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Liberal versus restrictive transfusion strategies in subarachnoid hemorrhage: a secondary analysis of the TRAIN study

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Abstract

Background The optimal hemoglobin (Hb) threshold to trigger red blood cell transfusions (RBCT) in subarachnoid hemorrhage (SAH) patients is unclear. This study evaluated the impact of liberal versus restrictive transfusion strategies on neurological outcome in patients with SAH.

Methods This is a pre-planned secondary analysis of the "TRansfusion Strategies in Acute brain INjured Patients" (TRAIN) study. We included all SAH patients from the original study that were randomized to receive RBCT when Hb levels dropped below 9 g/dL (liberal group) or 7 g/dL (restrictive group). The primary outcome was an unfavorable neurological outcome at 180 days, defined by a Glasgow Outcome Scale Extended score of 1–5.

Results Of the 190 SAH patients in the trial, 188 (98.9%) had data available for the primary outcome, with 86 (45.3%) in the liberal group and 102 (53.6%) in the restrictive group. Patients in the liberal group were older than in the restrictive group, but otherwise had similar baseline characteristics. Patients in the liberal group received more RBCT and showed higher Hb levels over time. At 180 days, 57 (66.3%) patients in the liberal group and 78 (76.4%) in the restrictive group had unfavorable outcomes (risk ratio, RR 0.87; 95% confidence intervals, 95% CI 0.71–1.04). Patients in the liberal group had a significantly lower risk of cerebral ischemia (RR 0.63; 95% CI 0.41–0.97). In a multivariate analysis, randomization to the liberal group was associated with a lower risk of unfavorable outcome (RR 0.83, 95% CI 0.70–0.99).

Conclusions A liberal transfusion strategy was not associated with a lower incidence of unfavorable outcome after SAH when compared to a restrictive strategy. However, in a multivariable analysis adjusted for confounders randomization to the liberal group was associated with lower risk of unfavorable outcome. The occurrence of cerebral ischemia was significantly lower in the liberal transfusion strategy group.

Trial registration ClinicalTrials.gov number—NCT02968654 registered on November 16th, 2016.

Keywords Stroke, Blood, Acute brain injury, Anemia

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Introduction

Spontaneous aneurysmal subarachnoid hemorrhage (SAH) accounts for about 5% of all acute cerebrovascular events and has a substantial impact on patients' morbidity and mortality [1]. SAH is often associated with anemia (40–50%), the cause of which is multifactorial [2–5]. Importantly, anemia may cause secondary brain injury through cerebral hypoxia, by reducing arterial oxygen content and cerebral oxygen delivery (DO_2) [6], thus potentially worsening outcome.

In healthy brain, isovolemic anemia can be compensated by an increased CBF, resulting from increased cardiac output [7], cerebral vasodilation and enhanced microcirculatory perfusion [6], and/or high oxygen extraction [8]; however, when Hb falls below 5 g/dL, these compensatory mechanisms are exhausted and brain tissue hypoxia may occur [6, 9]. Patients with SAH often experience hemodynamic instability and acute heart failure, which may compromise the compensatory increase in cardiac output [10]. Additionally, the cerebrovascular reserve may be decreased by impaired autoregulation, limiting vasodilation in case of arterial hypotension [11]. Moreover, local cerebral perfusion often become compromised when cerebral vasospasm and delayed cerebral ischemia occur [12]. Thus, clinically significant brain hypoxia may potentially occur at higher Hb concentrations, e.g. around 8–9 g/dL [13], with a large variability depending on the severity of SAH and the baseline functional status. Patients with low brain tissue oxygenation associated with anemia have an increased risk of cerebral ischemia and unfavorable neurological outcome [14, 15]. Thus**,** anemia has been shown to be an independent risk factor for poor outcome after SAH [5, 16–18].

However, the benefits of red blood cell transfusion (RBCT) on brain oxygenation has not been consistently demonstrated in all patients [19]. Additionally, it has been postulated that RBCT may increase the risk of delayed cerebral ischemia by increasing blood viscosity [17]. In the past, hemodilution was used to decrease blood viscosity to improve microcirculatory perfusion during vasospasm [20]; however, by decreasing hematocrit there was also a decrease in microcirculatory oxygen content which decreased oxygen delivery to areas already at risk of ischemia [21, 22] leading to the discontinuation of this strategy.

Moreover, the impact of RBCT on outcome remains unclear: some studies reported an association between RBCT and poor prognosis [5, 17, 23], while others did not [24]. One small randomized trial evaluated very high Hb thresholds (e.g. 10 g/dL vs. 11.5 g/dL) to initiate RBCT in SAH patients found no significant difference in the functional outcome of patients [25]; however, these thresholds do not reflect current practice. More recently, the TRansfusion Strategies in Acute Brain INjured Patients (TRAIN) trial [26] randomized anemic (i.e., Hb below 9 g/dL) patients with acute brain injury caused by trauma or spontaneous intracranial hemorrhage to receive RBCT when Hb was below 7 g/dL (restrictive group) or 9 g/dL (liberal group). This study showed a decreased risk of unfavorable neurological outcome at 180 days in patients randomized to the liberal compared to the restrictive group. Conversely, a randomized trial involving 742 patients with SAH found no significant difference in the incidence of unfavorable neurological outcomes between a liberal (e.g. initiating RBCT at Hb < 10 g/dL) and a restrictive transfusion strategy (e.g. initiating RBCT at Hb < 8 g/dL) [27].

In this secondary analysis of the TRAIN trial, we focused on the impact of these two transfusion strategies on the neurological outcome in the subgroup of patients with SAH included in the trial.

Methods

Study design

This is a secondary analysis of the TRAIN trial [26], a prospective, multi-center, phase 3, parallel-group, randomized, investigator-initiated, pragmatic, open-label, outcome-assessor blinded study conducted in 72 ICUs across 22 countries (NCT02968654). After obtaining approvals from ethics committees in each hospital (the "Comite d'Ethique Erasme-ULB" approved this multicentric study on the 14th of March 2016-P2015/327), patients were screened for eligibility. Written informed consent was obtained from a legal surrogate before enrollment. Whenever possible, deferred consent was also obtained from the patients who regained mental capacity. 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. Funding agencies were not involved in the protocol design, the execution of the trial, or the analysis and reporting of the data. This study adhered to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines [28].

Trial description

The TRAIN study included all adult patients (aged 18 years or older) admitted to the ICU with traumatic brain injury (TBI), SAH or intracerebral hemorrhage (ICH), who were screened for eligibility within the first 10 days following injury. In the present study, we analyzed only non-traumatic SAH patients enrolled in the TRAIN study. Importantly, in the original TRAIN study there was no predefined number of patients with

each pathology to be included; no separate sample size calculation to power the pre-planned analysis of SAH patients was performed.

Eligibility was not dependent on the need for surgical intervention or RBCT due to acute bleeding before randomization (these data were not collected). Patients with a Glasgow Coma Scale (GCS) score of 13 or lower, an anticipated ICU stay of at least three days and a Hb level of 9 g/dL or lower (e.g. measured using a valid point-of-care test) within ten days after the initial injury were eligible for inclusion. Detailed inclusion and exclusion criteria have been published elsewhere [26, 29]. After screening for eligibility, patients were randomly allocated in a 1:1 ratio to one of two strategies: a restrictive group, where transfusions were given when Hb levels dropped below 7 g/dL, or a liberal group, where transfusions were administered at levels below 9 g/dL. Each patient could be included in the study only once.

Stratification factors for randomization included the type of brain injury (TBI, SAH, or ICH), the GCS at randomization (3–5 vs. 6–9 vs. 10–13) and the center. The assigned RBCT thresholds were upheld for up to 28 days after randomization or until hospital discharge or death, whichever occurred first. After randomization, patients received one unit of packed red blood cells when their Hb level reached the designated threshold. Hb levels were measured daily in accordance with local practices, with values determined by blood gas analyses during the ICU stay also accepted. Any administration of a blood transfusion that did not adhere to the assigned threshold, or any cross-matching error, was considered a protocol violation. There were no additional restrictions on concurrent care or interventions. Decisions regarding the discontinuation of life-sustaining therapy were made by the attending physician based on local practice. While ICU and hospital staff were informed of the treatment assignments due to routine Hb monitoring, patients and their families remained unaware of the group allocations. Final neurological assessments were conducted by evaluators who were blinded to the treatment groups.

Data collection

We collected patients baseline characteristics, such as age, sex and pre-existing disease and use of anticoagulants and antiplatelets agents. On admission to the ICU, we collected severity scores, such as Acute Physiology And Chronic Health Evaluation (APACHE II) [30] and Sequential Organ Failure Assessment (SOFA) [31] score, GCS, World Federation of Neurosurgical Societies (WFNS) score, Fisher scale, pupillary light reflex, presence of hydrocephalus, sodium, glucose, Hb and source of admission. During ICU stay, we collected the need for mechanical ventilation, renal replacement therapy, intra-cranial pressure monitoring (ICP) monitoring within 48 h of admission and need for second tier therapy to treat intracranial hypertension (e.g. barbiturates, decompressive craniectomy or hypothermia) as well as the use of antiepileptic medication.

The development of cerebral vasospasm, of delayed ischemic neurology deficit (DIND) and delayed cerebral ischemia (DCI), as well as the date and the methods of their diagnosis was noted. Vasospasm was defined as a mean flow velocity in any vessel > 200 cm/s or > 120 cm/s and a Lindegaard ratio > 3 assessed by transcranial Doppler or the presence of a moderate-to-severe arterial narrowing (> 50%) on digital subtraction angiography or CT angiography not attributable to atherosclerosis, catheter-induced spasm, or vessel hypoplasia. Definition of DIND was based on the development of new focal neurological signs, deterioration in the level of consciousness, or both, when the cause is felt to be ischemia attributable to vasospasm after other possible causes of worsening (e.g., hydrocephalus, seizures, metabolic derangement, infection, or excessive sedation) have been excluded [32]; lastly, DCI was defined as the appearance of DIND and/or a new infarction on cerebral CT scan or magnetic resonance imaging (MRI), when the cause was attributed to vasospasm [32].

The use of induced hypertension with vasopressor, cardiac output augmentation with inotropes, intra-arterial administration of vasodilators and balloon angioplasty to treat one of these complications was also reported.

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) [33], which was dichotomized as "unfavorable" (GOS-E 1–5: death to lower moderate disability) or "favorable" (GOS-E 6–8: upper moderate disability to upper good recovery). The GOS-E assessment was recorded in a structured telephone or face-to-face interview with the patient or relatives by a healthcare professional, who was unaware of the intervention assignments.

Secondary outcome measures included 28-day mortality, ICU and hospital length of stay and the composite outcome of 28-day mortality and/or organ failure over the ICU stay [29]. Serious adverse events were reported as in the original study and included cerebral ischemia which was defined as a new ischemic lesion visible after randomization on brain imaging (either CT-scan or MRI) until 28 days, discharge or death

compared to the initial brain imaging performed on admission, regardless of the cause and including ischemia as a consequence of early brain injury, treatment of the aneurysm and/or delayed cerebral ischemia. Ischemic lesions previous to randomization were not considered as new ischemia. Cerebral ischemia was assessed by local radiologist part of the healthcare team who were blinded to which group patients were randomized.

Statistical analysis

Data were analyzed according to the intention-to-treat principle. Statistical analyses were conducted using the latest version of SPSS for Windows (29.0—Chicago, USA) and GraphPad from Prism (Version 10; Boston, USA). Normally distributed continuous variables were reported as mean and standard deviation and compared using t-Student test. Nonparametric continuous variables were reported as medians and 1st and 3rd quartiles and were analyzed using the Mann–Whitney for test independent samples. Categorical variables were analyzed using the Fisher exact test or chi square test. For repeated daily measurements (e.g. Hb values), a mixed model using time as a categorical variable was used to compare the differences between groups and over time. Primary outcome comparisons were assessed using a chi-square analysis and reported as risk ratio (RR) and the corresponding 95% confidence interval (CI). Ordinal logistic regression was used to compare the distributions of the 180-days GOS-E scores between the two groups and the resulting odds ratio (OR) and 95% confidence intervals (CI) were reported. Wald test and Likelihood ratio were used to confirm non- violation of proportional odds assumptions. All secondary outcomes were analyzed through independent sample Mann Whitney and chi-square tests, as appropriate, in a univariate analysis. Unadjusted risk ratios and their respective 95% confidence intervals were reported for secondary outcomes including cerebral ischemia. A Kaplan Meier analysis was performed to assess time to death at 28 days. We performed a multivariable analysis using a log-binomial regression to assess the association between transfusion strategy (liberal vs. restrictive) and neurological outcome at 180 days, adjusted for known variables associated with outcome in SAH patients and to account for imbalance in patients' characteristics; results were reported as RR and 95% CI. A *per protocol* analysis excluding patients with protocol violations was also performed. Subgroup exploratory analyses were conducted based on the original TRAIN study subgroups [26]; 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); SOFA score at randomization (< 8 vs. ≥ 8). Additional exploratory analyses based on clinically relevant complications following SAH, such as cerebral vasospasm, DIND and DCI (all occurring after randomization and during the ICU stay) were performed. Importantly, the sample size calculation aimed to detect a difference in poor functional outcome across the entire group of acutely brain-injured patients; no separate sample size calculation to power the pre-planned analysis of SAH patients was performed. A post hoc power analysis was conducted based on the results of the primary outcome analysis from this study.

Results

Study population

Of a total of 850 patients randomized in the trial, the 190 patients with SAH are included in the present analysis, with 188 having data available for the primary outcome. Among those, 86 (45.2%) were randomized to the liberal and 104 (54.7%) to the restrictive group. Patients were significantly older in the liberal than in the restrictive group (60 [± 10] years vs. 57 [± 12] years, $p = 0.03$); all other baseline characteristics were similar between groups (Table 1). Poor clinical grade on admission (e.g. WFNS 4 or 5) was observed in 65 (75.6%) patients of the liberal group and 72 (69.2%) of the restrictive group ($p = 0.42$); high Fisher scores (e.g. 3 or 4) were observed in 82 (95.3%) patients of the liberal group and in 94 (90.4%) of the restrictive group ($p = 0.27$).

Cerebral vasospasm occurred in 34/85 (40.0%) patients of the liberal and 42/101 (41.6%) of the restrictive group ($p = 0.88$); of those, 20/34 (58.8%) and 21/42 (50.0%) occurred after randomization ($p = 0.44$), respectively. DIND were reported in 25/85 (29.4%) patients of the liberal and in 41/101 (40.6%) of the restrictive group ($p = 0.13$); of those, 14/25 (56.0%) and 12/41 (29.3%) occurred after randomization ($p = 0.03$), respectively. Delayed cerebral ischemia was observed in 20/85 (23.5%) patients of the liberal and in 32/101 (31.7%) of the restrictive group ($p = 0.24$); of those, 17/20 (85.0%) and 22/32 (68.8%) occurred after randomization ($p = 0.19$), respectively.

Hemoglobin and transfusion

At randomization, the mean Hb levels were similar in both groups (liberal 8.6 [8.3–8.8] g/dL vs. restrictive 8.5 [8.3–8.8] g/dL; $p = 0.81$). The median time to randomization was 4 (3–7) days in both groups ($p = 0.79$). The liberal group received a median of 2 (1–3) units of RBCT, while the restrictive group a median of 0 (0–1) units of RBCT. Daily median minimum Hb values differed significantly between groups over time ($p < 0.001$ for the time and group, Fig. 1). A total of 79 patients (91.9%) in the liberal group and 49 (47.1%) in

Table 1 Characteristics of the SAH study population on admission, at randomization and interventions during the ICU stay

Characteristic	Liberal (n = 86)	Restrictive (n = 104)	*p* value
Age – years mean (SD)	60 (± 10)	57 (± 12)	0.03
Male – no. (%)	15 (17.4)	16 (15.4)	0.84
Days from admission to randomization – median (IQR)	4 (3–7)	4 (3–7)	0.79
Medical history			
Chronic obstructive pulmonary disease—no. (%)	6 (7.0)	2 (1.9)	0.14
Cancer—no. (%)	2 (2.3)	6 (5.8)	0.24
Metastatic cancer – no. (%)	0	0	–
Hematological cancer – no. (%)	1 (1.2)	1 (0.9)	0.99
Diabetes – no. (%)	5 (5.8)	4 (3.8)	0.73
Chronic heart failure – no. (%)	0	2 (1.9)	0.50
Liver cirrhosis – no (%)	1 (1.2)	1 (0.9)	0.99
Chronic steroid therapy—no (%)	3 (3.5)	0	0.09
HIV—no (%)	1 (1.2)	1 (0.9)	0.99
Immunosuppressive therapy—no (%)	2 (2.3)	2 (1.9)	0.99
Antiplatelets therapy—no (%)	9 (10.5)	8 (7.7)	0.99
Anticoagulant therapy—no (%)	3 (3.5)	4 (3.8)	0.99
On admission			
Source of admission			0.63
ER/ambulance – no. (%)	44 (51.2)	53 (50.9)	
OR/recovery – no. (%)	3 (3.5)	4 (3.8)	
Hospital floor – no. (%)	1 (1.2)	4 (3.8)	
Other hospital – no. (%)	37 (43.0)	39 (37.5)	
Others – no. (%)	1 (1.2)	2 (1.9)	
Missing – no (%)	0	2 (1.9)	
Initial GCS—median (IQR)	8 (3–12)	7 (4–13)	0.38
Initial m-GCS—median (IQR)	5 (1–6)	5 (2–6)	0.63
GCS on admission—median (IQR)	7 (3–11)	7 (3–11)	0.70
m-GCS on admission—median (IQR)	4 (1–5)	4 (1–6)	0.95
WFNS 4/5 – no (%)	65 (75.6)	72 (69.2)	0.42
Fisher score 3/4 – no (%)	95 (10.5)	94 (90.4)	0.27
Pupillary reactivity			0.09
Both reacting – no. (%)	68 (79.1)	90 (86.5)	
One reacting – no. (%)	8 (9.3)	10 (9.6)	
None reacting – no. (%)	10 (11.6)	4 (3.8)	
Sodium on admission, mmol/L – median (IQR)	139 (137–142), n = 86	140 (137–143), n = 101	0.26
Glucose on admission, mg/dL—median (IQR)	166 (144–200), n = 86	152 (125–188), n = 101	0.006
Hemoglobin on admission, g/dL – median (IQR)	12.2 (10.8–13.2)	12.0 (11.0–13.0)	0.65
APACHE II score on admission – median (IQR)	18 (15–23), n = 80	18 (14–24), n = 95	0.73
ICP monitoring within 48 h from admission – no. (%)	64/86 (74.4)	76/101 (75.2)	0.99
SOFA score on admission – median (IQR)	6 (4–8), n = 86	6 (4–8), n = 102	0.87
Hydrocephalus—n (%)	50/86 (58.1)	65/101 (64.4)	0.45
At Randomization			
GCS—median (IQR)	7 (3–9)	6 (3–9)	0.95
m-GCS—median (IQR)	4 (1–5)	4 (1–5)	0.85
Hemoglobin, g/dL—median (IQR)	8.6 (8.3–8.8)	8.5 (8.3–8.8)	0.81
During the ICU stay			
Mechanical ventilation – no. (%)	78 (90.7)	94 (90.4)	0.99

Table 1 (continued)

Characteristic	Liberal (n = 86)	Restrictive (n = 104)	*p* value
Renal replacement therapy – no. (%)	8 (9.3)	9 (8.7)	0.99
Salvage therapies for elevated ICP – no. (%)	25 (29.1)	29 (27.9)	0.87
Antiepileptic therapy – no. (%)	6 (7.0)	12 (11.5)	0.33
Neurological Complications and treatments			
Vasospasm– no. (%)	34/85 (40.0)	42/101 (41.6)	0.88
DIND – no. (%)	25/85 (29.4)	41/101 (40.6)	0.13
Induced hypertension – no. (%)	24/25 (96.0)	36/41 (87.8)	0.26
Inotropes – no. (%)	17/25 (68.0)	24/41 (58.5)	0.44
Intra-arterial vasodilators – no. (%)	15/25 (60.0)	18/41 (43.9)	0.20
Ballon angioplasty – no. (%)	3/25 (12.0)	6/41 (14.6)	0.76
DCI – no. (%)	20/85 (23.5)	32/101 (31.7)	0.25
Transfusion			
Patients that received RBCT – no (%)	79 (91.9)	49 (47.1)	< 0.001
Number of RBCT per patients – median (IQR)	2 (1–3)	0 (0–1)	< 0.001

Categorical data are presented as count and percentages; continuous data are presented as mean (standard deviation) or median (Interquartile range 25%-75%). The restrictive group had a hemoglobin threshold of 7 g per deciliter or less for transfusion, while the liberal group had a hemoglobin threshold of 9 g per deciliter or less for transfusion

HIV, human immunodeficiency virus; TBI, traumatic brain injury; SAH, subarachnoid hemorrhage; ICH, intracranial hemorrhage; ER, emergency room; OR, operative room; GCS, Glasgow Coma Scale; m-GCS, motor component of GCS; ICP, intracranial pressure; APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; IQR, interquartile range 25–75%

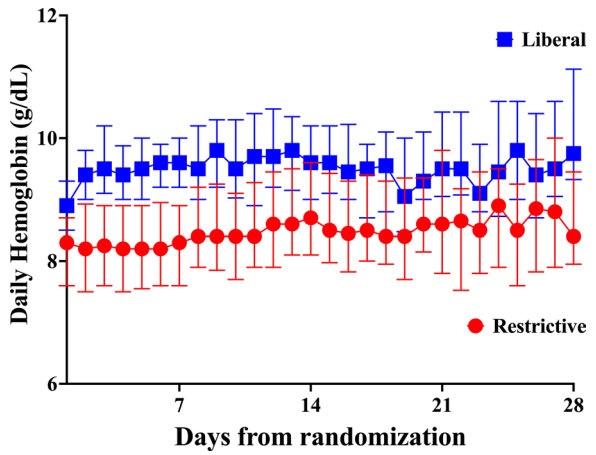

Fig. 1 Median daily lowest hemoglobin concentration at baseline and after randomization in the two groups. Baseline values were the last blood hemoglobin level measured before randomization. Day 1 was defined as the day after randomization. Bars indicate the 25th and 75th percentiles

the restrictive group received at least one RBCT during the study period ($p < 0.001$). There were 23 protocol violations, 16 in the liberal group and 7 in the restrictive group ($p = 0.03$). In the liberal group, 8 (9.3%) patients were transfused although Hb concentration was greater than 9 g/dL and 8 (9.3%) patients were not transfused although the hemoglobin level was below the threshold. In the restrictive group, 5 (4.8%) patients were transfused although Hb concentration was greater than 7 g/dL and 2 (1.9%) patients were not transfused although the hemoglobin level was below the threshold.

Study outcomes

Neurological outcome at 6 months was available for 86 (100.0%) patients in the liberal group and 102 (98.1%) patients in the restrictive group. Importantly, at 180 days after randomization, 57 out of 86 (66.2%) in the liberal group experienced an unfavorable neurological outcome, compared to 78 out of 102 (76.5%) patients in the restrictive group (RR = 0.87; 95% CI 0.71 − 1.04; absolute risk reduction = 10.3%; 95 CI 2.8% to 23.1%; number of patients to treat = 10—Table 2). The median GOS-E score was 4 (1–5) in the liberal group and 4 (1–6) in the restrictive group ($p = 0.95$—Table 2). The distribution of GOS-E scores between the groups was not statistically significant (OR 1.25 95%, CI 0.74 to 2.10, $p = 0.41$—Fig. 2). In a log-binomial regression model adjusted for age, presence of cerebral infarction, WFNS score and need for salvage therapies for elevated ICP, patients randomized to the liberal group had a lower probability of unfavorable outcome at 180 days (RR 0.83, 95% CI 0.70–0.99; Supplemental Table S1). The effect of the transfusion thresholds on neurological outcome at 180 days was consistent across most of prespecified subgroups (Supplemental Table S2, Supplemental Figure S1).

Table 2 Study outcomes and main adverse events

Outcome	Liberal (n = 86)	Restrictive (n = 104)	Risk ratio (95%CI)	Absolute risk reduction (%) (95%CI)	NNT (95% CI)	*p*- value
Primary outcome						
Unfavorable neurological outcome at 180 days—n (%)	57/86 (66.2)	78/102 (76.5)	0.87 (0.71 – 1.04)	10.19 (– 2.75 to 23.14)	9.8 (4.3 to infinity)	0.14
Secondary outcomes						
28-day mortality—n (%)	22/86 (25.6)	25/102 (24.5)	1.04 (0.63—1.69)	1.07 (– 11.37 to 13.51)	93.3 (7.4 to infinity)	0.87
ICU length of stay, days – median (IQR)	23 (15–32)	20 (13–30)	–	–		0.47
Hospital length of stay, days – median (IQR)	39 (21–60)	36 (18–61)	–	–		0.71
Composite outcome – n (%)	23/86 (26.7)	25/102 (24.5)	1.09 (0.67–1.75)	2.23 (– 10.30 to 14.77)	44.8 (6.8 to infinity)	0.74
Serious adverse events						
Patients with adverse events – no (%)	33 (38.4)	40 (38.5)	0.99 (0.69–1.43)	0.09 (– 11.82 to 13.98)	1118.0 (7.2 to infinity)	0.99
Severe hypertension	4 (4.7)	3 (2.9)	1.61 (0.37–7.01)	1.77 (– 3.73 to 7.26)	56.6 (13.8 to infinity)	0.70
Severe hypotension	13 (15.1)	9 (8.7)	1.75 (0.79–3.88)	6.49 (– 2.84 to 15.76)	15.5 (6.3 to infinity)	0.18
Venous thromboembolism	2 (2.3)	5 (4.8)	0.48 (0.10–2.44)	2.48 (– 2.72 to 7.68)	40.3 (13.0 to infinity)	0.46
Acute myocardial infarction	0	0	–	–	–	–
Cerebral ischemia	22 (25.6)	42 (40.4)	0.63 (0.41–0.97)	14.80 (3.6 to 62.0)	6.8 (3.6 to 62.0)	0.05
Intestinal ischemia	1 (1.2)	2 (1.9)	0.61 (0.06–6.67)	0.76 (– 2.72 to 4.24)	131.5 (23.6 to infinity)	0.99
Acute peripheral limb ischemia	0	1 (1.0)	0.98 (0.97–1.01)	0.96 (– 1.81 to 3.73)	104 (26.8 to infinity)	0.99
Anaphylaxis	0	0	–	–	–	–
ARDS	3 (3.5)	5 (4.8)	0.72 (0.20–2.94)	1.32 (– 4.33 to 6.97)	75.8 (14.3 to infinity)	0.73
TRALI	0	0	–	–	–	–
TACO	1 (1.2)	0	1.01 (0.99–1.03)	1.16 (– 1.87 to 4.20)	86 (23.8 to infinity)	0.45
Sepsis	7 (8.1)	11 (10.6)	0.77 (0.32–1.89)	2.44 (– 5.83 to 10.70)	41 (9.3 to infinity)	0.63
Multiple organ failure	6 (7.0)	7 (6.7)	1.03 (0.56–2.94)	0.25 (– 6.98 to 7.47))	406.5 (13.4 to infinity)	0.99
Infection	24 (27.9)	33 (31.7)	0.88 (0.57–1.37)	3.8 (– 9.21 to 16.86)	26.2 (5.9 to infinity)	0.63
Number of adverse events per patients – median (IRQ)	0 (0–2)	0 (0–2)	–	–	–	0.84

The restrictive group had a hemoglobin threshold of 7 g per deciliter or less for transfusion, the liberal group had a hemoglobin threshold of 9 g per deciliter or less for transfusion. Neurological outcome was assessed by GOSE (unfavorable outcome defined as GOSE 1–5). Categorical data are presented as count and percentages; continuous data are presented median (Interquartile range 25–75%).ICU, intensive care unit; ARDS, acute respiratory distress syndrome; TRALI, transfusion-associated acute lung injury; TACO, transfusion-associated cardiovascular overload. ARDS, acute respiratory distress syndrome; IQR, interquartile range; NNT, number needed to treat

The 28-days mortality rates were similar in both groups, with 22 (25.6%) deaths in the liberal group and 25 (24.5%) in the restrictive group (RR = 1.04, 95% CI 0.63–1.69, $p = 0.87$—Table 2 and Fig. 3). The median ICU and hospital length of stay was similar between groups.

Notably, 22 (25.6%) patients in the liberal group and 42 (40.7%) patients in the restrictive group experienced cerebral ischemia due to any cause after randomization (RR = 0.63 95% CI 0.41–0.97). There were no differences on occurrence of the other serious adverse events between groups (Table 2).

Per protocol analysis

After the exclusion of the 23 patients who had protocol violations, the primary outcome was available in 70 patients of the liberal group and in 96 patients of the restrictive group. Patients randomized to the liberal group had a non-significant lower risk of unfavorable neurological outcome at 180 days compared to patients randomized to the restrictive group (RR 0.84, 95% CI 0.68–1.04; Supplemental Table S3). Patients in the liberal group had a lower risk of cerebral ischemia compared to the restrictive group.

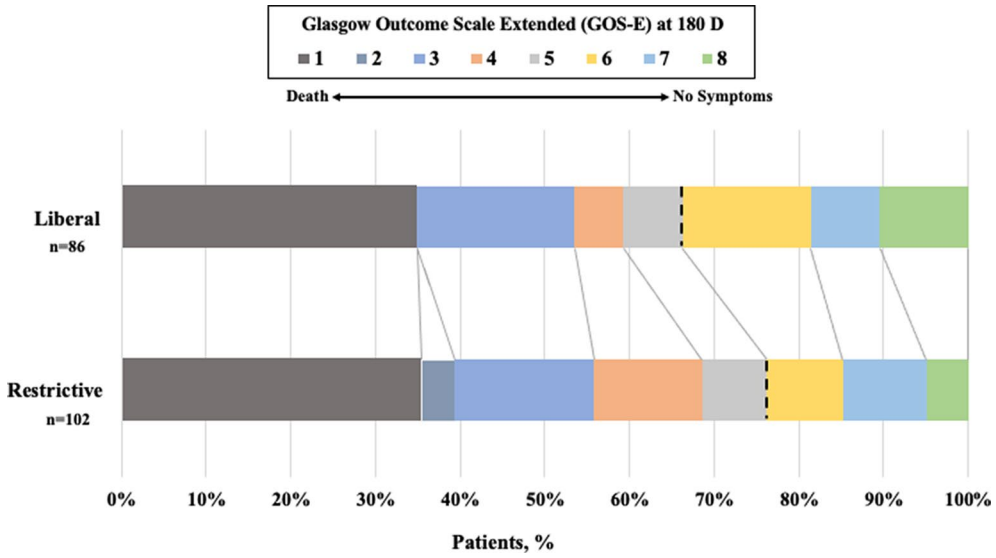

Fig. 2 Distribution of Glasgow Outcome Scale–Extended scores at 180 days after randomization in the restrictive and liberal group. Each cell corresponds to a score on the scale; the width of each cell represents the proportion of patients with equivalent scores. The vertical dashed line indicates the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

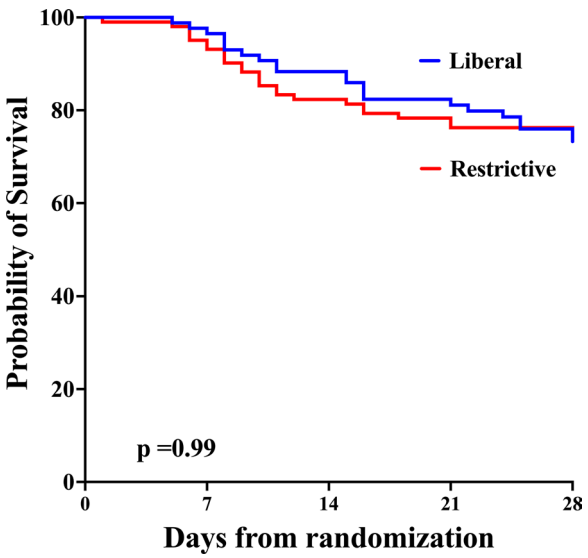

Fig. 3 Time to Death. This figure shows the survival curves, with data censored at 28 days, in the two groups in the intention-to-treat population. Kaplan–Meier analysis showed that the survival time did not differ significantly between the two groups (log-rank $P = 0.99$ by Mantel-Cox analysis)

Discussion

In this secondary analysis of the TRAIN study, we observed no significant difference in the occurrence of long-term unfavorable neurological outcome—neither as a dichotomic variable nor as an ordinal variable—between a liberal and restrictive transfusion strategy. However, there was an absolute difference of 10% in favor of the liberal group, which might suggest the study cohort was underpowered to adequately respond to the main research question. Additionally, in a multivariate log-binomial regression, the randomization to the liberal strategy was associated with a lower risk of unfavorable outcome compared to patients in the restrictive group. Importantly, patients in the liberal group also had a lower occurrence of cerebral ischemia due to any cause, which reinforces anemia as an important cause of secondary brain injury.

The impact of RBCT on the outcome of SAH patients has been previously investigated in small, mostly observational studies showing conflicting results. Some studies have shown a negative impact on patient outcomes [14, 17, 23, 34–37] and an increased risk of medical complications [38] after SAH, possibly reflecting the severity of illness in these patients. Conversely, some studies found that maintaining a higher Hb after SAH was associated with lower likelihood of mortality, disability and DCI [24, 39–41]. DCI occurs in about 30% of patients [12], and is a major cause of disability in SAH patients. It is characterized by reduced CBF and therefore oxygen delivery to the brain. Treatment strategies usually aim to restore CBF in affected brain regions, with fluid administration, induced hypertension, and possibly increased cardiac output [42]. Additionally, transfusions represent another possible strategy. Indeed, Dhar et al. [43] compared induced hypertension, fluid bolus and RBCT in SAH patients with an Hb < 9.0 g/dL and found that RBCT produced the highest increase in cerebral DO_2, assessed by positive emission tomography

scan. In our study, the occurrence of DCI was statistically similar between the two groups; however, we found a lower incidence of cerebral ischemia due to any cause, which included DCI, but also early brain injury and the perioperative period, in patients transfused liberally compared to others. This finding suggests that transfusion may play a critical role in reducing the risk of ischemia during the early phase. Notably, research has increasingly focused on secondary brain injuries, such as anemia, that occur within the first 72 h following SAH, a period referred to as "early brain injury" [44]. Further studies are warranted to assess the impact of various transfusion strategies during this critical time window after aneurysm rupture.

Additionally, in SAH patients, anemia may be associated with brain tissue hypoxia and metabolic dysfunction [45]. Indeed, acute brain injury patients with anemia and low brain tissue oxygenation have an increased higher risk of cerebral ischemia [14] and unfavorable neurological outcomes [15]. RBCT may increase brain oxygenation ($PbtO_2$): Kurtz et al. found a consistent increase in $PbtO_2$ at 2 and 4 h after RBCT, which may last up to 10 h in some patients [46]. Another study found that while in 78% of patients there was an increase of $PbtO_2$ at 3 h post transfusion, only in half of those patients this increase was sustained for 24 h [47]. Interestingly, a retrospective study [19] conducted in anemic patients with acute brain injury found that lower baseline $PbtO_2$ was independently associated with a significant improvement in brain oxygenation after RBCT. The study also suggested that RBCT might fail to increase $PbtO_2$ if the underlying cause of tissue hypoxia is not reduced arterial oxygen content but rather low CBF or increased brain metabolism. In this context, integrating other physiological data with Hb thresholds might help individualize therapy and merits to be investigated in further studies.

The recent HEMOTION trial including 742 TBI patients found no significant differences in 6-month neurological outcome between patients randomized to liberal transfusion strategy (RBCT for $Hb \leq 10$ g/dL) and those randomized to a restrictive one (RBCT for $Hb \leq 7$ g/dL); however, functional independence and quality of life were improved in the liberal group with a 6% absolute reduction in the occurrence of unfavorable neurological outcome [48]. Importantly, these results in TBI patients cannot be easily translated to SAH patients, as the risk factors for secondary brain injury and cerebral ischemia may differ between the two pathologies [49]. The recently published multicenter randomized SAHARA trial [27] found no significant difference in the primary outcome, e.g. unfavorable neurological outcome, defined as a modified Rankin Scale (mRS) score of 4–6, between liberal and restrictive transfusion strategies. However, in the liberal group, a non-significant but clinically relevant 6% reduction in patients with mRS scores of 3–6 was observed, a threshold commonly used in interventional trials for ischemic stroke. In the SAHARA trial, the mean Hb levels in the restrictive group were approximately 9 g/dL, potentially reducing the risk of brain hypoxia compared to the lower 7 g/dL threshold used in restrictive group of the TRAIN study [26]. Furthermore, as reaching an Hb threshold of 10 g/dL would occur easier than lower thresholds, SAH patients in the SAHARA trial required less frequently mechanical ventilation, had lower clinical severity at admission and lower 6-month mortality than in our cohort, suggesting a lower disease severity. To achieve a power of 85% at a 2-sided $\alpha = 0.05$ to detect a decrease in poor neurological outcome from 76 to 66% (an absolute reduction of 10), a total of 736 (e.g. 368 in each group) SAH patients would have been required.

Notably, the occurrence of serious adverse events previously described as related to RBCT, such as increased risk of infection [37], vasospasm [33, 36, 50] and thromboembolic events [50], were similar in both groups in our study and in SAHARA trial [27], reinforcing the safety of targeting a liberal Hb threshold, which may provide beneficial effects on the injured brain, by reducing the incidence of cerebral ischemia by any cause, an important mechanism of secondary brain injury as shown in this analysis. Presently, SAH guidelines do not provide recommendations regarding ideal transfusion thresholds [51–53]; the results of the TRAIN [26] and SAHARA [27] studies should be pooled in a meta-analysis to provide robust evidence to update current guidelines.

Our study has strengths. The multicentric data collection approach in the original study reduced biases from local practices and improved the generalizability and applicability of the results across different centers and geographic regions. Also, the pragmatic trial design makes it easier for clinicians to translate the results to clinical practices.

This study has also several limitations. First, there is a potential bias caused by imbalances in the characteristics of patients in the two groups, as the original study was not designed specifically for SAH patients. Second, there is a potential for bias due to the awareness of group assignments by investigators, clinicians, and patients, as well as the incomplete assessment of all concomitant interventions. Third, some patients might have received RBCT before randomization potentially obscuring differences in hemoglobin levels and RBCT exposure between groups. Fourth, in the original TITAN study patients were eligible for inclusion up to 10 days after

injury, which can be considered a broad time window to account for different anemia etiologies and may have impacted our results as patients could have been included during early brain injury and delayed brain injury phases. Fifth, the occurrence of protocol violations may also have impacted our results; however, the per protocol analysis yielded similar results than in the entire cohort. Sixth, we did not assess the impact of different non-traumatic SAH etiologies (aneurysmal vs. non-aneurysmal) on our results, as this data was not available. Finally, definitions used to describe vasospasm, DIND and DCI may not be generalizable. For instance, we did not use the gold standard—digital subtraction angiography- to define vasospasm, but rather easily available tools such as transcranial doppler and CTA to allow all centers form low-income and high-income countries to report this data. Similarly, treatment strategies to address these complications may have varied in the study centers, which may have impacted our results.

Finally, future studies should focus on identifying which patients may benefit from a liberal transfusion threshold, including a holistic approach that integrates patients' characteristics, the phase of the disease (early brain injury vs. delayed brain injury) and physiological data, including assessment of brain hemodynamics, oxygenation and metabolism.

Conclusions

In this secondary analysis of a large, randomized trial, in anemic patients with SAH who were randomized to a restrictive or liberal RBCT strategy, a multivariable analysis indicated that being randomized to the liberal group was independently associated with higher rates of favorable outcome. Interestingly, patients that had a liberal transfusion strategy exhibited a lower incidence of cerebral ischemia of any cause.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05270-5.

Supplementary Material 1.

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Author contributions
All the authors provided substantial contributions to conception or design of the work, or the acquisition, analysis, or interpretation of data. EGB, CT and FST drafted the initial version of the manuscript, which has been critically revised by all other authors for important intellectual content. All authors have approved the final version of the submitted manuscript. All the authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. All other relevant data is presented in the manuscript and in the supplementary electronic material.

Declarations

Ethics approval and consent to participate
This is a secondary analysis of the TRAIN study. The TRAIN study was approved by the ethics committees in each hospital. The primary ethics committee, "Comite d'Ethique Erasme-ULB", approved this multicentric study on the 14th of March 2016 (P2015/327). Written informed consent was obtained from a legal surrogate before enrollment. Whenever possible, deferred consent was also obtained from the patients who regained mental capacity.

Consent for publication
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Competing interests
Jean Louis Vincent is editor in chief of critical care. No other authors have reported competing interests.

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