefore, observations were not missing at random, and we used multiple imputations to account for the uncertainty of these missing values.

The comparison of the available data (Fig. 2, top left graph) with available data plus imputed data (Fig. 2, top right graph) suggests that ignoring the informative dropouts (mainly patients who improved over time and were no longer monitored) can lead to misleading later ICP values. Other methods for dealing with this problem could have been used. We could have limited the analysis to the first 2–3 days when there were few missing values, but the differences in hemoglobin concentration between the two groups increased over time and were relatively small in the first couple of days after injury.

Others have examined ICP separately in patients who had ICP monitoring discontinued during the first week after injury.¹⁹ Their approach, however, has limitations because of the large number of parameters that need to be estimated in the model. To our knowledge, this is the first analysis of this type of data using multiple imputation. Further, we did not impute PbtO₂ values because of the difficulty in justifying models clinically with respect to the patterns of missing values; hence, the GEE model for this outcome may be biased.

Although we observed a few differences in hemodynamic outcomes between the two hemoglobin concentration threshold groups, none were of clinical significance and did not affect long-term neurological outcome nor support the possible differences in mortality. These data do not support the use of a higher transfusion threshold even in the early resuscitation period. As with all critically ill patients, decision to transfuse in the early resuscitation period remains a clinical decision about hemodynamic stability.

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Author Disclosure Statement

No competing financial interests exist.

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