Stroke

CLINICAL AND POPULATION SCIENCES

A Restrictive Versus a Liberal Transfusion Strategy in Patients With Spontaneous Intracerebral Hemorrhage: A Secondary Analysis of TRAIN Randomized Clinical Trial

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BACKGROUND: Red blood cell transfusions are commonly administered to anemic patients with spontaneous intracerebral hemorrhage (ICH); however, the optimal hemoglobin threshold to initiate transfusion is uncertain in this population. Therefore, we aimed to assess the impact of 2 different hemoglobin thresholds to guide transfusion on the neurological outcome of anemic critically ill patients with ICH.

METHODS: This is a secondary analysis of a prospective, multicenter, phase 3 randomized study conducted in 72 intensive care units across 22 countries from 2017 to 2022. Eligible patients for the original trial had an acute brain injury, hemoglobin values ≤9 g/dL within the first 10 days after admission, and an expected intensive care unit stay of at least 72 hours; in this study, only patients with spontaneous ICH were assessed. Patients were randomly assigned to undergo a restrictive (transfusion triggered by hemoglobin ≤7 g/dL) or a liberal (transfusion triggered by hemoglobin ≤9 g/dL) strategy over a 28-day period. The primary outcome was the occurrence of an unfavorable neurological outcome, defined as a Glasgow Outcome Scale Extended score of 1 to 5, at 180 days following randomization.

RESULTS: A total of 144 patients with spontaneous ICH were analyzed: 45.8% of them were men with a mean age of 58.4 (SD, 13.4). Mean Glasgow Coma Scale on admission was 7.3 (SD, 3.3), and 75.7% of patients had a volume of hematoma >30 mL. Among all patients, 73 were randomized to the restrictive transfusion strategy, while 71 to the liberal one. Baseline characteristics were comparable between the 2 groups. At 180 days after randomization, patients assigned to the liberal transfusion strategy had a nonsignificant decrease in the probability of unfavorable neurological outcome (71.8 versus 84.7%; risk ratio, 0.85 [95% CI, 0.71–1.01]; P=0.06). Also, the occurrence of the composite outcome (mortality and organ failure at day 28) was significantly lower in the liberal group (71.8% versus 87.7%, risk ratio, 0.82 [95% CI, 0.69–0.97]; P=0.02).

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CONCLUSIONS: A liberal transfusion strategy was associated with a lower risk of mortality and organ failure, but not of unfavorable outcome in patients presenting with spontaneous ICH, compared with a restrictive strategy. However, the study cohort might have been underpowered to detect clinically relevant differences between the 2 interventions.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: anemia ■ brain injury ■ disability ■ intracerebral hemorrhage ■ stroke ■ transfusion

Nonstandard Abbreviations and Acronyms

CONSORT	Consolidated Standards of Reporting Trials
GCS	Glasgow Coma Scale
GOS-E	Glasgow Coma Scale Extended
ICH	intracerebral hemorrhage
ICU	intensive care unit
RBCT	red blood cell transfusion
TRAIN	Transfusion Strategies in Acute Brain Injured Patients

Intracerebral hemorrhage (ICH) is a severe form of cerebrovascular injury, representing 10% to 20% of all strokes[1]; ICH is associated with high early mortality and limited potential for recovery or improvement in functional outcomes over time.[2,3] The incidence of spontaneous ICH is anticipated to rise due to the aging population and the increasing use of novel anticoagulants.[4] Various therapeutic approaches have been proposed to improve outcomes following ICH, including blood pressure reduction, reversal of anticoagulation, intraventricular fibrinolysis and minimally invasive surgery[5–8]; however, results from these interventions remain controversial, despite being effective in selected patients.

Secondary brain injuries prevention is a pivotal aspect of managing ICH. Whether early and aggressive management of the systemic variables (eg, glucose, sodium, or temperature)[9] might contribute to minimizing the progression of cerebral damage and improving functional outcomes remains unknown. Among these, anemia is a frequent medical complication following ICH, affecting 20% to 25% of patients.[10,11] Observational studies have reported a significant association between anemia, hematoma expansion, and poor outcomes.[10–15] Moreover, it has been suggested that red blood cell transfusion (RBCT) might improve 30-day mortality after spontaneous ICH.[16] Nevertheless, there is no consensus on the optimal hemoglobin threshold to guide transfusion in this context.

A recent large randomized controlled trial,[17] comparing a liberal and a restrictive transfusion strategy, demonstrated a significant reduction in the risk of unfavorable neurological outcomes in the liberal group in a mixed population of patients with acute brain injury. In addition, the liberal strategy group exhibited a lower risk of cerebral ischemic events. This secondary analysis aimed to determine whether these benefits were observed specifically in patients with spontaneous ICH.

METHODS

Data Sharing Statement

Data from the database can be shared according to specific requests, but depending on potential restrictions due to ethical decisions.

Study Design and Setting

This is a secondary analysis of the TRAIN study (Transfusion Strategies in Acute Brain Injured Patients),[17] which was a prospective, multicenter, phase 3, parallel-group, randomized, investigator-initiated, pragmatic, and open-label study conducted in 72 intensive care units (ICUs) across 22 countries.

Ethical approval was obtained from the appropriate committees at each participating hospital, including the Comité d'Éthique Erasme-ULB, which approved this multicenter study on March 14, 2016 (reference P2015/327). Patients were screened for eligibility following these approvals. Written informed consent was obtained from a legal surrogate before enrollment. In cases where patients regained mental capacity, deferred consent was subsequently sought whenever possible. The trial was designed under the guidance of the steering committee, while the management committee was responsible for monitoring the study, ensuring protocol adherence, and verifying the accuracy of collected data. The funding agencies had no role in the study's design, conduct, data analysis, or reporting, ensuring the research's independence and integrity. This study, like the original article, adhered to the CONSORT (Consolidated Standards of Reporting Trials) reporting guidelines.[18]

Trial Description

The TRAIN study enrolled adult patients (aged ≥18 years) admitted to the ICU with traumatic brain injury, subarachnoid hemorrhage, or ICH within the first 10 days following injury. For this secondary analysis, only patients with spontaneous ICH from the initial cohort were included. Eligibility criteria did not depend on the need for surgical intervention or RBCT due to acute bleeding before randomization, and such data were not collected. Patients were eligible for inclusion if they had a Glasgow Coma Scale (GCS) score of ≤13, an anticipated ICU stay of at least 3 days, and a hemoglobin level ≤9 g/dL

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(measured by a validated point-of-care test) within 10 days after the initial injury. Comprehensive inclusion and exclusion criteria have been published elsewhere.[17,19]

Eligible patients were randomly assigned in a 1:1 ratio to 1 of 2 transfusion strategies: a restrictive group (transfusion triggered at hemoglobin <7 g/dL) or a liberal group (transfusion triggered at hemoglobin <9 g/dL). Each patient could participate only once. Randomization was stratified by the type of brain injury, GCS at randomization (3–5 versus 6–9 versus 10–13), and study center. The assigned transfusion thresholds were maintained for up to 28 days post-randomization or until hospital discharge or death, whichever occurred first. When the hemoglobin level reached the specified threshold, patients received 1 unit of packed red blood cells. Hemoglobin levels were measured daily, either through routine laboratory testing or blood gas analyses during the ICU stay. Protocol violations included any transfusions administered outside the assigned thresholds or cross-matching errors. No restrictions were imposed on concurrent medical management or interventions. Decisions regarding the withdrawal of life-sustaining therapies were made by the attending physician according to local practices. While ICU and hospital staff were aware of treatment assignments due to routine hemoglobin monitoring, patients and their families remained blinded to the group allocations. Final neurological assessments were conducted by evaluators blinded to the treatment groups.

Data Collection

We collected patients baseline characteristics, such as age, sex, preexisting disease, and use of anticoagulant and antiplatelet agents. On admission to the ICU, we collected severity scores, such as Acute Physiology and Chronic Health Evaluation[20] and Sequential Organ Failure Assessment score,[21] GCS,[22] pupillary light reflex, presence of hydrocephalus, sodium, glucose, hemoglobin levels, and source of admission. During the ICU stay, we collected data on the need for mechanical ventilation, renal replacement therapy, intracranial pressure monitoring within 48 hours of admission, and need the for second-tier therapy to treat intracranial hypertension (eg, barbiturates, decompressive craniectomy, or hypothermia), as well as the use of antiepileptic medication. We also collected data on hematoma volume (eg, ≤30 or >30 mL), the presence of intraventricular hemorrhage, and location of the ICH.

Study Outcomes

The primary outcome was the occurrence of an unfavorable neurological outcome at 180 days after randomization. Neurological outcome was assessed through the Glasgow Outcome Scale Extended (GOS-E),[23] dichotomized as unfavorable (GOS-E score ranging between 1 and 5) and favorable (GOS-E score from 6 to 8). The secondary outcomes mirrored those of the main study and included: 28-day mortality; distribution of GOS-E in the restrictive and in the liberal group; ICU and hospital length of stay; incidence of organ failure, evaluated through daily assessment of Sequential Organ Failure Assessment score and composite outcome, defined as the 28-day occurrence of death and/or organ failure. We also evaluated the occurrence of serious adverse events during the 28 days after randomization, as defined in the original study (Table S1).

Outcome assessment was conducted, as reported in the TRAIN study,[17] either through telephone interviews or in-person follow-up appointments, using a structured interview.

Statistical Analysis

Data were analyzed according to both the intention-to-treat and the per-protocol principles. Continuous variables are presented as medians and quartiles and were analyzed using the Wilcoxon rank-sum test. Categorical variables were analyzed using the Fisher exact test or χ^2 test. Primary outcome comparisons were assessed using a χ^2 analysis and reported as the relative risk and absolute risk reduction of an unfavorable neurological outcome, along with the corresponding 95% CI. We also performed a multivariate logistic regression analysis to study the association of a liberal transfusion strategy with neurological outcome at 6 months, adjusted for clinically relevant confounders to correct for the imbalance of variables between the favorable and unfavorable neurological outcome group ($P<0.005$). Collinearity and interaction among variables were tested during modeling. Subgroup exploratory analyses according to age, GCS at randomization, Sequential Organ Failure Assessment score, ICH volume, presence of intraventricular hemorrhage, presence of hydrocephalus, intracranial pressure monitoring within 48 hours from admission, intracranial hypertension salvage therapies, and sepsis were also performed for the primary outcome. For repeated daily measurements (eg, hemoglobin values), a generalized mixed model was used to compare the differences between groups and over time. All secondary outcomes were analyzed using independent-sample Mann-Whitney *U* tests and χ^2 tests, as appropriate. A Kaplan-Meier curve analysis was performed to assess time to death at 28 days. All secondary outcomes were analyzed using independent-sample *t* tests and χ^2 tests, as appropriate, without additional adjustments. We also performed a sensitivity analysis.

All analyses were conducted by an independent statistician using IBM SPSS Statistics version 29.0 (IBM Corp, Armonk, NY). No imputation was performed for missing outcome data. A $P<0.05$ was considered statistically significant. Notably, the sample size calculation was aimed at detecting differences in the primary outcome across the entire cohort; no independent-sample size calculation was conducted to specifically power the preplanned analysis of patients with ICH.

RESULTS

Study Population

From a total of 850 patients randomized to the original trial, 144 (16.9%) presented with spontaneous ICH and were analyzed for this study; 71 patients were randomized to the liberal and 73 patients to the restrictive transfusion strategy group. Baseline characteristics and clinical profiles were comparable between the 2 groups (Table 1). Mean age was 58.4 (±13.4) with a prevalence of female patients (54.2%). The majority of patients presented with a hematoma >30 mL (n=109, 75.7%), with the concomitant presence of intraventricular hemorrhage in 83 (57.6%) patients and hydrocephalus in 64 (44.4%) patients. Deep ICH localization was the most represented (n=88, 61.1%).

Table 1. Characteristics of the Study Population on Admission, at Randomization and Interventions During the ICU Stay

Characteristic	All patients (N=144)	Liberal (n=71)	Restrictive (n=73)
Age, y; mean (SD)	58.4 (13.4)	59.5 (12.9)	57.2 (13.8)
Male, n (%)	66 (45.8)	33 (46.5)	33 (45.2)
Days from admission to randomization, median (IQR)	4 (2–7)	3 (2–7)	4 (2–7)
Medical history			
Chronic obstructive pulmonary disease, n (%)	13 (9)	8 (11.3)	5 (6.8)
Cancer, n (%)	13 (9)	2 (2.8)	2 (2.7)
Metastatic cancer, n (%)	4 (2.8)	1 (1.4)	0
Hematologic cancer, n (%)	1 (0.7)	1 (1.4)	1 (1.4)
Diabetes, n (%)	16 (11.1)	7 (9.9)	9 (12.3)
Chronic heart failure, n (%)	8 (5.6)	4 (5.6)	4 (5.5)
Liver cirrhosis, n (%)	2 (1.4)	0	2 (2.7)
Chronic steroid therapy, n (%)	4 (2.8)	3 (4.2)	1 (1.4)
HIV, n (%)	10 (6.9)	0	10 (13.7)
Immunosuppressive therapy, n (%)	6 (4.2)	3 (4.2)	3 (4.1)
Characteristics of brain injury			
Source of admission*			
ER/ambulance, n (%)	78 (54.9)	45 (64.3)	33 (45.8)
OR/recovery, n (%)	8 (5.6)	4 (5.7)	4 (5.6)
Hospital floor, n (%)	4 (2.8)	3 (4.3)	1 (1.4)
Other hospital, n (%)	51 (35.9)	17 (24.3)	34 (47.2)
Others, n (%)	1 (0.7)	1 (1.4)	0 (0)
Initial GCS, mean (SD)	8.4 (3.6)	8.7 (3.6)	8.2 (3.7)
Initial m-GCS, mean (SD)	4.2 (1.8)	4.4 (1.7)	4.0 (1.9)
GCS on admission, mean (SD)	7.3 (3.3)	7.4 (3.2)	7.1 (3.4)
m-GCS on admission, mean (SD)	3.8 (1.9)	4.0 (1.9)	3.7 (1.9)
Pupillary reactivity			
Both reacting, n (%)	110 (76.4)	54 (76.1)	56 (76.7)
One reacting, n (%)	17 (11.8)	7 (9.9)	10 (13.7)
None reacting, n (%)	17 (11.8)	10 (14.1)	7 (9.6)
Sodium on admission, mmol/L; mean (SD)†	138 (4.5)	139 (4.1)	138 (4.9)
Glucose on admission, mg/dL; mean (SD)†	170 (52.2)	168 (51.9)	172 (52.8)
Hemoglobin on admission, g/dL; median (IQR)	11.9 (10.2–12.9)	11.8 (10.0–13.0)	11.9 (10.3–12.9)
APACHE II score on admission, mean (SD)‡	19 (7.9)	18.0 (7.4)	19.9 (8.4)
ICP monitoring within 48 h from admission, n (%)	94 (65.3)	44 (62.0)	50 (68.5)
SOFA score on admission, mean (SD)*	6.7 (2.9)	6.7 (3.4)	6.6 (2.4)
Antiplatelet therapy before injury, n (%)	46 (31.9)	23 (32.4)	23 (31.5)
Anticoagulant therapy before injury, n (%)	18 (12.5)	12 (16.9)	6 (8.2)
ICH characteristics			
Volume of hematoma >30 mL, n (%)	109 (75.7)	54 (76.1)	55 (75.3)
Localization of ICH, n (%)			
Deep	88 (61.1)	45 (63.4)	43 (58.9)
Cortical	41 (28.5)	20 (28.2)	21 (28.8)
Infratentorial	15 (10.4)	6 (8.5)	9 (12.3)
Intraventricular hemorrhage on admission, n (%)	83 (57.6)	39 (54.9)	44 (60.3)
Hydrocephalus on admission, n (%)	64 (44.4)	29 (40.8)	35 (47.9)
At randomization			
GCS, mean (SD)	6.8 (2.7)	6.9 (2.6)	6.8 (2.7)

(*Continued*)

Table 1. Continued

Characteristic	All patients (N=144)	Liberal (n=71)	Restrictive (n=73)
m-GCS, mean (SD)	3.7 (1.7)	3.7 (1.7)	3.6 (1.8)
Hemoglobin, g/dL; mean (SD)	8.4 (0.6)	8.4 (0.6)	8.4 (0.6)
During the ICU stay			
Nadir hemoglobin, g/dL; median (IQR)	7.9 (7.1 to 8.5)	8.5 (8 to 8.6)	7.2 (6.8 to 7.8)
Cumulative fluid balance, mL; median (IQR)	721 (−5488 to 6601)	−194 (−456.8 to 28.54)	−36.19 (−136.1 to 267.3)
Mechanical ventilation, n (%)	132 (91.7)	65 (91.5)	67 (91.8)
Renal replacement therapy, n (%)	18 (12.5)	6 (8.5)	12 (16.4)
Second-tier therapies for ICP, n (%)	31 (21.5)	14 (19.7)	17 (23.3)
Antiepileptic therapy, n (%)	20 (13.9)	7 (9.9)	13 (17.8)

Data are reported as count (%), mean (SD) or median (25th; 75th percentiles). APACHE indicates Acute Physiologic Assessment and Chronic Health Evaluation; ER, emergency room; GCS, Glasgow Coma Scale; HIV, human immunodeficiency virus; ICH, intracranial hemorrhage; ICP, intracranial pressure; IQR, interquartile range; m-GCS, motor component of GCS; OR, operative room; SOFA, Sequential Organ Failure Assessment; and TBI, traumatic brain injury.

*n=142.

†n=141.

‡n=128.

Intracerebral hemorrhage characteristics (such as volume, localization, presence of intraventricular hemorrhage, and hydrocephalus on admission) were also similar in the 2 groups; no difference was found in the use of antiplatelet and anticoagulant therapies at randomization.

Hemoglobin and Transfusion Practices

The median time from ICU admission to randomization was 3 (2–7) days in the liberal group and 4 (2–7) days in the restrictive group. The mean hemoglobin concentration at randomization was 8.4 (±0.6) g/dL in both groups. Following randomization, there was a significant difference in the lowest daily hemoglobin over time ($P<0.001$; Table 1) and daily lowest hemoglobin concentrations between the groups ($P<0.001$; Figure 1).

A total of 151 blood transfusions were administered in the liberal group, compared with the 54 in the restrictive group ($P<0.001$); 63 patients in the liberal group (88.7%) required transfusion administration during the 28-day trial, compared with 31 patients in the restrictive group (42.4%; $P<0.001$). The liberal group received a median of 2 (1–3) units of blood transfusions, while the restrictive group received a median of 0 (0–1) units of blood transfusions ($P<0.001$). Protocol violation was observed in 5 (7.0%) patients in the liberal group and 1 (1.4%) in the restrictive group.

Primary Outcome

The primary outcome was available in 143 (99.3%) patients, 71 in the liberal and 72 in the restrictive group. At 180 days following randomization, 51 of 71 (71.8%) patients in the liberal group and 61 of 72 (84.7%) in the restrictive group had an unfavorable neurological outcome (risk ratio, 0.85 [95% CI, 0.71–1.01]; $P=0.06$;

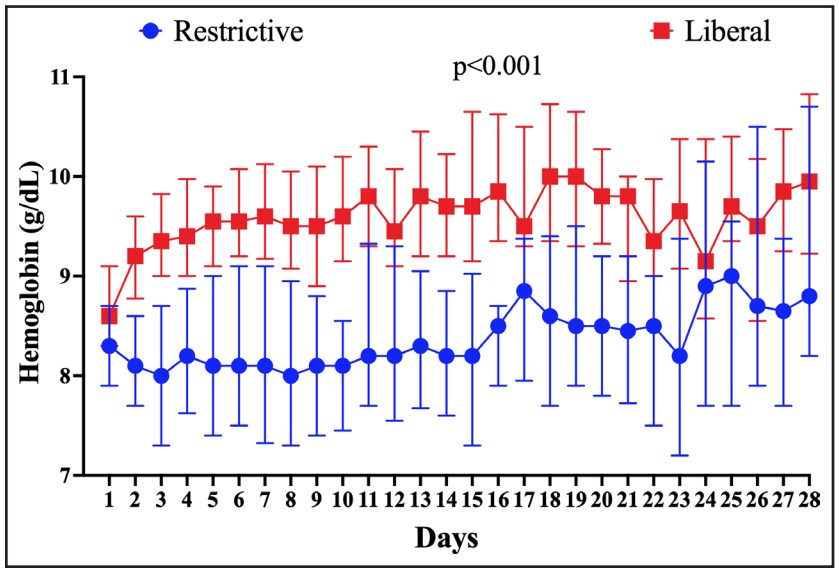

Figure 1. Median daily lowest hemoglobin concentration at baseline and after randomization in the 2 groups.
Baseline values were the last blood hemoglobin level measured before randomization. Day 1 was defined as the day after randomization. Bars indicate the 25th and 75th percentiles.

absolute risk difference: −12.9; [95% CI, −26.3 to 0.47]; Table 2). The median extended Glasgow Outcome Scale at 180 days was 3 (1–6) in the liberal group, while in the restrictive group it was 4 (1–5).

In a multivariate analysis, adjusted for hematoma volume >30 mL, presence of hydrocephalus on admission, and GCS on admission, being randomized to a liberal transfusion strategy (odds ratio, 2.31 [95% CI, 0.89–5.99]; *P*=0.082) was not significantly associated with the primary outcome (Table S2). Importantly, the lowest hemoglobin during ICU stay was similar in patients with favorable (8.1 g/dL [interquartile range, 7.45–8.5]) and unfavorable outcome (7.8 g/dL [interquartile range, 7.1–8.5]).

Per-protocol analysis showed similar results: 47 of 66 (71.2%) patients in the liberal group and 60 of 71 (84.5%) in the restrictive group had an unfavorable neurological outcome at 180 days (risk ratio, 0.84 [95% CI, 0.70–1.00]; *P*=0.06; Table S3).

In an exploratory post hoc analysis including patients with GCS 6 to 13 at randomization, 34 of 52 (65.4%) patients in the liberal group and 40 of 47 (85.1%) in the restrictive group had an unfavorable neurological outcome (risk ratio, 0.77 [95% CI, 0.61–0.97]; *P*=0.02; absolute risk difference: −19.72 [95% CI, −36.18 to −3.27]; Table S4).

There were no differences in the primary outcome between the liberal and restrictive group in all the others subgroup exploratory analyses (Table S5).

Secondary Outcomes

No difference was found in 28-day mortality nor in prevalence of organ failure between the liberal and the restrictive groups. ICU and hospital lengths of stay were also similar between the 2 groups. At 28 days after randomization, 51 of 71 (71.8%) patients in the liberal group met the criteria of the composite outcome compared with 64 of 73 (87.7%) patients in the restrictive group (risk ratio, 0.82 [95% CI, 0.69–0.97]; *P*=0.02; Table 2). The distribution analysis of GOS-E showed no significant shift between the liberal and the restrictive groups (odds ratio, 1.37 [95% CI, 0.73–2.37]; *P*=0.37; Figure 2).

The 28-day median cumulative fluid balance was statistically similar between the 2 groups: −194 mL (interquartile range, −456.8 to 28.54) in the liberal group and −36.19 mL (interquartile range, −136.1 to 267.3) in the restrictive group (*P*=0.1; Table 1). In addition, daily fluid balance followed a comparable pattern over time in both groups (Figure S1).

Table 2. Study Outcomes and Main Adverse Events

Outcome	Liberal (n=71)	Restrictive (n=73)	Risk ratio (95% CI)	Absolute risk reduction (95% CI)	*P* value
Primary outcome					
Unfavorable neurological outcome at 180 d, n (%)	51/71 (71.8)	61/72 (84.7)	0.85 (0.71–1.01)	−12.89 (−26.25 to 0.47)	0.06
Secondary outcomes					
28-day mortality, n (%)	18/71 (25.4)	18/72 (25)	1.01 (0.58–1.78)	0.35 (−14.58 to 13.88)	0.96
ICU length of stay, d; mean (SD)	21.0 (16.9)	21.6 (14.1)	…	−0.60 (−5.68 to 4.48)	0.33
Hospital length of stay, d; mean (SD)	48.2 (46.2)	39.9 (33.1)	…	8.30 (−4.80 to 21.40)	0.61
Composite outcome, n (%)	51/71 (71.8)	64/73 (87.7)	0.82 (0.69–0.97)	−15.84 (−28.74 to −2.94)	0.02
Serious adverse events					
Severe hypotension	6/71 (8.5)	9/73 (12.3)	0.69 (0.26–1.83)		0.45
Severe hypertension	4/71 (5.6)	7/73 (9.6)	0.59 (0.18–1.92)		0.38
Venous thromboembolism	4/71 (5.6)	5/73 (6.9)	0.82 (0.23–2.94)		0.77
Acute myocardial infarction	…	…	…		…
Cerebral ischemia	2/71 (2.8)	2/73 (2.7)	1.03 (0.15–7.10)		0.98
Intestinal ischemia	1/71 (1.4)	2/73 (2.7)	0.51 (0.05–5.54)		0.58
Acute peripheral limb ischemia	…	…	…		…
Anaphylaxis	…	…	…		…
ARDS	7/71 (9.9)	9/73 (12.3)	0.80 (0.32–2.03)		0.64
TRALI	…	…	…		…
TACO	…	…	…		…
Sepsis	7/71 (9.9)	17/73 (23.3)	0.42 (0.19–0.96)		0.03
Multiple organ failure	7/71 (9.9)	13/73 (17.8)	0.55 (0.24–1.31)		0.17

ARDS indicates acute respiratory distress syndrome; ICU, intensive care unit; TACO, transfusion-associated cardiovascular overload; and TRALI, transfusion-associated acute lung injury.

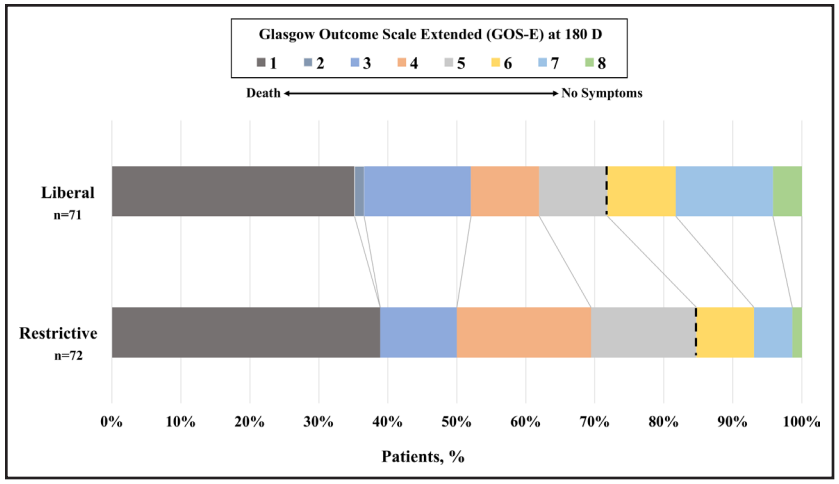

Figure 2. Distribution of Glasgow Outcome Scale Extended (GOS-E) scores at 180 days after randomization in the restrictive and liberal group.
Each cell corresponds to a score on the scale; the width of each cell represents the proportion of patients with equivalent scores. The vertical dashed line indicates the GOS-E score used for dichotomization.

Adverse Events

In the liberal group, 7 of 71 (9.9%) patients developed sepsis over the study period, compared with 17 of 73 (23.3%) patients in the restrictive group (risk ratio, 0.42 [95% CI, 0.19–0.96]; *P*=0.003). In a multivariate analysis adjusted for the occurrence of sepsis, being allocated to the liberal transfusion strategy (odds ratio, 2.31 [95% CI, 0.88–6.09]) was not independently associated with unfavorable outcome at 180 days (Table S6). No differences were found in other prespecified adverse events (Table 2).

DISCUSSION

In this secondary analysis of the TRAIN trial focusing on patients with spontaneous ICH, we found no statistically significant reduction in the risk of unfavorable neurological outcomes at 180 days for patients randomized to a liberal transfusion strategy compared with those assigned to a restrictive transfusion strategy. Patients in the liberal transfusion group exhibited a lower risk of the composite outcome. Furthermore, among patients with significant organ dysfunction at admission, those randomized to the liberal strategy demonstrated a reduced risk of unfavorable outcomes compared with those in the restrictive group.

Anemia has been reported frequently after spontaneous ICH[10,11] and is recognized as a contributor to secondary brain injury, by reducing arterial oxygen content and altering brain metabolism.[24–27] Specifically, anemia has been linked to a higher risk of brain hypoxia, impaired cerebral autoregulation, increased expression of inflammatory mediators, and disruptions in cellular energy metabolism,[10,24] all of which may negatively affect patient outcomes. Three meta-analyses[10,28,29] have highlighted that anemic patients with stroke have significantly higher mortality and an increased risk of poor neurological outcome compared with nonanemic patients. However, these meta-analyses included only a limited number of studies and exhibited significant heterogeneity in defining anemia (eg, hemoglobin thresholds ranging from 10 to 14 g/dL), assessing neurological outcome and determining follow-up duration. Notably, both Li et al[28] and Barlas et al[10] included patients with both ischemic and hemorrhagic stroke, which may have a different susceptibility to anemia, potentially leading to confounding of overall findings.

Interestingly, 2 observational studies[14,30] included in the meta-analyses evaluated the impact of nadir hemoglobin levels on outcome. Diedler et al[14] demonstrated that both lower admission hemoglobin and nadir hemoglobin values were associated with poor outcome at discharge, defined as a modified Rankin Scale score of 5 to 6. Similarly, Chang et al[30] found that nadir hemoglobin was independently associated with poorer functional outcome (eg, modified Rankin Scale, 5–6) at discharge and longer hospital length of stay. Conversely, in our study, the nadir hemoglobin value was statistically similar in patients with favorable and unfavorable outcome.

A prospective cohort study on spontaneous ICH[11] found that anemia, as defined by the World Health Organization criteria,[31] was associated with larger hematoma volume and higher 30-day mortality rate. Taken together, these findings suggest that anemia may exacerbate secondary brain injury and worsen outcomes in patients with ICH.

Evidence regarding the relationship between RBCT and neurological outcome in ICH is limited, primarily consisting of observational studies. Roh et al[12] reported that RBCT was associated with poor outcomes, including both in-hospital mortality and rate of discharge at home. Conversely, other observational studies[16,32] suggested improved outcomes in transfused patients with ICH, including reduced mortality and better neurological scores at discharge. It is crucial to emphasize that patients receiving RBCT often have greater medical comorbidities and higher illness severity compared with those not requiring transfusions. This, confounding by indication likely influences the observed outcomes in these studies.

In this study, we reported that a liberal transfusion strategy in patients with ICH was safe, as both groups exhibited a similar incidence of most adverse events. Notably, the incidence of transfusion-associated circulatory overload and transfusion-related acute lung injury was comparable between groups, which may be attributed to an overall restrictive approach to fluid administration. Conversely, the incidence of sepsis was higher in the restrictive group, potentially due to a higher prevalence of HIV-positive patients in this cohort. Moreover, infection and subsequent sepsis are a common complication following ICH.[33,34] Importantly, sepsis is an important mechanism of secondary brain injury, which may have impacted our results.[35]

The latest guidelines for the management of spontaneous ICH[36] did not provide specific recommendations regarding the hemoglobin threshold for initiating RBCT. This lack of guidance highlights the limited evidence available on the impact of anemia and RBCT in ICH patients, especially when compared with other forms of acute brain injury. For traumatic brain injury patients, the HEMOTION trial[37] evaluated the effect of liberal (transfusion trigger at hemoglobin <10 g/dL) versus restrictive (transfusion trigger at hemoglobin <7 g/dL) transfusion strategies on neurological outcomes; this study found a nonsignificant difference in the risk of unfavorable neurological outcomes between the 2 strategies (eg, 6% lower in the liberal group). In patients with subarachnoid hemorrhage, several retrospective studies have demonstrated an association between anemia and worse neurological outcomes.[38,39] A recent meta-analysis[40] further confirmed that anemia, even when mild, was independently associated with poor outcomes, both at discharge and during follow-up. To address these gaps in evidence in this population, the recently published SAHARA trial (Subarachnoid Hemorrhage Red Cell Transfusion Strategies and Outcome)[41] investigated the impact on neurological outcome at 12 months of a liberal versus restrictive transfusion strategy, using the same definition of anemia as the HEMOTION trial (Hemoglobin Transfusion Threshold in Traumatic Brain Injury Optimization)[37]: this study showed no significant reduction of unfavorable neurological outcome at 12 months, with a nonsignificant difference in the risk between the 2 strategies (eg, 4% lower in the liberal group).

As a secondary analysis of the TRAIN trial, this study inherits several limitations from the original study. Notably, the trial was unblinded due to the nature of the intervention, transfusions before randomization were not accounted for, and there was no standardization in neuro-prognostication practices; however, outcome assessors were blinded for group allocation. Importantly, we have no data reporting if the patients were managed medically andr if they underwent hematoma drainage and decompressive craniectomy, which could have significantly influenced neurological recovery and survival. In addition, this analysis faces challenges inherent to its design. With only 144 spontaneous patients with ICH included out of 850 participants, this study lacked sufficient statistical power to detect meaningful effects. This limited sample size increases the margin of error and the risk of unreliable findings, particularly when considering the potential for multiple hypothesis testing. As such, all secondary analyses should be considered as exploratory and hypothesis-generating.

Despite these limitations, this secondary analysis provides valuable insights. Given that the existing body of research on ICH is largely limited to observational studies, the findings from this robust randomized trial offer a foundation for future research to build on and guide clinical practice.

CONCLUSIONS

In this study, patients with spontaneous ICH randomized to a liberal transfusion strategy with a hemoglobin threshold of 9 g/dL demonstrated a nonsignificant reduction in the rate of unfavorable neurological outcomes at 180 days compared with those assigned to a restrictive strategy with a hemoglobin threshold of 7 g/dL. The study may have been underpowered to detect statistically significant differences in this population. Further high-quality, randomized clinical trials are needed to provide definitive evidence and clear guidance on optimal transfusion thresholds for patients with ICH.

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Disclosures

None.

Supplemental Material

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