ORIGINAL ARTICLE

Liberal or Restrictive Transfusion Strategy in Patients with Traumatic Brain Injury

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ABSTRACT

BACKGROUND

The effect of a liberal transfusion strategy as compared with a restrictive strategy on outcomes in critically ill patients with traumatic brain injury is unclear.

METHODS

We randomly assigned adults with moderate or severe traumatic brain injury and anemia to receive transfusion of red cells according to a liberal strategy (transfusions initiated at a hemoglobin level of ≤10 g per deciliter) or a restrictive strategy (transfusions initiated at ≤7 g per deciliter). The primary outcome was an unfavorable outcome as assessed by the score on the Glasgow Outcome Scale–Extended at 6 months, which we categorized with the use of a sliding dichotomy that was based on the prognosis of each patient at baseline. Secondary outcomes included mortality, functional independence, quality of life, and depression at 6 months.

RESULTS

A total of 742 patients underwent randomization, with 371 assigned to each group. The analysis of the primary outcome included 722 patients. The median hemoglobin level in the intensive care unit was 10.8 g per deciliter in the group assigned to the liberal strategy and 8.8 g per deciliter in the group assigned to the restrictive strategy. An unfavorable outcome occurred in 249 of 364 patients (68.4%) in the liberal-strategy group and in 263 of 358 (73.5%) in the restrictive-strategy group (adjusted absolute difference, restrictive strategy vs. liberal strategy, 5.4 percentage points; 95% confidence interval, –2.9 to 13.7). Among survivors, a liberal strategy was associated with higher scores on some but not all the scales assessing functional independence and quality of life. No association was observed between the transfusion strategy and mortality or depression. Venous thromboembolic events occurred in 8.4% of the patients in each group, and acute respiratory distress syndrome occurred in 3.3% and 0.8% of patients in the liberal-strategy and restrictive-strategy groups, respectively.

CONCLUSIONS

In critically ill patients with traumatic brain injury and anemia, a liberal transfusion strategy did not reduce the risk of an unfavorable neurologic outcome at 6 months. (Funded by the Canadian Institutes of Health Research and others; HEMOTION ClinicalTrials.gov number, NCT03260478.)

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*The HEMOTION Trial Investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Anemia develops in most critically ill patients with traumatic brain injury and may decrease oxygen delivery to a vulnerable brain[1] and contribute to poor outcomes.[2] Although standard practice for the treatment of anemia has shifted toward transfusion at lower hemoglobin levels, there are concerns regarding potential harms of a restrictive transfusion strategy in these patients.

Trials assessing red-cell transfusion strategies in the critically ill population showed no mortality benefit of maintaining high hemoglobin levels.[3,4] However, these trials included very few patients with neurologic injuries and focused on mortality; they thus provide insufficient guidance for the care of patients with traumatic brain injury, for whom long-term neurologic function is the most important outcome.[5,6] Clinical guidelines and reviews comparing the effects of liberal transfusion strategies with those of restrictive transfusion strategies emphasize that current data are not sufficient to guide transfusion practices in patients with traumatic brain injury.[7,8]

We conducted a randomized trial to compare the effects of a liberal strategy for red-cell transfusion with those of a restrictive strategy on mortality and long-term functional and patient-centered outcomes in critically ill adult patients with moderate-to-severe traumatic brain injury. We hypothesized that a liberal strategy would result in better outcomes than a restrictive strategy.

Methods

Trial Design and Oversight

We conducted the Hemoglobin Transfusion Threshold in Traumatic Brain Injury Optimization (HEMOTION) pragmatic trial at 34 centers in Canada, the United Kingdom, France, and Brazil using the Prospective Randomized Open Blinded End-Point (PROBE) trial design.[9] The protocol was published previously,[10] and the statistical analysis plan was publicly disseminated on ClinicalTrials.gov. Both the protocol and the statistical analysis plan are available with the full text of this article at NEJM.org. The trial was overseen by a steering committee, and operations were overseen by an executive committee. An independent data and safety monitoring committee reviewed data after each 25% increment of the target enrollment was reached and evaluated the results of a protocol-specified formal interim analysis that was performed when enrollment was at 50% of the target. The trial protocol was approved by the research ethics board at Centre Hospitalier Universitaire de Québec-Université Laval and at each participating center. Written informed consent (or oral consent in a few cases during the Covid-19 pandemic) was obtained initially from surrogate decision makers or through a deferred-consent approach. Consent was subsequently sought from surrogate decision makers and from patients, if they regained capacity. Data analysts and investigators were unaware of the group assignments. The trial was conducted in accordance with the guidelines for Good Clinical Practice. The principal investigators (the first, second, and last authors) drafted the manuscript and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The analyses were supervised by a statistical analysis committee (details are provided in the Supplementary Appendix, available at NEJM.org). All the authors reviewed the manuscript and approved the version submitted for publication.

A Quick Take is available at NEJM.org

Patients

Participating centers were trauma hospitals with specialized neurocritical care. Patients were screened for eligibility at the time of admission to the intensive care unit (ICU) and were reassessed daily during the ICU stay. We enrolled patients 18 years of age or older with acute moderate or severe traumatic brain injury (specified as a score on the Glasgow Coma Scale [GCS] of 3 to 12; scores range from 3 to 15, with lower scores indicating a lower level of consciousness) and anemia (a hemoglobin level of ≤10 g per deciliter). We excluded patients who received transfusion after ICU admission but before randomization and who had contraindications or objection to transfusion. Patients who received transfusion before ICU admission were not excluded. Detailed criteria are listed in the Supplementary Appendix.

Trial Procedures

We randomly assigned patients to receive red-cell transfusion according to a liberal strategy (triggered by a hemoglobin level of ≤10 g per deciliter) or a restrictive strategy (triggered by a hemoglobin level of ≤7 g per deciliter). We used a central, concealed, computer-generated randomization system to assign patients in a 1:1 ratio with the use of

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Liberal Strategy (N=369)	Restrictive Strategy (N=367)
Demographics		
Age — yr	48.9±18.8	48.4±19.0
Female sex — no. (%)	89 (24.1)	112 (30.5)
Race or ethnic group — no. (%)†		
Black	12 (3.3)	12 (3.3)
Asian	26 (7.0)	21 (5.7)
First Nations or Aboriginal	14 (3.8)	12 (3.3)
Hispanic or Latino	7 (1.9)	3 (0.8)
White	261 (70.7)	275 (74.9)
Other or unknown	49 (13.3)	44 (12.0)
Relevant medical history — no. (%)		
Positive qualitative drug screen	42 (11.4)	43 (11.7)
Positive blood ethanol screen	87 (23.6)	79 (21.5)
Congestive heart failure	2 (0.5)	5 (1.4)
Ischemic heart disease or myocardial infarction	20 (5.4)	24 (6.5)
Previous traumatic brain injury, including concussion	56 (15.2)	44 (12.0)
Chronic anemia	2 (0.5)	5 (1.4)
Nature of injury		
Cause of injury — no./total no. (%)		
Motor vehicle collision	58 (15.7)	72 (19.6)
Pedal cycle, motorcycle, scooter, or other all-terrain vehicle collision	75 (20.3)	71 (19.3)
Vehicle–pedestrian collision	39 (10.6)	40 (10.9)
Assault	15 (4.1)	25 (6.8)
Other	182 (49.3)	159 (43.3)
Extracranial injury — no. (%)	238 (64.5)	260 (70.8)
Injury Severity Score‡	30±11	32±11
TBI-IMPACT prognostic model variables on admission§		
Moderate traumatic brain injury — no. (%)¶	98 (26.6)	99 (27.0)
Median GCS motor score (IQR)	4 (1–5)	4 (1–5)
GCS motor score — no./total no. (%)		
1: No movement	95/366 (26.0)	120/367 (32.7)
2: Extension	24/366 (6.6)	21/367 (5.7)
3: Abnormal flexion	40/366 (10.9)	27/367 (7.4)
4: Normal flexion	79/366 (21.6)	86/367 (23.4)
5: Localization	99/366 (27.0)	93/367 (25.3)
6: Obedience to commands	29/366 (7.9)	20/367 (5.4)
Pupil reactivity — no./total no. (%)		
None	45/362 (12.4)	51/362 (14.1)
One	32/362 (8.8)	51/362 (14.1)
Both	285/362 (78.7)	260/362 (71.8)
Hypotension — no./total no. (%)‖	83/366 (22.7)	105/364 (28.8)
Hypoxemia — no./total no. (%)**	94/365 (25.8)	96/361 (26.6)
Marshall injury classification based on CT — no. (%)††		
I	5 (1.4)	12 (3.3)
II	188 (50.9)	192 (52.3)
III or IV	39 (10.6)	41 (11.2)
V or VI	137 (37.1)	122 (33.2)
Traumatic subarachnoid hemorrhage — no. (%)	324 (87.8)	324 (88.3)
Epidural hematoma — no./total no. (%)	65 (17.6)	67 (18.3)
Glucose — mmol/liter	9.2±3.6	9.1±3.8

Table 1. (Continued.)

Characteristic	Liberal Strategy (N=369)	Restrictive Strategy (N=367)
Hemoglobin — g/dl	13.3±1.8	13.1±1.7
TBI-IMPACT probability of unfavorable outcome at 6 months‡‡	0.54±0.23	0.55±0.22
Intervention before randomization — no. (%)		
Monitoring of intracranial pressure	207 (56.1)	233 (63.5)
Invasive monitoring of brain oxygenation	17 (4.6)	23 (6.3)
Hyperosmolar therapy	147 (39.8)	131 (35.7)
Active cooling	77 (20.9)	75 (20.4)
Neuromuscular blocking agent	185 (50.1)	188 (51.2)
Barbiturates	17 (4.6)	10 (2.7)
Neurologic procedure before randomization — no. (%)		
Decompressive craniectomy	52 (14.1)	42 (11.4)
Surgery for progressive hemorrhage with bone flap left out	61 (16.5)	52 (14.2)
Evacuation of epidural hematoma	28 (7.6)	19 (5.2)
Evacuation of subdural hematoma	95 (25.7)	98 (26.7)
Evacuation of intracerebral hematoma	19 (5.1)	15 (4.1)
Red-cell transfusion before randomization§§		
Any transfusion — no./total no. (%)	57 (15.4)	67 (18.3)
Median units per patient (IQR)	0 (0–0)	0 (0–0)
Median units per patient transfused (IQR)	2 (2–4)	3 (1–4)
Secondary insult before randomization — no./total no. (%)		
Episode of hypotension	94/369 (25.5)	91/367 (24.8)
Episode of hypoxemia	65/369 (17.6)	60/367 (16.3)
Episode of intracranial hypertension¶¶	73/205 (35.6)	77/231 (33.3)
Episode of cerebral hypoperfusion¶¶	45/204 (22.1)	40/231 (17.3)
Episode of brain tissue hypoxia¶¶	14/16 (87.5)	17/22 (77.3)
Hemoglobin at randomization — g/dl	9.1±0.8	9.1±0.8
Median time from injury (IQR)‖‖		
To first hospital admission — min	64 (39–103)	63 (40–98)
To randomization — hr	55 (38–90)	56 (37–83)

* Plus–minus values are means ±SD. CT denotes computed tomography.
† Race or ethnic group was reported by the patients or by surrogate decision makers.
‡ The Injury Severity Score ranges from 0 to 75, with higher scores indicating greater severity of injury. Data were missing for 5 patients in the liberal-strategy group and for 6 in the restrictive-strategy group.
§ The International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (TBI-IMPACT) prognostic model is validated in patients with traumatic brain injury and a Glasgow Coma Scale (GCS) score of less than 13 (scores range from 3 to 15, with lower scores indicating a lower level of consciousness). It is adjusted according to age, GCS motor score, pupil reactivity, status with regard to hypoxemia and hypotension, injury classification on the basis of CT, the presence or absence of traumatic subarachnoid hemorrhage on CT scan and of epidural hematoma, and blood glucose and hemoglobin levels on admission. A total of 14 patients in the liberal-strategy group and 11 in the restrictive-strategy group had data missing for at least one of the components.
¶ Moderate traumatic brain injury corresponds to a GCS score between 9 and 12. The overall score is the sum of scores for the motor, verbal, and eye-opening components. The last GCS score recorded in the emergency department (or the last GCS score recorded before intubation if the patient left the emergency room intubated) was used.
‖ Hypotension was specified as a systolic blood pressure of less than 90 mm Hg regardless of the use of vasopressors.
** Hypoxemia was specified as an oxygen saturation of less than 90% according to arterial blood gas or pulse oximetry measurement.
†† The Marshall classification of injury severity is based on a review of CT scans of the head within 24 hours after injury, with a score of I indicating normal findings, II diffuse injury, III or IV radiologic signs of elevated intracranial pressure, and V or VI any lesion that was surgically evacuated or a mass lesion of more than 25 ml, respectively. Scans showing the most severe findings were used for review.
‡‡ The mean probability of an unfavorable outcome, which was specified as a score of ≤4 on the Glasgow Outcome Scale–Extended (scores range from 1 [death] to 8 [upper good recovery, indicating a full return to normal life]), at 6 months among patients at baseline was calculated on a scale from 0.00 (no probability) to 1.00 (certainty).
§§ Data are shown for patients who received red-cell transfusion before admission to the intensive care unit (ICU); patients who received transfusion after admission to the ICU but before randomization were excluded from the trial.
¶¶ The total number is the number of patients who were monitored.
‖‖ Data for time from injury to first hospital admission were missing for 55 patients in the liberal-strategy group and for 63 in the restrictive-strategy group; data for time from injury to randomization were missing for 54 and 63 patients in the two groups, respectively.

variable permuted blocks of four and six, with stratification according to center. The transfusion strategy was applied until the patient's discharge from the ICU.

The transfusion thresholds were selected on the basis of available evidence, expert opinion, and clinical equipoise and were similar to those considered acceptable by clinicians in an international survey.[11] The liberal threshold was selected because maintaining hemoglobin levels above 10 g per deciliter may improve brain oxygenation.[12,13] The restrictive threshold reflects the standard of care for critically ill patients.[3,4]

Patients received leukoreduced red cells, 1 unit at a time, when the specified hemoglobin threshold was met. Additional units were transfused when hemoglobin levels measured as part of routine care met the specified threshold. In both treatment groups, we aimed to transfuse red cells within 3 hours after the threshold was reached. Otherwise, patient management was left to the discretion of the medical team. Adherence to the Brain Trauma Foundation guidelines was encouraged.[14]

ADHERENCE TO THE INTERVENTION

We monitored centers for adherence to the protocol and accuracy of data. Potential protocol deviations and violations were evaluated as described in the protocol.[10]

OUTCOMES

The primary outcome was an unfavorable outcome (yes or no) at 6 months as assessed with the Glasgow Outcome Scale–Extended (GOS-E).[15] The GOS-E is an ordinal scale ranging from 1 (death) to 8 (upper good recovery, indicating a full return to normal life), with intermediate levels including vegetative state (minimal responsiveness), lower and upper severe disability (need for full or partial assistance with activities of daily living, respectively), lower and upper moderate disability (independence but with inability or limited ability to participate in previous activities, respectively), and lower good recovery (minor deficits affecting daily living). We defined an unfavorable outcome using a sliding dichotomy of the GOS-E according to the prognosis of each patient at baseline; patients were categorized into one of three risk levels (worst, intermediate, or best) and were considered to have an unfavorable outcome if the GOS-E score at 6 months was less than or equal to 3, 4, or 5, respectively.

Secondary outcomes assessed at 6 months were mortality and scores on the Functional Independence Measure (FIM; range, 18 to 126) to assess motor and cognitive function[16]; the EuroQol visual analogue scale (range, 0 to 100) and EuroQol five-dimension, five-level (EQ-5D-5L) utility index (range, −0.59 to 1) to evaluate health-related quality of life[17]; the Quality of Life after Brain Injury (Qolibri) scale (range, 1 to 100)[18]; and the nine-item Patient Health Questionnaire (PHQ-9; range, 0 to 27) to evaluate depression.[19] Higher scores on the FIM, the EuroQol visual analogue scale and EQ-5D-5L utility index, and the Qolibri scale indicate better health states. Higher scores on the PHQ-9 indicate worse symptoms. Minimally important differences for traumatic brain injury have not been established (the various scales are summarized in the Supplementary Appendix). Mortality in the ICU and in the hospital was also assessed. Tertiary outcomes were the number of units of red cells transfused in the ICU, the lowest daily hemoglobin level, infections, complications related to transfusion, the duration of mechanical ventilation, and the lengths of stay in the ICU and in the hospital. Primary and secondary outcomes were assessed centrally by research personnel who were unaware of the group assignments.

SUBGROUP ANALYSES

We conducted prespecified subgroup analyses of the primary outcome according to age (>55 vs. ≤55 years), sex, severity of traumatic brain injury (moderate [GCS score of 9 to 12] vs. severe [GCS score of 3 to 8]), country, the presence or absence of heart disease, neurosurgical intervention, and administration of red-cell transfusion before randomization.

STATISTICAL ANALYSIS

We determined that a sample size of 712 patients would provide the trial with 80% power to detect an absolute difference between groups of 10 percentage points in the primary outcome at a 5% significance level. We used a pooled-variance z-test under the assumption that 40% of patients in the restrictive-strategy group would have an unfavorable outcome (specified as a GOS-E score of ≤4).[20,21] After our interim analysis, we increased

the target sample size to 742 patients to account for our estimate that 2% of patients would be lost to follow-up.[22] The data and safety monitoring committee, whose members were unaware of the group assignments, reviewed the results of the interim analysis with the use of the Haybittle–Peto criterion (P<0.001) for superiority and recommended continuation of the trial.

Baseline characteristics are presented as descriptive statistics — means and standard deviations or medians and interquartile ranges, as appropriate. All analyses were conducted according to the intention-to-treat principle. We report results with 95% confidence intervals. No adjustments for multiplicity were made, and the widths of confidence intervals may not be used in place of hypothesis testing.

In the main analysis of our primary outcome, we used a sliding-dichotomy approach.[23] In this method, the definition of an unfavorable outcome varies according to the prognostic risk at baseline. We used a prognostic model from the International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (TBI-IMPACT), which has been externally validated, to assess the probability of an unfavorable outcome at 6 months for each patient.[24] We performed single imputation by conditional estimation for missing prognostic covariates.[25] To express treatment effects as risk ratios, we used a robust hierarchical Poisson regression model with a random intercept for centers and adjustment for sex. The model was estimated with the use of maximum likelihood with adaptive quadrature, and the likelihood-based sandwich estimator was adjusted with the use of the Morel–Bokossa–Neerchal bias correction.[26] We used an identity link to calculate absolute risk difference.[27]

Prespecified sensitivity analyses for the primary outcome included complete-case, per-protocol, and best-case–worst-case scenarios. The primary outcome was also analyzed with the use of a hierarchical proportional-odds regression, with a random intercept for center and adjustment for TBI-IMPACT model covariates and sex. Using a GOS-E score of less than or equal to 4 as the definition of an unfavorable outcome, we conducted a robust hierarchical Poisson regression with the same covariate adjustments and an unadjusted chi-square analysis.

Analyses of secondary outcomes were adjusted for center, the TBI-IMPACT model covariates,

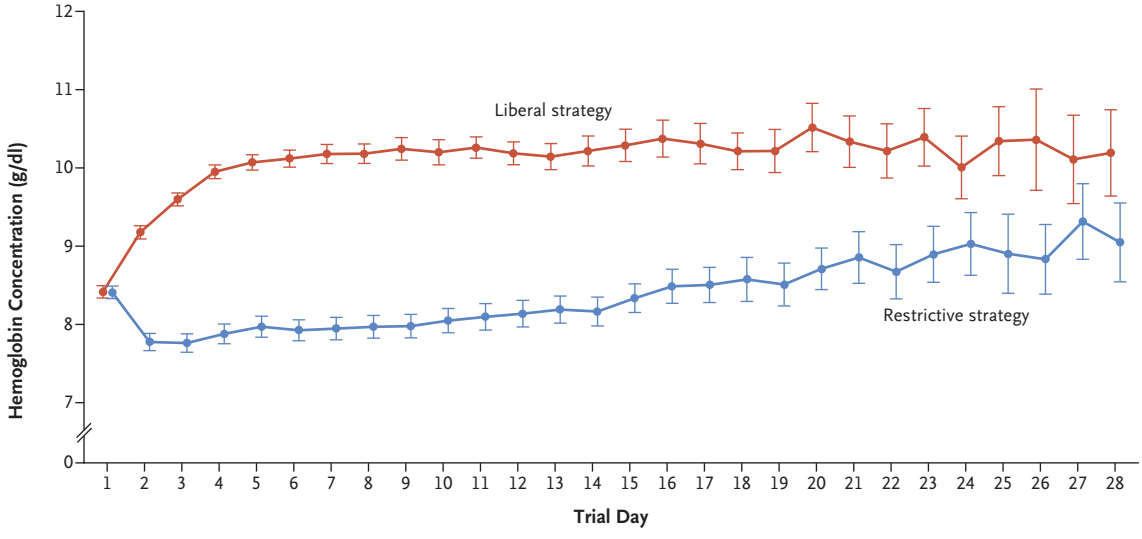

Figure 1. Lowest Mean Daily Hemoglobin Concentration during the First 28 Days.
I bars indicate 95% confidence intervals.

and sex. Frailty models were used for mortality, and linear quantile mixed models were used for scores on the FIM, the EuroQol visual analogue scale and the EQ-5D-5L utility index, the Qolibri, and the PHQ-9 among survivors. A robust hierarchical Poisson regression was also used for PHQ-9 scores. Median differences between groups were assessed with the use of quantile regression.

SAS software, version 9.4 (SAS Institute), and R statistical software, version 4.2.0 (R Core Team, 2022), were used. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

PATIENTS

Among 6188 patients assessed for eligibility, 742 underwent randomization between September 1, 2017, and April 13, 2023 (Fig. S1). Two patients with aneurysmal subarachnoid hemorrhage were erroneously included among the patients who underwent randomization, and 4 patients withdrew consent; therefore, the intention-to-treat cohort comprised 736 patients (369 in the liberal-strategy group and 367 in the restrictive-strategy

Table 2. Outcomes.*

Outcome	Liberal Strategy (N=369)	Restrictive Strategy (N=367)	Risk or Hazard Ratio (95% CI)†‡	Median Difference (95% CI)‡
Primary outcome: unfavorable outcome on GOS-E at 6 mo — no./total no. (%)§				
Sliding dichotomy				
Overall	249/364 (68.4)	263/358 (73.5)	0.93 (0.83–1.04)	
Worst-prognosis group: GOS-E score ≤3	89/119 (74.8)	98/121 (81.0)	0.92 (0.79–1.08)	
Intermediate-prognosis group: GOS-E score ≤4	81/120 (67.5)	84/121 (69.4)	0.96 (0.81–1.14)	
Best-prognosis group: GOS-E score ≤5	79/125 (63.2)	81/116 (69.8)	0.90 (0.76–1.07)	
Dichotomized as GOS-E score ≤4	225/364 (61.8)	240/358 (67.0)	0.92 (0.83–1.03)	
Secondary outcomes¶				
Death — no./total no. (%)‖				
In the ICU	63/369 (17.1)	56/367 (15.3)	1.13 (0.77–1.65)	
In the hospital	85/369 (23.0)	79/367 (21.5)	1.07 (0.78–1.47)	
At 6 mo	99/369 (26.8)	96/365 (26.3)	1.01 (0.76–1.35)	
Median score on Functional Independence Measure (IQR)**				
Overall	119 (95–125)	115 (76–124)		4.34 (0.22–8.45)
Motor	88 (71–91)	86 (50–91)		3.95 (0.63–7.27)
Cognitive	32 (24–35)	30 (22–34)		1.15 (–0.16 to 2.46)
Median score on EuroQol visual analogue scale (IQR)††	70 (50–80)	60 (40–75)		5.19 (0.52–9.86)
Median score on EQ-5D-5L utility index (IQR)‡‡	0.74 (0.45–0.87)	0.64 (0.33–0.82)		0.06 (0.01–0.10)
Median score on Qolibri scale (IQR)§§	64 (45–80)	56 (39–77)		3.72 (–1.13 to 8.56)
PHQ-9¶¶				
Median score (IQR)	7 (3–13)	8 (3–14)		–0.51 (–1.91 to 0.90)
Score ≥10 — no./total no. (%)	82/227 (36.1)	95/222 (42.8)	0.85 (0.63–1.17)	
Tertiary outcomes‖‖				
Red-cell units transfused***				
Total no.	1516	307		
Median no. per patient (IQR)	3 (2–5)	0 (0–1)		3.0 (3.0–10.82)

Table 2. (Continued.)

Outcome	Liberal Strategy (N=369)	Restrictive Strategy (N=367)	Risk or Hazard Ratio (95% CI)†‡	Median Difference (95% CI)‡
Infection or transfusion-related complication — no./total no. (%)				
Any infection	204/369 (55.3)	192/367 (52.3)	1.06 (0.92–1.21)	
Pneumonia	130/369 (35.2)	121/367 (33.0)	1.07 (0.87–1.31)	
Bacteremia	24/369 (6.5)	27/367 (7.4)	0.88 (0.52–1.50)	
Sepsis or septic shock	21/369 (5.7)	28/367 (7.6)	0.75 (0.43–1.29)	
Ventriculitis, meningitis, or brain abscess	12/369 (3.3)	15/367 (4.1)	0.80 (0.38–1.68)	
Transfusion reaction†††	6/365 (1.6)	1/141 (0.7)	2.33 (0.35–58.32)	
Median duration of mechanical ventilation (IQR) — days	12 (8–17)	11 (7–17)		1.00 (–0.52 to 2.52)
Median length of ICU stay (IQR) — days	15 (10–22)	15 (10–22)		0.00 (–1.85 to 1.85)
Median length of hospital stay (IQR) — days	33 (18–50)	33 (19–55)		0.00 (–4.20 to 4.20)

* CI denotes confidence interval, ICU intensive care unit, and IQR interquartile range.
† Values are risk ratios, except in the case of death, for which the values are hazard ratios.
‡ Confidence intervals have not been adjusted for multiplicity.
§ The primary outcome was centrally assessed at 6 months by trained personnel who were unaware of the group assignment. The Glasgow Outcome Scale–Extended (GOS-E) comprises eight ranking levels from 1 (death) to 8 (upper good recovery). A sliding dichotomy was used to categorize scores as favorable or unfavorable according to each patient's baseline prognosis. Analyses were adjusted for site (random intercept) and sex. The sliding dichotomy is based on the TBI-IMPACT prognostic model, which includes admission characteristics (age, GCS motor score, pupil reactivity, status with regard to hypoxemia and hypotension, injury classification on the basis of CT, the presence or absence of traumatic subarachnoid hemorrhage on CT scan and of epidural hematoma, and blood glucose and hemoglobin levels). When necessary, conditional estimation was used for missing covariates to calculate an individual TBI-IMPACT score for each patient. Patients were divided into thirds according to their predicted risk of an unfavorable outcome: patients in the worst prognosis group were considered to have an unfavorable outcome if the GOS-E score at 6 months was 3 or lower (i.e., death, vegetative state, or lower severe disability); patients in the intermediate prognosis group were considered to have an unfavorable outcome if the GOS-E score was 4 or lower (i.e., death, vegetative state, lower severe disability, or upper severe disability); and patients in the best prognosis group were considered to have an unfavorable outcome if the GOS-E score was 5 or lower (i.e., death, vegetative state, lower severe disability, upper severe disability, or lower moderate disability). Data for patients dichotomized as GOS-E score ≤4 are from an unadjusted analysis with a chi-square test.
¶ Secondary outcomes were centrally assessed at 6 months by trained personnel who were unaware of the group assignments. All analyses were adjusted for center (random intercept), sex, and admission covariates used in the TBI-IMPACT prognostic model.
‖ A decision to withdraw life-sustaining therapies in the ICU was made for 50 patients in each group, and a decision to withdraw life-sustaining therapies in the hospital was made for 63 patients in each group.
** The Functional Independence Measure evaluates the amount of assistance required to perform 18 basic daily activities (13 physical and 5 cognitive). Each component is scored on a 7-point scale. The final score ranges from 18 to 126, with 18 indicating complete dependence and 126 indicating complete independence. Data were missing for 14 of the 270 patients in the liberal-strategy group and for 20 of 271 in the restrictive-strategy group who survived to 6 months.
†† The EuroQol visual analogue scale is a generic instrument for assessing health-related quality of life; scores range from 0 (the worst imaginable state of health) to 100 (the best imaginable state of health). Data were missing for 23 of the 270 patients in the liberal-strategy group and for 29 of 271 in the restrictive-strategy group who survived to 6 months.
‡‡ Data from the EuroQol five-dimension, five-level (EQ-5D-5L) measure of health status were transformed into a utility index with the use of country value sets that assigned scores from –0.59 (representing a health condition considered to be worse than death) to 1 (indicating optimal health). In the absence of a value set for Brazil, the United States value set was used, according to the recommendation of the instrument developer. Data were missing for 23 of the 270 patients in the liberal-strategy group and for 30 of 271 in the restrictive-strategy group who survived to 6 months.
§§ The Quality of Life after Brain Injury (Qolibri) scale assesses health-related quality of life and is specific to persons with traumatic brain injury. Scores range from 0 (the worst imaginable state of health) to 100 (the best imaginable state of health). Data were missing for 41 of the 270 patients in the liberal-strategy group and for 52 of 271 in the restrictive-strategy group who survived to 6 months.
¶¶ The nine-item Patient Health Questionnaire (PHQ-9) assesses the frequency of depressive symptoms within the past 2 weeks. Scores range from 0 to 27, with higher numbers indicating greater frequency of symptoms. Data were missing for 43 of the 270 patients in the liberal-strategy group and for 49 of 271 in the restrictive-strategy group who survived to 6 months.
‖‖ Tertiary outcomes were assessed locally with the use of standardized definitions by trained personnel who were aware of assigned treatment groups.
*** The number of red-cell units transfused between randomization and discharge from the ICU is shown.
††† Numbers shown are the numbers of patients who had a transfusion reaction after randomization and before discharge from the ICU. Detailed descriptions of transfusion reactions are provided in Table S15.

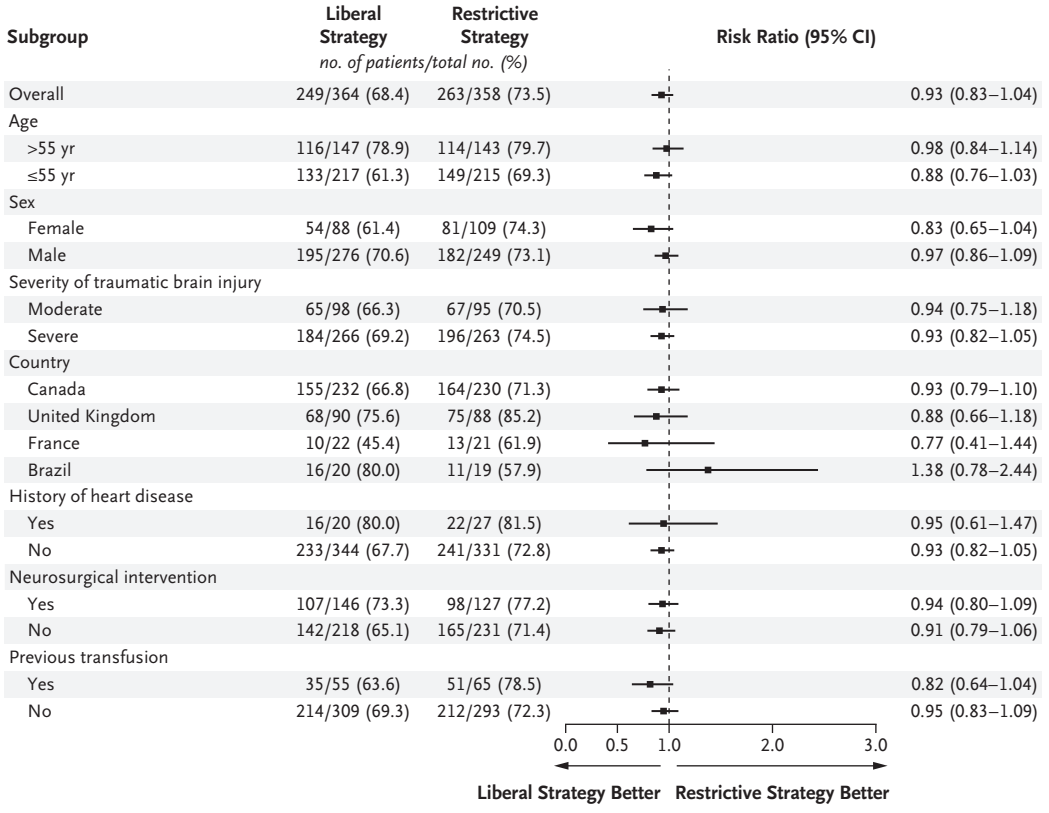

Figure 2. Subgroup Analysis of the Primary Outcome.

The primary outcome was an unfavorable outcome as assessed by the score on the Glasgow Outcome Scale–Extended (with scores ranging from 1 [death] to 8 [upper good recovery, indicating a full return to normal life]), at 6 months, according to a sliding dichotomy that was based on the prognosis of each patient at baseline. Analyses were conducted in the intention-to-treat population with the use of robust hierarchical Poisson regression, which was adjusted for sex (except in the case of the sex subgroups) and used a random intercept for the site. Moderate traumatic brain injury corresponds to a score on the Glasgow Coma Scale between 9 and 12 (scores range from 3 to 15, with lower scores indicating a lower level of consciousness). History of heart disease refers to heart disease detected before admission and includes congestive heart failure, myocardial infarction, and ischemic heart disease. Neurosurgical intervention refers to interventions that took place before randomization and includes surgical drainage (with or without bone flap removal) and decompressive craniectomy. Previous transfusion refers to transfusion before randomization and includes transfusion in the emergency department and in the operating room before intensive care unit admission. CI denotes confidence interval.

group). The primary outcome at 6 months was ascertained for 722 patients (98.1%).

Most of the patients were men (72.7%), the mean (±SD) age was 48.7±18.9 years, and 73.2% had a severe traumatic brain injury (Table 1). More than two thirds had extracranial injuries. The median GCS motor score in both groups was 4 (interquartile range, 1 to 5). We observed some baseline imbalances between the groups. More women, more patients with a GCS motor score of 1, more patients with no pupillary reactivity, and more patients who had an episode of hypotension were enrolled in the restrictive-strategy group than in the liberal-strategy group. A higher percentage of patients in the liberal-strategy group than in the restrictive-strategy group had episodes of low cerebral perfusion pressure and a Marshall score of V or VI (indicating any lesion that was surgically evacuated or a mass lesion of more than 25 ml, respectively). Before randomization, the majority of patients underwent monitoring of intracranial pressure, but few

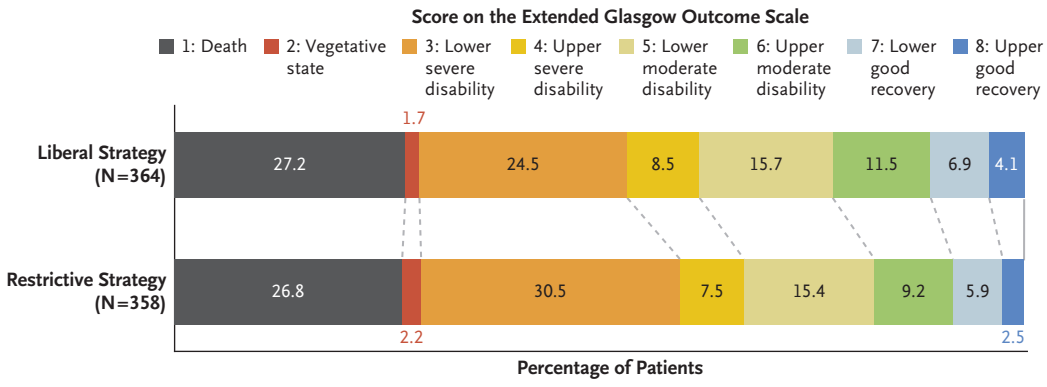

Figure 3. Scores on the Glasgow Outcome Scale–Extended at 6 Months According to Trial Group.

underwent invasive monitoring of brain oxygenation, decompressive craniectomy, or surgery for progressive hemorrhage (Table 1). Other cointerventions and secondary injuries after randomization are summarized in Table S2 and Figures S2 to S6 in the Supplementary Appendix. The representativeness of the trial population is summarized in Table S3.

ADHERENCE TO THE INTERVENTION

The median hemoglobin level during the ICU stay was 10.8 g per deciliter (interquartile range, 10.3 to 11.5) in the liberal-strategy group and 8.8 g per deciliter (interquartile range, 8.1 to 9.6) in the restrictive-strategy group (median difference, 2.00 g per deciliter; 95% confidence interval [CI], 1.97 to 2.03). Figure 1 shows the lowest mean daily hemoglobin level during the ICU stay. The median time between the measurement of hemoglobin and transfusion of red cells was 134 minutes (interquartile range, 57 to 190) in the liberal-strategy group and 104 minutes (interquartile range, 75 to 215) in the restrictive-strategy group (Fig. S7). Among patients who underwent randomization, 365 of 369 (98.9%) in the liberal-strategy group and 141 of 367 (38.4%) in the restrictive-strategy group received at least one red-cell transfusion, with a total of 1516 and 307 red-cell units transfused in the two groups, respectively (Table 2). The median number of red-cell units transfused per patient after randomization was 3 (interquartile range, 2 to 5) in the liberal-strategy group and 0 (interquartile range, 0 to 1) in the restrictive-strategy group. Fourteen patients (3.8%) in the liberal-strategy group and 7 (1.9%) in the restrictive-strategy group had protocol violations (Fig. S8).

PRIMARY OUTCOME

In the sliding-dichotomy analysis of the GOS-E score at 6 months, 249 of 364 patients (68.4%) in the liberal-strategy group had an unfavorable outcome, as compared with 263 of 358 (73.5%) in the restrictive-strategy group (adjusted absolute difference, restrictive strategy vs. liberal strategy, 5.4 percentage points; 95% confidence interval [CI], –2.9 to 13.7). The overall relative risk of an unfavorable outcome in the liberal group as compared with the restrictive group was 0.93 (95% CI, 0.83 to 1.04), with findings consistent across groups of patients with the worst, intermediate, and best predicted prognoses (Table 2) and across prespecified subgroups (Fig. 2 and Tables S4 to S10); the results of sensitivity analyses were similar (Tables S11 to S13). The distribution of the GOS-E scores is presented in Figure 3, and distributions of scores in subgroups and in sensitivity analyses are shown in Figures S9 to S26.

SECONDARY OUTCOMES

Mortality at 6 months was 26.8% in the liberal-strategy group and 26.3% in the restrictive-strategy group (hazard ratio for death, 1.01; 95% CI, 0.76 to 1.35). (A Kaplan–Meier analysis of survival is presented in Fig. S27.) Among patients who survived to 6 months, we observed a median difference between the liberal-strategy and restrictive-strategy groups of 4.34 points (95% CI, 0.22 to 8.45) in the overall FIM score, 5.19 points (95% CI, 0.52 to 9.86) in the score on

the EuroQol visual analogue scale and 0.06 points (95% CI, 0.01 to 0.10) in the EQ-5D-5L utility index score, 3.72 points (interquartile range, –1.13 to 8.56) in the Qolibri score, and –0.51 points (95% CI, –1.91 to 0.90) in the PHQ-9 score. The risk ratio for depression in the liberal group as compared with the restrictive group was 0.85 (95% CI, 0.63 to 1.17) (Table 2 and Table S14).

TERTIARY OUTCOMES

During the trial period, an infection developed in a majority of patients (53.8%); the most common infection was pneumonia. The median lengths of stay in the ICU and the hospital were similar in the two groups (Table 2).

SAFETY

Among patients who received a transfusion of red cells, 6 of 365 patients (1.6%) in the liberal-strategy group and 1 of 141 (0.7%) in the restrictive-strategy group had a reaction to the transfusion (Table 2 and Table S15). None of the reactions were severe. Adverse events are summarized in Table S16. Venous thromboembolic events occurred in 31 of 369 patients (8.4%) in the liberal-strategy group and in 31 of 367 (8.4%) in the restrictive-strategy group, and acute respiratory distress syndrome occurred in 12 of 369 (3.3%) and 3 of 367 (0.8%), respectively. Two serious adverse events were reported and were deemed by the data and safety monitoring committee to be unrelated to the intervention.

DISCUSSION

In this trial involving critically ill patients with moderate or severe traumatic brain injury and anemia, no significant difference in the risk of an unfavorable neurologic functional outcome at 6 months was seen with the use of a liberal transfusion strategy as compared with a restrictive strategy. Subgroup and sensitivity analyses yielded findings consistent with the overall results. No difference in mortality was observed. A liberal transfusion strategy appeared to be associated with better scores on several measures of motor function and quality of life among survivors at 6 months, but confidence intervals were not adjusted for multiple testing.

Very few trials of red-cell transfusion thresholds have examined long-term neurologic outcomes in any patient population, with only two trials conducted specifically in patients with traumatic brain injury.[28,29] The larger of these trials, which was conducted at two centers and involved 200 patients who did not have anemia, did not show separation of hemoglobin levels between groups, which negated the ability to detect a clinically significant difference in outcomes.[29] Moreover, that trial showed an increased risk of venous thromboembolic events with a liberal transfusion strategy as compared with a restrictive strategy, a finding not replicated in our trial.

Our findings with regard to mortality are consistent with the results of previous randomized trials in different critically ill populations.[7] Although mortality is important to consider, critically ill patients with traumatic brain injury and their caregivers may place greater value on other, patient-centered outcomes, since most survivors will live with severe neurologic deficits and various levels of dependency.[6]

Two trials of thresholds for transfusion — one involving a mixed, neurocritically ill population[30] and one involving patients with subarachnoid hemorrhage (ClinicalTrials.gov number, NCT03309579) — will provide further evidence to complement our findings. The completion of these trials also offers the opportunity to pool individual patient data to more precisely estimate the effect of a liberal red-cell transfusion strategy in neurocritically ill populations.

In addition to the previously mentioned trials, two trials (NCT03754114 and Australian New Zealand Clinical Trials Registry number, ACTRN12619001328167) are assessing the effects of bundled interventions, including red-cell transfusion, guided by invasive monitoring of brain-tissue oxygenation to improve clinical outcomes. The results of a recent trial showed no significant effect on long-term functional outcomes of monitoring brain-tissue oxygenation and provided limited data with regard to hemoglobin levels and transfusion frequency.[31] By contrast to these trials, our trial focused on transfusion thresholds driven by hemoglobin measurement, which offers a pragmatic approach applicable across various ICU settings, irrespective of brain monitoring or resources available within health care systems.

Our trial has several strengths. It was international and included a wide range of patients in centers with varying health care practices, which increases its generalizability. It involved provid-

ers of blood products, acute care communities, and patient representatives throughout the process to ensure the relevance of the trial and to facilitate rapid application of the findings. Outcomes were evaluated centrally by trained assessors who were unaware of the group assignments. The loss to follow-up was minimal. We collected data on relevant patient- and caregiver-centered outcomes. Adherence to the protocol was closely monitored and ensured an early and sustained difference in hemoglobin levels between groups. Our analyses were adjusted for center and sex. Finally, the use of a sliding dichotomy allowed for the effective use of the GOS-E as an ordinal scale.

Our trial also has limitations. By recruiting solely patients with anemia, we selected a population with more severe traumatic brain injury, which may explain the higher-than-expected baseline risk of an unfavorable outcome. Detection of small treatment effects becomes more challenging as the baseline risk increases. We also observed imbalances between the groups at baseline, which included some prognostic variables of the TBI-IMPACT score that may have suggested a better prognosis at baseline in the liberal-strategy group. Our prespecified analyses were adjusted for center and sex, and we performed a series of sensitivity analyses with adjustment for imbalanced covariates, all of which yielded similar results. Finally, it was not possible to mask the treatment assignments from the clinical team.

Our trial was designed to assess the superiority of a liberal transfusion strategy at reducing unfavorable neurologic outcomes at 6 months. Although several patient-reported outcomes suggest potentially better results with a liberal strategy, firm conclusions may not be drawn. The trial was not designed to assess the noninferiority of a more restrictive transfusion strategy, so the possibility of harm with such a strategy cannot be excluded.

In this international, randomized trial, a liberal transfusion strategy did not decrease the risk of an unfavorable neurologic outcome at 6 months as measured with the GOS-E in critically ill patients with traumatic brain injury.

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