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Restrictive vs Liberal Transfusion Strategy in Patients With Acute Brain Injury
The TRAIN Randomized Clinical Trial

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IMPORTANCE Blood transfusions are commonly administered to patients with acute brain injury. The optimal hemoglobin transfusion threshold is uncertain in this patient population.

OBJECTIVE To assess the impact on neurological outcome of 2 different hemoglobin thresholds to guide red blood cell transfusions in patients with acute brain injury.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, phase 3, parallel-group, investigator-initiated, pragmatic, open-label randomized clinical trial conducted in 72 intensive care units across 22 countries. Eligible patients had traumatic brain injury, aneurysmal subarachnoid hemorrhage, or intracerebral hemorrhage; hemoglobin values below 9 g/dL within the first 10 days after injury; and an expected intensive care unit stay of at least 72 hours. Enrollment occurred between September 1, 2017, and December 31, 2022. The last day of follow-up was June 30, 2023.

INTERVENTIONS Eight hundred fifty patients were randomly assigned to undergo a liberal (transfusion triggered by hemoglobin <9 g/dL; n = 408) or a restrictive (transfusion triggered by hemoglobin <7 g/dL; n = 442) transfusion strategy over a 28-day period.

MAIN OUTCOMES AND MEASURES The primary outcome was occurrence of an unfavorable neurological outcome, defined as a Glasgow Outcome Scale Extended score between 1 and 5, at 180 days following randomization. There were 14 prespecified serious adverse events, including occurrence of cerebral ischemia after randomization.

RESULTS Among 820 patients who completed the trial (mean age, 51 years; 376 [45.9%] women), 806 had available data on the primary outcome, 393 in the liberal strategy group and 413 in the restrictive strategy group. The liberal strategy group received a median of 2 (IQR, 1-3) units of blood, and the restrictive strategy group received a median of 0 (IQR, 0-1) units of blood, with an absolute mean difference of 1.0 unit (95% CI, 0.87-1.12 units). At 180 days after randomization, 246 patients (62.6%) in the liberal strategy group had an unfavorable neurological outcome compared with 300 patients (72.6%) in the restrictive strategy group (absolute difference, −10.0% [95% CI, −16.5% to −3.6%]; adjusted relative risk, 0.86 [95% CI, 0.79-0.94]; *P* = .002). The effect of the transfusion thresholds on neurological outcome at 180 days was consistent across prespecified subgroups. In the liberal strategy group, 35 (8.8%) of 397 patients had at least 1 cerebral ischemic event compared with 57 (13.5%) of 423 in the restrictive strategy group (relative risk, 0.65 [95% CI, 0.44-0.97]).

CONCLUSIONS AND RELEVANCE Patients with acute brain injury and anemia randomized to a liberal transfusion strategy were less likely to have an unfavorable neurological outcome than those randomized to a restrictive strategy.

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The indications for red blood cell transfusion in the absence of life-threatening bleeding are controversial. In critically ill patients, anemia is associated with increased morbidity and mortality rates, but blood transfusions have also been associated with a higher risk of complications, such as secondary infection or lung injury.[1-3] Several randomized clinical trials have been conducted to compare different transfusion strategies in this patient population, and most have suggested that a restrictive transfusion strategy may be as safe and effective as a more liberal approach.[4-7]

None of these studies specifically targeted patients with acute brain injury. Observational studies showed that hemoglobin levels below 9 g/dL were linked to poorer outcomes in patients with traumatic brain injury (TBI) or subarachnoid hemorrhage.[8,9] A liberal transfusion strategy might benefit these patients by improving oxygen delivery and reducing brain tissue hypoxia, especially with impaired cerebral blood flow or autoregulation.[10] However, blood transfusions in this context also increased the risk of complications or mortality.[11] These findings, being observational, did not establish the optimal hemoglobin threshold for transfusion.[12]

In a randomized clinical trial, there were no significant differences in occurrence of favorable neurological outcomes between a restrictive transfusion strategy and a liberal transfusion strategy after TBI. Moreover, the higher transfusion threshold was associated with a greater incidence of thromboembolic events.[13] Another small randomized trial found that using a lower hemoglobin threshold resulted in fewer transfusions than a higher threshold after TBI, but it was associated with significantly higher hospital mortality and unfavorable neurological outcomes.[14] A recent large randomized trial involving 742 patients with TBI showed a nonsignificant 5.4% reduction in occurrence of unfavorable neurological outcomes in patients randomized to a liberal transfusion strategy compared with those in a restrictive strategy group.[15]

Given the absence of clear evidence on hemoglobin transfusion thresholds and the existing safety concerns associated with transfusion, we initiated the Transfusion Strategies in Acute Brain Injured Patients (TRAIN) trial to assess the impact on neurological outcome of using different hemoglobin thresholds to guide red blood cell transfusions in patients with acute brain injury necessitating admission to the intensive care unit (ICU).

Key Points

Question How does use of a liberal or restrictive strategy of blood transfusion influence neurological outcome among patients with acute brain injury?

Findings In this randomized clinical trial that included 850 patients with acute brain injury and a hemoglobin level below 9 g/dL, those who were treated with a liberal transfusion strategy triggered by hemoglobin below 9 g/dL had a lower probability of unfavorable neurological outcome at 180 days than those treated with a restrictive strategy triggered by hemoglobin below 7 g/dL (62.6% vs 72.6%, respectively; adjusted relative risk, 0.86).

Meaning A liberal transfusion strategy compared with a restrictive strategy resulted in a lower rate of unfavorable neurological outcome among patients with acute brain injury.

Methods

Trial Design

This multicenter, phase 3, parallel-group, investigator-initiated, pragmatic, open-label, outcome assessor-blinded, randomized clinical trial was conducted in 72 ICUs across 22 countries (eTable 1 in Supplement 1). After obtainment of approvals from ethics committees in each hospital, patients were screened for eligibility. Written informed consent was obtained from legal surrogates before enrollment. Whenever possible, written consent was also obtained from patients who regained mental capacity. This study adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.[16]

The study protocol has been published[17] and is also available in Supplement 2. The steering committee was responsible for designing the trial, while the management committee ensured monitoring and adherence to the protocol, as well as verifying the accuracy of the data (Supplement 2).

Participant Enrollment

All adult (≥18 years of age) patients admitted to the ICU with TBI, subarachnoid hemorrhage, or intracerebral hemorrhage were screened for eligibility within 10 days following their initial injury. Eligibility was not contingent on the need for surgical intervention or red blood cell transfusion due to acute bleeding. Patients with a Glasgow Coma Scale score of 13 or less on the day of randomization, an expected ICU stay of at least 3 days, and a hemoglobin level of 9 g/dL or less, measured using a valid point-of-care test (eg, hospital laboratory or gas analyzer), were eligible for inclusion. Once the eligibility criteria were met, the study protocol had to be initiated within a maximum of 24 hours. Detailed inclusion and exclusion criteria are reported in eTable 2 in Supplement 1. Each patient was eligible for inclusion in the study only once. Enrollment occurred between September 1, 2017, and December 31, 2022, and the last day of follow-up was June 30, 2023.

Randomization and Blinding

After eligibility screening, patients were randomly allocated in a 1:1 ratio to 1 of 2 thresholds to determine when red blood cell transfusion should be given, at a hemoglobin concentration of less than 7 g/dL (restrictive strategy group) or at that of less than 9 g/dL (liberal strategy group). Randomization was conducted using a web-based, computer-generated random sequence with variable block sizes of 4, 6, and 8. Stratification was performed based on center, type of brain injury (TBI, subarachnoid hemorrhage, or intracerebral hemorrhage), and Glasgow Coma Scale score at the time of randomization (3-5, 6-9, or 10-13). The ICU and hospital health care staff were aware of the treatment assignments. Patients and family members were blinded to the treatment assignments. The final neurological evaluations of patients were conducted by assessors who were blinded to the treatment assignments.

Trial Intervention

The allocated transfusion thresholds were maintained for a maximum of 28 days after randomization or until hospital discharge or death, whichever event occurred first. Following randomization, all patients received 1 unit of packed red blood cells at a time when they met their allocated hemoglobin concentration threshold. In both treatment groups, there was no protocolization for the timing of transfusion once the trigger threshold was met, although it was recommended to administer the red blood cell transfusion within a few hours. Hemoglobin concentrations were measured daily according to local practices; values obtained from blood gas analyses during the ICU stay were also acceptable. Administration of a blood transfusion in conflict with the assigned trigger level or an error in crossmatching was defined as a protocol violation. No additional restrictions were imposed on concurrent care and interventions. All decisions regarding discontinuation of life-sustaining therapy were made by attending physicians according to local practice. Due to limited resources and the large number of participating countries, on-site monitoring was conducted for 417 (49.0%) of the 850 patient records. The monitoring team worked closely with local trial teams to verify data against source documents, including admission registers, emergency department notes, ICU records, and outcome assessments.

Outcome Measures

The primary outcome measure was the proportion of patients with unfavorable neurological outcome at 180 days after randomization. Neurological outcome was assessed using the Glasgow Outcome Scale Extended (GOS-E), which was dichotomized as unfavorable (GOS-E score of 1-5) or favorable (GOS-E score of 6-8); this scale ranges from 1 to 8, with death being included in the scale (GOS-E score of 1), and higher scores indicate better outcome (eTable 3 in Supplement 1). The decision to categorize a GOS-E score of 5 as an unfavorable outcome was made because this value includes patients who are unable to participate in 1 or more life roles, significantly affecting their quality of life and social activities. The GOS-E assessment was recorded 180 days after randomization in structured telephone or face-to-face interviews[18] with patients or relatives by health care professionals who were unaware of the intervention assignments. The GOS-E interview schedule is designed to facilitate the scoring process by providing questions that elicit key information and help define the boundaries between scored categories. Experienced interviewers have demonstrated a high level of independent agreement in GOS-E score assignments.[19]

Secondary outcome measures included 28-day survival; distribution of GOS-E scores in the 2 groups (ie, ordinal outcome analysis) at 180 days; ICU and hospital lengths of stay; presence of organ failure, assessed using daily Sequential Organ Failure Assessment (SOFA) scores (organ failure being defined as >2 points on 1 of the 6 components of the score [respiratory, cardiovascular, hepatic, coagulation, renal, and neurological organ systems], occurring from randomization to ICU discharge) during the ICU stay; composite outcome including death and/or organ failure at day 28; and daily fluid balance during the ICU stay. A complete list of predefined serious adverse events occurring after randomization until ICU discharge or for a maximum of 28 days and their definitions is available in eTable 4 in Supplement 1. All data were collected in the electronic case report file.

Sample Size Calculation

The initial sample size calculation was based on estimated mortality and poor neurological outcome rates of 15% and 35%, respectively (corresponding to a GOS-E score of 1-5 in 50% of cases). This calculation indicated that each group was required to have 2095 patients to achieve a statistical power of 90% at a 2-sided $\alpha = .05$ or less. This power was deemed sufficient to detect a reduction in the rate of poor neurological outcome at 180 days from 50% to 45% (an absolute reduction of 5% or a relative reduction of 10%) in 1 of the 2 groups. The sample size calculation was subsequently adjusted twice. As a result of slow patient enrollment, instead of considering a reduction from 50% to 45% in the rate of unfavorable neurological outcome at 180 days, we considered a reduction from 50% to 40% (an absolute reduction of 10% or a relative reduction of 20%). This adjustment was approved by the ethics committee in Brussels (August 2019). The second adjustment, approved by the ethics committee in Brussels in June 2022, was made due to the inability to recruit the expected number of patients before the study deadline of December 31, 2022. Therefore, a further reduction was made in the unfavorable neurological outcome rate at 180 days from 50% to 39% (an absolute reduction of 11% or a relative reduction of 22%) in 1 group to achieve a statistical power of 85% with a 2-sided $\alpha = .05$. Factoring in a potential 5% loss to follow-up, the total sample size required to complete the study was determined to be 794 patients (397 per group); however, since the study deadline was December 31, 2022, it was decided to allow randomization to continue until that date if the number of included patients exceeded 794. These decisions were initiated by the principal investigator and assessed by an independent statistician and were driven by the disruptions caused by the COVID-19 pandemic, which significantly impacted recruitment and blood availability for transfusion and introduced uncertainty regarding future recruitment prospects.[20] The results of the interim analysis did not influence adjustments of the sample size.

Statistical Analysis

Data for the study outcomes and serious adverse events were analyzed including all randomly assigned patients in the groups to which they were randomized except those for whom consent was withdrawn. Statistical analyses were conducted using SPSS version 29.0 (IBM). The significance threshold for the primary outcome was set at $P < .05$. All statistical tests were 2-sided to ensure rigorous evaluation of the data, accounting for the possibility of effects in either direction. Initially, 2 interim analyses were planned at specified intervals, ie, after enrollment of 200 and 700 patients, to monitor protocol adherence, assess primary outcomes, and evaluate serious adverse events. However, a decision was made to conduct a single interim analysis after enrolling 300 patients to specifically assess primary outcome, protocol adherence (eg, protocol violations), and data completeness. The O'Brien-Fleming method for the α spending function was used to maintain the study-wide type I error rate at a 2-sided $\alpha = .05$. This interim analysis was carried out

by an independent statistician who had access to the entire database, while maintaining blinding for all data regarding the study groups. Following the analysis of this interim report, the independent data and safety monitoring committee (eAppendix in Supplement 1), whose members were unaware of group assignment, reviewed the findings of the interim analysis and recommended that the study continue recruitment.

Continuous variables are summarized using medians and IQRs and were analyzed using the Wilcoxon rank sum test. Categorical variables were analyzed using the Fisher exact test. Primary outcome assessment was performed using complete case analysis and comparisons were performed using a χ^2 analysis and are reported as the absolute risk reduction of a poor outcome, along with its corresponding 95% CI. Confidence intervals for means were calculated based on a normal distribution, while those for proportions were derived from a binomial distribution. In cases where there were zero cells, 0.5 was added to all cells to allow for proper calculation. The primary outcome analysis was adjusted by stratification variables (center, type of brain injury, and Glasgow Coma Scale score at randomization) using a log-binomial regression. For the secondary post hoc analysis of the primary outcome, best-worst and worst-best sensitivity analyses were performed, along with multiple imputation, including the 14 patients with missing data.[21] In the best-worst-case scenario, a dataset was generated assuming that all participants lost to follow-up in the liberal strategy group had a favorable outcome, while those with missing outcomes in the restrictive strategy group had an unfavorable outcome. Conversely, the worst-best-case scenario assumed that all participants lost to follow-up in the liberal strategy group had an unfavorable outcome, while those in the restrictive strategy group had a beneficial outcome. Multiple imputation was conducted using the multiple imputation by chained equations method. An additional post hoc analysis of the primary outcome using a different definition of unfavorable neurological outcome (GOS-E score 1-4) was also performed.

All secondary outcomes were analyzed through independent sample *t* tests and χ^2 tests, as appropriate, without additional adjustments. For repeated daily measurements (eg, hemoglobin values, SOFA score, fluid balance), a generalized mixed model with the Geisser-Greenhous correction and Tukey multiple correction test, which accounted for missing values and early deaths, was used. For the analysis of 28-day mortality, the Cox proportional hazard model was used to determine time-to-event hazard ratios and their associated 95% CIs. Ordinal logistic regression was used to compare the distribution of the GOS-E score at 180 days between the 2 groups and the resulting odds ratios and 95% CIs were reported.

Subgroup analyses were conducted based on the following criteria: underlying brain injury (TBI, subarachnoid hemorrhage, or intracerebral hemorrhage); Glasgow Coma Scale score at the time of randomization (3-5, 6-9, or 10-13); requirement for specific therapies to reduce intracranial pressure at randomization; age (<45 years or ≥45 years); and SOFA score at randomization (<8 vs ≥8). Post hoc analyses encompassed high-income countries vs middle- to low-income countries and high recruiting centers (>25 patients) vs others. Given the potential for type I error due to multiple comparisons of the secondary end points and serious adverse events, these findings should be interpreted with caution and considered exploratory in nature.

Results

Trial Population

A total of 850 patients underwent randomization (**Figure 1**). After randomization, consent was withdrawn for 30 patients (17 by patients, 9 by attending physicians, and 4 by patients' surrogates), resulting in a study population of 820, 397 in the liberal strategy group and 423 in the restrictive strategy group. The median time from ICU admission to randomization was 3 days (IQR, 2-5 days) in the liberal strategy group and 3 days (IQR, 2-6 days) in the restrictive strategy group. Baseline characteristics were comparable in the 2 groups (**Table 1**; eTables 5 and 6 in Supplement 1). The primary outcome was available in 806 patients (94.8%), 393 in the liberal strategy group and 413 in the restrictive strategy group.

Hemoglobin Concentrations

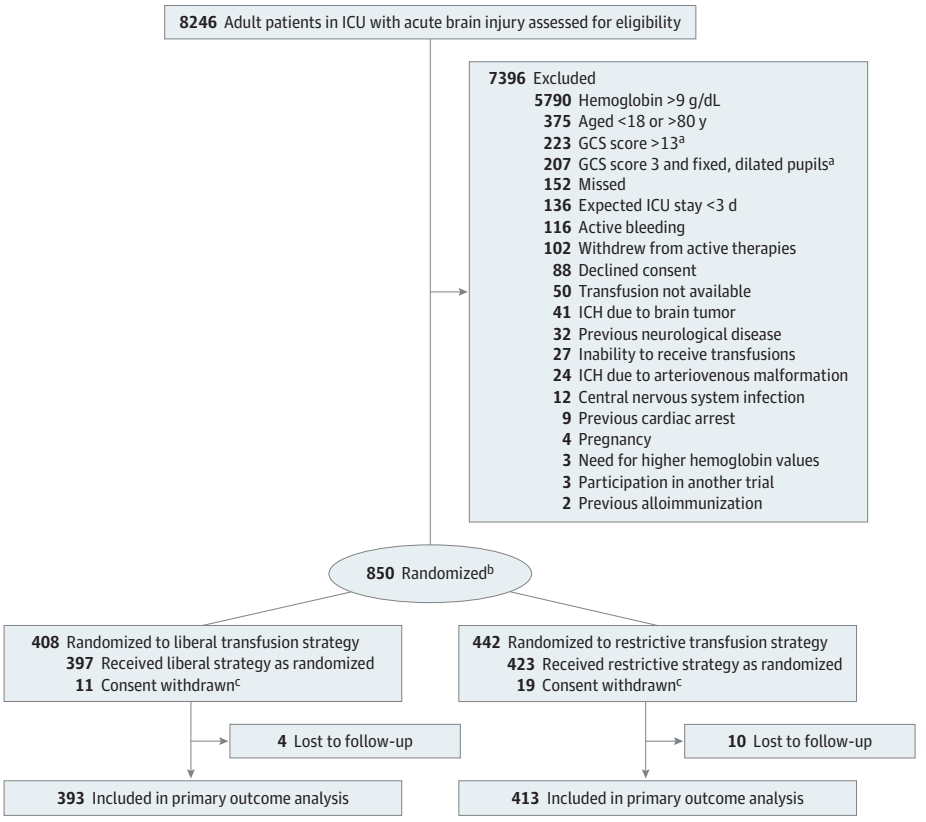
The lowest and highest blood hemoglobin concentrations in the 2 study groups at baseline and after randomization are shown in **Figure 2** and eFigures 1-3 in Supplement 1. The median hemoglobin concentration at randomization was 8.5 g/dL in both groups. Following randomization, there was a significant difference in the median daily lowest hemoglobin concentrations between the groups ($P < .001$) (Figure 2).

A total of 910 blood transfusions were administered in the liberal strategy group during the study period and 373 transfusions in the restrictive strategy group ($P < .001$). The median cumulative count of blood transfusions after randomization was 2 (IQR, 1-3) units in the liberal strategy group and 0 (IQR, 0-1) units in the restrictive strategy group (absolute mean difference, 1.0 [95% CI, 0.87-1.12]; $P < .001$). A total of 357 patients (89.9%) in the liberal strategy group required transfusion during their ICU stay compared with 205 patients (48.5%) in the restrictive strategy group ($P < .001$). The incidence of protocol violations was similar in both groups (eTable 7 in Supplement 1).

Study Outcomes

At 180 days following randomization, 246 (62.6%) of 393 patients in the liberal strategy group and 300 (72.6%) of 413 patients in the restrictive strategy group had an unfavorable neurological outcome (absolute difference, −10.0% [95% CI, −16.5% to −3.6%]; unadjusted relative risk, 0.86 [95% CI, 0.78-0.95]; adjusted relative risk, 0.86 [95% CI, 0.79-0.94]; $P = .002$) (**Table 2**). Post hoc best-worst, worst-best, and multiple imputation analyses indicated that missing data did not affect the results of the analyses of neurological outcome (relative risks, 0.85 [95% CI, 0.78-0.93], 0.89 [95% CI, 0.82-0.98], and 0.87 [95% CI, 0.79-0.95], respectively). Post hoc analysis of the primary outcome using a different definition of unfavorable neurological outcome (GOS-E score of 1-4) reported similar results (relative risk, 0.83 [95% CI, 0.73-0.94]) (eTable 8 in Supplement 1). The median GOS-E score at 180 days was 4 (IQR, 1-6) in both groups. The effect of the transfusion thresholds on neurological outcome at 180 days was consistent across most prespecified subgroups (**Figure 3**).

Figure 1. Flow of Participants in the TRAIN Trial



GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; and ICU, intensive care unit.

[a]The GCS is a neurological assessment tool used by medical and nursing staff to monitor the clinical progression of a patient's consciousness after acute brain injury. The scale is based on 3 types of responses to stimuli (eye, verbal, and motor); the overall score is the sum of the individual assessments for each function. The maximum score is 15, indicating a normal state of consciousness, while the minimum score is 3, indicating a deep state of unconsciousness.

[b]Patients were randomly allocated in a 1:1 ratio to a restrictive strategy (hemoglobin concentration <7 g/dL) or a liberal strategy (hemoglobin concentration <9 g/dL) to determine when red blood cell transfusion should be given. Stratification was performed based on center, type of brain injury (traumatic brain injury, subarachnoid hemorrhage, or intracerebral hemorrhage), and GCS score at the time of randomization (3-5, 6-9, or 10-13).

[c]Among the 30 patients excluded after randomization because consent was withdrawn, no further data were registered, including outcome data.

There was no evidence of a difference in 28-day survival between the liberal and restrictive strategy groups (82/397 [20.7%] vs 94/418 [22.5%]; relative risk, 0.95 [95% CI, 0.74-1.22]) (Table 2; eFigure 4 in Supplement 1). The distribution of GOS-E scores between the groups showed a significant shift toward a larger proportion of patients distributed in higher GOS-E subscores in the liberal strategy group compared with the restrictive strategy group (odds ratio, 1.37 [95% CI, 1.07-1.75]; $P = .01$) (**Figure 4**). Other secondary outcomes were not significantly different between groups (Table 2; eFigures 5 and 6 in Supplement 1). The effect of the transfusion thresholds on neurological outcome at 180 days was also consistent in post hoc subgroup analyses (eFigures 7 and 8 in Supplement 1).

Adverse Events

Prespecified adverse events are reported in Table 2. In the liberal strategy group, 35 (8.8%) of 397 patients had at least 1 cerebral ischemic event compared with 57 (13.5%) of 423 in the restrictive strategy group (relative risk, 0.65 [95% CI, 0.44-0.97]). There was no evidence of a difference in other prespecified adverse events.

Discussion

In this international, multicenter randomized clinical trial among patients with acute brain injury, patients randomized to a strategy of transfusion at a threshold of 9 g/dL had a lower risk of unfavorable neurological outcome at 180 days than those randomized to a threshold of 7 g/dL. These differences were consistent across the prespecified subgroups of patients. The risk of having at least 1 cerebral ischemic event was also lower in the liberal strategy group than in the restrictive strategy group.

Our findings substantially expand the existing evidence in relation to transfusion thresholds for patients in the ICU with an acute brain injury. In a small single-center trial including 44 patients with TBI and using identical transfusion thresholds to those used in the current study,[14] the liberal transfusion strategy group also had better neurological status at 6 months (62% vs 44%) than the restrictive strategy group. However, the limitations of a single-center design and the small cohort introduced relevant methodological bias, limiting the ability to draw definitive conclusions. In the recently published HEMOTION trial, a liberal transfusion strategy was associated with a nonsignificant 5.4% absolute reduction (95% CI, −2.9% to 13.7%) in the risk of unfavorable neurological outcomes at 6 months in patients with TBI compared with a restrictive strategy.[15] Moreover, among survivors, the liberal strategy was linked to higher scores on some, but not all, scales assessing functional independence and quality of life. The main differences between that trial and ours include the hemoglobin transfusion threshold selected for the control group (10 vs 9 g/dL), the definition of unfavorable neurological outcome (GOS-E score of 1-4 vs 1-5), the predefined subgroup analyses, and the target population (TBI vs a more heterogeneous acute brain injury cohort). Taken

Table 1. Characteristics of the Study Population[a]

Characteristics	Liberal strategy (n = 397)	Restrictive strategy (n = 423)
Age, mean (SD), y	52 (16)	51 (16)
Sex, No. (%)		
Female	179 (45.1)	197 (46.6)
Male	218 (54.9)	226 (53.4)
Time from admission to randomization, median (IQR), d	3 (2-5)	3 (2-6)
Medical history, No. (%)		
Diabetes	25 (6.3)	24 (5.7)
Chronic obstructive pulmonary disease	21 (5.3)	22 (5.2)
Immunosuppressive therapy	13 (3.3)	11 (2.6)
Cancer	10 (2.5)	15 (3.5)
Metastatic	4 (1.0)	0
Hematological	3 (0.8)	2 (0.5)
Chronic heart failure	8 (2.0)	8 (1.9)
Long-term steroid therapy	8 (2.0)	3 (0.7)
Liver cirrhosis	5 (1.3)	4 (0.9)
HIV	5 (1.3)	12 (2.8)
Type of brain injury, No. (%)		
Traumatic brain injury	240 (60.5)	246 (58.2)
Subarachnoid hemorrhage	86 (21.7)	104 (24.6)
Intracerebral hemorrhage	71 (17.9)	73 (17.3)
Source of admission, No. (%)	n = 396	n = 419
Emergency department/ambulance	268 (67.7)	266 (63.5)
Operating room/recovery	24 (6.1)	24 (5.7)
Hospital floor	6 (1.5)	10 (2.4)
Other hospital	93 (23.5)	115 (27.4)
Unknown	5 (1.3)	4 (1.0)
APACHE II score on admission, mean (SD)[b]	19 (8) [n = 356]	19 (8) [n = 368]
SOFA score on admission, mean (SD)[c]	7 (3) [n = 393]	7 (3) [n = 418]
Intracranial pressure monitoring within 48 h of admission, No./total (%)	279/395 (70.6)	289/418 (69.1)
Antiplatelet therapy before injury, No./total (%)	56/392 (14.2)	58/417 (13.9)
Anticoagulant therapy before injury, No./total (%)	30/394 (7.6)	20/417 (4.8)
Physical examination on admission		
Initial GCS score, median (IQR)[d]	7 (4-11)	8 (4-12)
Initial m-GCS score, median (IQR)[d]	4 (2-5)	4 (2-5)
GCS score on admission, median (IQR)[d]	7 (3-9)	6 (3-9)
m-GCS score on admission, median (IQR)[d]	4 (1-5)	4 (1-5)
Pupillary reactivity, No./total (%)		
Both pupils reacting	296/396 (74.7)	327/418 (78.2)
One pupil reacting	40/396 (10.1)	44/418 (10.5)
No pupils reacting	60/396 (15.2)	47/418 (11.2)
Laboratory findings on hospital admission		
Sodium, mean (SD), mmol/L	140 (5) [n = 395]	140 (6) [n = 418]
Glucose, mean (SD), mg/dL	165 (54) [n = 395]	162 (58) [n = 418]
Hemoglobin, median (IQR), g/dL	11.8 (10.2-13.0)	11.9 (10.2-12.9)
Clinical and hemoglobin values at randomization		
GCS score, median (IQR)	6 (3-8)	6 (3-8)
m-GCS score, median (IQR)	3 (1-5)	3 (1-5)
Hemoglobin, median (IQR), g/dL	8.5 (7.9-8.8)	8.5 (8.0-8.8)

(continued)

Table 1. Characteristics of the Study Population[a] (continued)

Characteristics	Liberal strategy (n = 397)	Restrictive strategy (n = 423)
Therapies during intensive care unit stay, after randomization		
Mechanical ventilation, No. (%)	360 (90.7)	390 (92.2)
Duration, median (IQR), d[e]	14 (7-21)	14 (9-21)
Salvage therapies for elevated intracranial pressure, No. (%)	110 (27.7)	135 (31.9)
Kidney replacement therapy, No. (%)	29 (7.3)	39 (9.2)
Antiepileptic therapy, No. (%)	27 (6.8)	50 (11.8)

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

[a] The restrictive strategy had a hemoglobin threshold of <7 g/dL for transfusion, while the liberal strategy had a threshold of <9 g/dL. Medical history was collected by local investigators from medical record review, long-term steroid therapy counted any oral or intravenous steroid therapy for any condition for more than 4 weeks, and immunosuppressive therapy indicated any immunosuppressive therapy except steroids. Second-tier therapies for intracranial pressure indicate hypothermia, barbiturates, or decompressive craniectomy (primary or secondary).

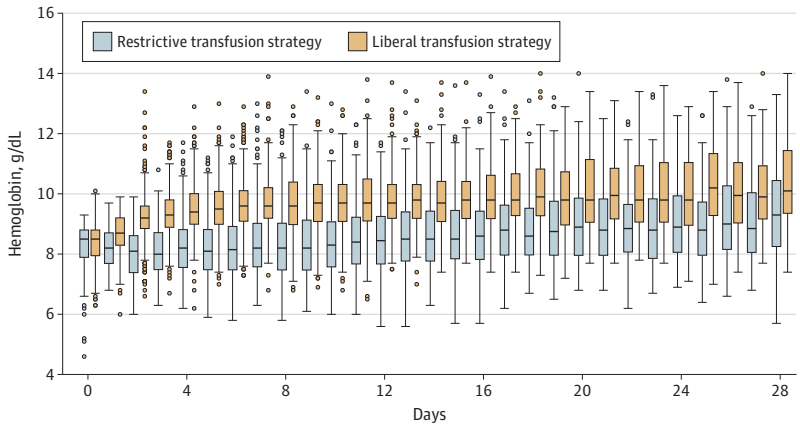
[b] The Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II is a general measure of disease severity based on physiological measurements, age, and previous health conditions that aids in assessing patients to determine the level and degree of diagnostic and therapeutic intervention. The score ranges from 0 to 71, with higher scores indicating increased risk of hospital death.

[c] The Sequential Organ Failure Assessment (SOFA) is used to determine the extent of organ dysfunction or failure in patients in the intensive care unit based on assessments of 6 organ systems, respiratory, cardiovascular, hepatic, coagulation, renal, and neurological. The score ranges from 0 to 24, with higher scores indicating increased risk of death.

[d] The Glasgow Coma Scale (GCS) is a neurological scale used to assess level of consciousness after acute brain injury, determined by evaluating 3 components, eye-opening response, verbal response, and motor response (m-GCS). Each component is scored individually then summed for an overall score, which ranges from 3 to 15, where 3 indicates deep unconsciousness or coma and 15 signifies full alertness and orientation. Higher scores indicate better neurological function; lower scores suggest more severe impairment. The m-GCS assesses ability to respond to stimuli with purposeful movement, ranging from 1 to 6, with 6 indicating that a patient obeys commands (eg, moving a limb when asked), demonstrating intact motor function; 5, localized movement in response to pain, indicating some degree of purposeful response; 4, withdrawal from pain, showing basic protective reflexes; 3, abnormal flexion (decorticate posturing); 2, abnormal extension (decerebrate posturing); and 1, no motor response (last 3 scores indicate progressively increasing brain dysfunction).

[e] Duration of mechanical ventilation after intensive care unit admission.

Figure 2. Median Daily Lowest Hemoglobin Concentration at Baseline and After Randomization



No. at risk

Liberal strategy	393	366	356	300	252	177	131	87
Restrictive strategy	413	423	397	327	263	202	154	101

Baseline values were the last blood hemoglobin level measured before randomization. Day 0 was the day of randomization. Boxes indicate IQRs; bars inside the boxes, medians; whiskers, highest and lowest values within 1.5 times the IQRs; and circles outside the boxes, outlying data. See eFigure 1 in Supplement 1 for presentation showing medians (95% CIs) and eFigure 2 in Supplement 1 for median daily highest hemoglobin concentrations.

together, these findings suggest that a liberal transfusion strategy in patients with acute brain injury might be associated with improved neurological outcome.

However, our results are not in agreement with those of a larger trial in patients with severe TBI, in which there were no significant differences in neurological outcomes between groups.[13] Notably, in that trial, the liberal transfusion group had a higher hemoglobin threshold for transfusion (10 g/dL) than in our study, and the study groups had much higher mean hemoglobin levels throughout the study than those in our trial. Coenrollment of patients receiving erythropoietin in that study[13] is another significant methodological difference from our research. In a separate pilot randomized trial exclusively in patients with subarachnoid hemorrhage at high risk of cerebral vasospasm, the hemoglobin thresholds for transfusion were set at 10 g/dL or 11.5 g/dL.[22] That trial reported similar rates of unfavorable neurological outcomes and comparable numbers of cerebral infarctions on brain imaging in the 2 groups.[23] As such, clinical practice still exhibits substantial variability in the hemoglobin thresholds used to initiate transfusions. The selection of the current study's specific thresholds (7 and 9 g/dL) was informed by the outcomes of a comprehensive survey involving

Table 2. Study Outcomes and Main Adverse Events[a]

	Liberal strategy	Restrictive strategy	Absolute difference, % (95% CI)	Relative risk (95% CI)
Primary outcome				
Unfavorable neurological outcome at 180 d, No./total (%)[b]	246/393 (62.6)	300/413 (72.6)	−10.0 (−16.5 to −3.6)	0.86 (0.79-0.94)[c]
Secondary outcomes				
28-d Mortality, No./total (%)	82/397 (20.7)	94/418 (22.5)	−1.8 (−7.5 to 3.8)	0.95 (0.74-1.22)
Composite outcome, No./total (%)[d]	318/397 (80.1)	328/419 (78.3)	1.8 (−3.7 to 7.4)	1.03 (0.97-1.10)
Organ failure, No./total (%)	293/373 (78.6)	314/405 (77.5)	1.0 (−4.8 to 6.8)	1.03 (0.96-1.10)
Intensive care unit length of stay, mean (SD), d	21.4 (15.7) [n = 397]	22.5 (15.6) [n = 417]	−1.19 (−3.34 to 0.97)	
Hospital length of stay, mean (SD), d	42.0 (34.8) [n = 397]	45.5 (39.3) [n = 417]	−3.50 (−8.62 to 1.62)	
Serious adverse events, No./total (%)				
Sepsis	45/397 (11.3)	64/423 (15.1)		0.75 (0.53-1.07)
Severe hypotension	42/397 (10.6)	40/423 (9.5)		1.06 (0.83-1.30)
Cerebral ischemia	35/397 (8.8)	57/423 (13.5)		0.65 (0.44-0.97)
Acute respiratory distress syndrome	29/397 (7.3)	36 /423 (8.5)		0.86 (0.54-1.37)
Venous thromboembolism	19/397 (4.8)	17/423 (4.0)		1.19 (0.63-2.26)
Severe hypertension	11/397 (2.8)	13/423 (3.1)		0.90 (0.41-1.99)
Intestinal ischemia	4/397 (1.0)	5/423 (1.2)		0.85 (0.23-3.15)
Brain tissue hypoxia[e]	5/397 (1.3)	3/423 (0.7)		1.78 (0.43-7.38)
Transfusion-associated cardiovascular overload	2/397 (0.5)	2/423 (0.5)		1.02 (0.15-7.53)
Acute peripheral limb ischemia	1/397 (0.3)	2/423 (0.5)		0.53 (0.05-5.85)
Anaphylaxis	2/397 (0.5)	0		5.33 (0.26-110.61)
Transfusion-associated acute lung injury	0	2/423 (0.5)		0.21 (0.01-4.42)
Acute myocardial infarction	0	1/423 (0.2)		0.36 (0.01-8.69)

[a] The restrictive strategy had a hemoglobin threshold of <7 g/dL for transfusion, while the liberal strategy had a threshold of <9 g/dL.

[b] Neurological outcome at 180 days after randomization was assessed using the Glasgow Outcome Scale Extended (GOS-E), dichotomized as unfavorable (GOS-E score, 1-5) or favorable (GOS-E score, 6-8); the score ranges from 1 to 8, with death included in the scale (GOS-E score, 1) and a higher score indicating a better outcome. Organ failure was defined as more than 2 points on 1 of the 6 components of the daily Sequential Organ Failure Assessment score (respiratory, cardiovascular, hepatic, coagulation, renal, or neurological organ systems), occurring between randomization and intensive care unit discharge.

[c] $P = .002$. For the primary outcome, the relative risk was adjusted for center, type of brain injury (traumatic brain injury, subarachnoid hemorrhage, or intracerebral hemorrhage), and Glasgow Coma Scale score at the time of randomization.

[d] The composite outcome included death and any organ failure at day 28 after randomization.

[e] The total number of patients undergoing brain tissue oxygenation monitoring is not available.

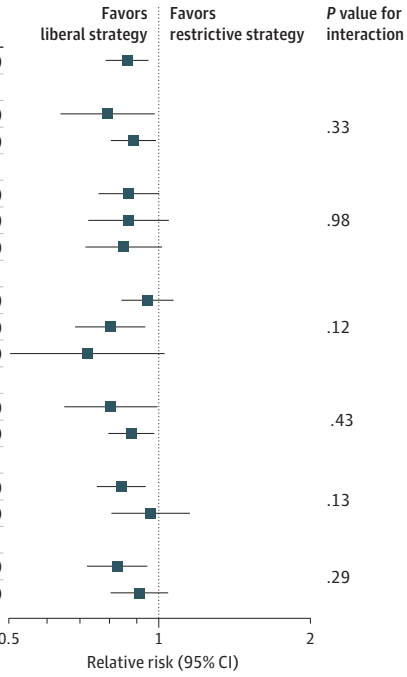
more than 800 respondents, which identified these 2 hemoglobin concentrations as the most used thresholds for transfusion in patients with brain injuries in clinical practice.[24] This wide variation in practice highlights the importance of conducting large-scale clinical trials in this population. One ongoing large trial (NCT03309579) should provide further evidence regarding optimal hemoglobin thresholds to help inform transfusion decisions for patients with subarachnoid hemorrhage.

No other significant differences in secondary outcomes were observed between the study groups. This finding aligns with findings from the HEMOTION trial,[15] which also reported a lower proportion of patients with unfavorable neurological outcome in the liberal strategy group (although not statistically significant), with no significant difference in secondary outcomes between groups. This lack of difference in secondary outcomes could be attributed to the similar intensity of care provided to both groups, leading to comparable ICU and hospital stays (eg, no early discharge in the restrictive strategy group), as well as the overall level of medical interventions. The absence of a difference in mortality suggests that while a liberal transfusion approach may not influence survival, it could contribute to better neurological recovery among survivors. This benefit appears to be associated with a lower occurrence of cerebral infarction in the liberal transfusion group.

The effect of transfusion thresholds on rates of cerebral infarction has not been reported in previous trials. In a secondary analysis of a study in patients with severe TBI, those randomized to a transfusion threshold of 10 g/dL had a higher adjusted risk of progressive hemorrhagic injury than those assigned to a lower threshold[25]; occurrence of progressive hemorrhagic injury was significantly associated with a prolonged ICU length of stay and poorer outcomes at 6 months. However, no data regarding occurrence of new ischemic events were reported. In a retrospective study, blood transfusion was associated with a marked improvement in brain tissue oxygenation in only 41% of patients[26]; therefore, the impact of transfusion in preventing cerebral ischemia remains unsettled. Importantly, presence of tissue hypoxia at baseline may predict improvement in brain oxygenation with transfusion, whereas baseline hemoglobin concentration did not show a similar predictive value.[26] These observations suggest that blood hemoglobin concentrations may not be the most

Figure 3. Relative Risk of the Primary Outcome of Unfavorable Neurological Outcome at 180 Days Among All Patients and in Prespecified Subgroups

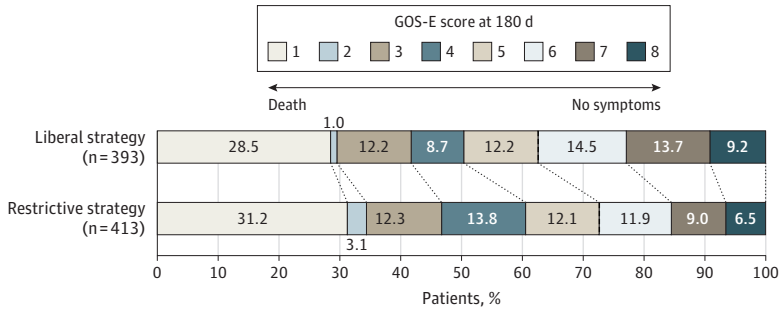
Subgroup	Unfavorable neurological outcome, No./total No. (%)		Absolute difference, % (95% CI)	Relative risk (95% CI)	*P* value for interaction
	Liberal strategy	Restrictive strategy			
Overall	246/393 (62.6)	300/413 (72.6)	-10.0 (-16.5 to -3.6)	0.86 (0.78 to 0.95)	
Age, y					
<45	62/124 (50.0)	87/137 (63.5)	-13.5 (-25.4 to -1.6)	0.79 (0.63 to 0.98)	.33
≥45	184/269 (68.4)	213/276 (77.2)	-8.8 (-16.2 to -1.3)	0.89 (0.80 to 0.98)	
Type of brain injury					
Traumatic brain injury	138/236 (58.5)	161/239 (67.4)	-8.9 (-17.5 to -0.2)	0.87 (0.76 to 1.00)	
Subarachnoid hemorrhage	57/86 (66.3)	78/102 (76.5)	-10.2 (-23.1 to 2.8)	0.87 (0.72 to 1.04)	.98
Intracerebral hemorrhage	51/71 (71.8)	61/72 (84.7)	-12.9 (-26.3 to 0.5)	0.85 (0.71 to 1.01)	
Glasgow Coma Scale score at randomization					
3 to 5	134/186 (72.0)	147/193 (76.2)	-4.1 (-12.9 to 4.7)	0.95 (0.84 to 1.07)	
6 to 9	85/140 (60.7)	112/147 (76.2)	-15.5 (-26.1 to -4.9)	0.80 (0.68 to 0.94)	.12
10 to 13	27/67 (40.3)	41/73 (56.2)	-15.9 (-32.2 to 0.5)	0.72 (0.50 to 1.02)	
ICP monitoring within first 48 h					
No	60/114 (52.6)	83/126 (65.9)	-13.2 (-25.6 to -0.9)	0.80 (0.65 to 0.99)	.43
Yes	185/277 (66.8)	216/284 (76.1)	-9.3 (-16.7 to -1.8)	0.88 (0.79 to 0.98)	
Salvage therapies for elevated ICP					
No	191/318 (60.1)	235/328 (71.6)	-11.6 (-18.8 to -4.3)	0.84 (0.75 to 0.94)	.13
Yes	55/75 (73.3)	65/85 (76.5)	-3.1 (-16.6 to 10.3)	0.96 (0.80 to 1.15)	
SOFA score[a]					
<8	132/229 (57.6)	166/237 (70.0)	-12.4 (-21.1 to -3.7)	0.82 (0.72 to 0.95)	.29
≥8	111/160 (69.4)	131/172 (76.2)	-6.8 (-16.4 to 2.8)	0.91 (0.80 to 1.04)	



ICP indicates intracranial pressure and SOFA, Sequential Organ Failure Assessment. Neurological outcome 180 days after randomization was assessed using the Glasgow Outcome Scale Extended (GOS-E), which was dichotomized as unfavorable (GOS-E score of 1-5) or favorable (GOS-E score of 6-8); the scale ranges from 1 to 8, with death being included in the scale (GOS-E score of 1) and higher scores indicating better outcome. The size of each box is proportional to the size of the corresponding subgroup.

[a]The SOFA score is calculated from 6 baseline variables; scores range from 0 to 24, with higher scores indicating greater severity of disease.

Figure 4. Distribution of Glasgow Outcome Scale Extended (GOS-E) Scores 180 Days After Randomization (Secondary Outcome)



Each cell corresponds to a score on the scale; the width of each cell represents the percentage of patients with that score. The vertical dashed line indicates the GOS-E score used for dichotomization.

appropriate or the only trigger to guide transfusions in this context. Other studies have indicated that additional monitoring tools, such as positron emission tomography or noninvasive cerebral oxygenation measurements, may be valuable in assessing the impact of transfusion on brain hemodynamics or in optimizing the timing of transfusion in these patients.[27,28] In our trial, evaluation of cerebral infarction was not based on a protocolized assessment and relied on a decision by the attending physician to conduct brain imaging, potentially resulting in an underestimation of its occurrence and introducing significant detection bias. Additionally, the size of cerebral ischemic events, a critical factor influencing poor outcomes and long-term disability, was not objectively evaluated. As such, given these limitations, these results remain exploratory and should be interpreted with caution.

Our trial has several strengths, including concealed group assignment at randomization and blinding of outcome assessors to the assigned intervention. Recruitment of patients from various geographic regions enhances generalizability. The pragmatic trial protocol ensured that routine clinical practices were maintained, except for the specified hemoglobin thresholds for transfusion.

Limitations

This study has several limitations. First, the awareness of study group assignments by investigators and clinicians, coupled with an incomplete assessment of all concomitant interventions, could potentially introduce bias. However, the multicenter, large-scale nature of the trial and the use of stratified randomization make it less likely that imbalances in concomitant interventions would have significantly affected the overall results. Second, some patients may have received blood transfusions before randomization, which could have reduced the differences in hemoglobin values and transfusion exposure between the groups. Moreover, data on the administration of blood transfusions before randomization as well as the time between measurement of hemoglobin and transfusions were not collected. Nonetheless, there was a clear distinction between the groups in daily hemoglobin levels and numbers of transfusion, and the number of protocol violations was limited. Third, the inclusion of patients with different types of brain injury raises the possibility that there may be varied susceptibility to cerebral ischemia from anemia. However, the consistent results across different types of brain injury suggest that the study conclusions apply to acute traumatic and nontraumatic brain injuries. Fourth, the study may have had limited power to detect differences in some subgroup analyses. Fifth, achieving hemoglobin levels greater than 9 g/dL may not entirely prevent occurrence of secondary brain injury; however, this hypothesis was not assessed in this study. Sixth, no attempt was made to standardize neuroprognostication, which might introduce potential bias. However, the mortality rate, which is also influenced by decisions to withdraw life-sustaining therapies, was similar between groups. Additionally, establishing a blinded neuroprognostication process for various brain injuries across numerous centers would likely have been impractical. Seventh, there was no recommendation for screening of venous thromboembolic events, which may have led to an underestimation of their true incidence. Eighth, we observed a larger occurrence of unfavorable neurological outcome compared with other studies in patients with acute brain injury.[29,30] This finding could be attributed to the decision to include only patients with anemia and to dichotomize neurological outcomes using GOS-E score ranges of 1 to 5 and 6 to 8, whereas other trials used ranges of 1 to 4 and 5 to 8.[29] However, an analysis of the distribution of GOS-E scores indicated an overall improvement in neurological function, with a significant shift toward higher scores, reflecting better neurological function, in the liberal strategy group.

Conclusions

Patients with anemia and acute brain injury randomized to a liberal strategy of red blood cell transfusion at a hemoglobin threshold of 9 g/dL had a lower probability of unfavorable neurological outcome at 180 days than patients randomized to a restrictive strategy of transfusion at a hemoglobin threshold of 7 g/dL.

ARTICLE INFORMATION

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