

Liberal or Restrictive Transfusion Strategy in Patients with Traumatic Brain Injury

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Abstract:

Background: The comparison between a restrictive and a liberal transfusion strategy in terms of the outcomes for critically ill patients with traumatic brain injury remains ambiguous. **Patients and Methods:** This randomized clinical trial included 500 adults with moderate to severe traumatic brain injury and anemia. Participants were assigned to receive red blood cell transfusions relied on either a liberal strategy (initiating transfusions at a hemoglobin level of ≤ 10 g/dL) or a restrictive strategy (initiating transfusions at ≤ 7 g/dL). **Results:** In both groups, the median GCS motor score was 4 (1-5) with most cases demonstrating 5 (localization) in both groups followed by 1 (no movement), then 6 (Obedience to commands). The worst-prognosis group (GOS-E score ≤ 3) was the most prevalent between groups; the Restrictive group had a notably higher unfavorable outcome rate (81.8% vs. 75.9%). At 6 months, mortality was 26.8% in the liberal strategy group and 26.4% in the restrictive strategy group, with insignificant differences across the two groups. QOL assessments reveal that the Liberal treatment strategy scores greater across EuroQol, EQ-5D-5L, and Qolibri scales, with more patients experiencing moderate to severe depression in the Restrictive group. Liberal group received significantly more red-cell units than Restrictive.

Conclusions: A liberal transfusion approach did not lower the risk of negative neurological outcomes for six months for critically ill individuals with anaemia and traumatic brain injury.

Keywords: Traumatic Brain Injury, Anemia, Transfusion Strategy, Liberal strategy

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Received:

Accepted:

Introduction

Critical illness, anemia, is one in which the patient's hemoglobin level is so low that endogenous erythropoietin does not produce enough red blood cells to compensate for red blood cells loss. Given the frequent occurrence of anemia in the Intensive Care Unit (ICU), a comprehensive assessment and review of available treatment alternatives is essential ⁽¹⁾.

The damaged brain may signify an organ that is more susceptible to reduced oxygen detrimental effects delivery. Observational studies have investigated individuals with closed-head injuries and shown a correlation between death and worse neurological outcomes and instances of hypotension or hypoxemia ⁽²⁾.

The Advanced Trauma Life Support guidelines advise administering 2 liters of crystalloid fluid to unstable trauma patients, followed by the transfusion of blood products. This resuscitation method is predicated on the assumption that restoring tissue perfusion would reduce subsequent damage and mortality ⁽³⁾.

Studies evaluating red-cell transfusion techniques in critically sick patients showed no mortality advantage in sustaining elevated hemoglobin levels ⁽⁴⁾. Nonetheless, these investigations encompassed a limited number of those suffering from neurological impairments and concentrated on mortality; hence, they provide inadequate direction for managing those with traumatic brain injury, for whom long-term neurological function is the paramount result ⁽⁵⁾.

Clinical recommendations and studies contrasting liberal transfusion procedures with restricted transfusion strategies highlight that existing data are inadequate to inform transfusion practices in traumatic brain injury patients ^(6,7).

With the objective for comparing the impact of liberal versus restrictive transfusion strategies in critically ill adult patients with moderate-to-severe TBI, a randomized trial was carried out.

We suggested that a liberal approach would provide superior results compared to a restricted one.

Patients and Methods:

This randomized clinical trial study encompassed 500 critically ill adult patients of both sexes who were 18 years of age or older and had moderate-to-severe TBIs with a Glasgow Coma Scale [GCS] score of 3 to 12 and Hb level ≤ 10 g/dL who were admitted to trauma hospitals with specialized neurocritical care.

The study was carried out after acquiring approval from our institute's Ethical **Committee** (RC23-10-2024) from December 2022 to October 2024 at Benha University Hospitals. The patients' authorized representatives provided written informed consent.

Patients were not permitted to participate in the study if they had transfusions after ICU admission but before randomization, as well as those with contraindications or objections to transfusion.

Randomization

Patients were equally randomized into 1:1 using opaque sealed envelopes into 2 groups; group 1: received red-cell transfusions in accordance with a liberal strategy (triggered by a haemoglobin level of ≤ 10 g/dL), whereas group 2 received red-cell transfusions in accordance with a restrictive strategy (triggered by a haemoglobin level of ≤ 7 g/dL).

Procedures

The TBI-IMPACT prognostic model, which has been verified for patients with below 13 reflecting reduced levels of consciousness), was utilized for estimating results for all subjects. This

model considers factors such as age, GCS motor score, pupil reactivity, hypoxemia and hypotension status, CT injury classification, presence of traumatic subarachnoid hemorrhage or epidural hematoma, and blood glucose and hemoglobin levels upon admission.

A GCS score of nine to twelve was considered to indicate moderate traumatic brain injury. The most recent GCS score obtained in the emergency room (or before intubation if the patient was intubated upon arrival) is used for evaluation. The sum of the verbal, eye-opening, and motor components makes up the overall GCS score. Injury severity was also classified depending on the Marshall CT scan grading, based on head scans taken within 24 hours post-injury. Normal findings are represented by grade I, diffuse injury by grade II, radiologic signs of elevated intracranial pressure by grades III and IV, and lesions requiring surgical evacuation or a mass lesion larger than 25 ml by grades V and VI, respectively. The most serious CT results were utilized to categorize.

As a score of ≤ 4 on goes, indicating a full return to normal life), at 6 months estimated utilization.

The transfusion thresholds were estimated relied on existing evidence, expert opinion, and clinical equipoise, and were aligned with those deemed acceptable by clinicians in an international survey ⁽⁸⁾. The liberal threshold was chosen because keeping hemoglobin levels above 10 g/dL could potentially enhance brain oxygenation ⁽⁹⁾. On the other hand, the restrictive threshold aligns with the standard care for critically ill patients ⁽⁴⁾.

Patients got one unit of leukoreduced red blood cells at a time upon reaching the designated hemoglobin level. Supplementary units were

administered when hemoglobin levels, assessed during normal treatment, reached the designated threshold. In both therapy groups, the goal was to administer red blood cell transfusions within three hours of reaching the threshold. Patient care was otherwise entrusted to the medical team's discretion.

Outcomes

The primary outcome was categorized as unfavorable (yes or no) at 6 m, determined by the Glasgow Outcome Scale–Extended (GOS-E) ⁽¹⁰⁾. The GOS-E is an ordinal scale that spans (optimal, signifying complete daily activities). Intermediate scores correspond to a vegetative state (minimal responsiveness), as well as varying levels of severe disability (requiring full or partial assistance) and moderate disability (independence with limited or no ability to engage in prior activities, respectively), and lower good recovery (minor deficits impacting daily living). An unfavorable outcome was delineated utilizing a sliding dichotomy of the GOS-E based on each patient's baseline prognosis; patients were classified into one of three risk categories (worst, intermediate, or best) and deemed to have a poor outcome if their GOS-E score at six months is 3, 4, 5, or less.

At 6 months, secondary outcomes comprised mortality and scores on the Functional Motor and cognitive function is estimated utilizing the Independence Measure (FIM; range: 18 to 126) ⁽¹¹⁾; health-related quality of life is evaluated utilizing the EuroQol the (range: –0.59 to 1) ⁽¹²⁾; the Quality of Life after Brain Injury (Qolibri) scale (range: 1 to 100) ⁽¹³⁾; and depression is determined utilizing the range: 27) ⁽¹⁴⁾. Whereas greater PHQ-9 scores indicate more severe depressive symptoms, higher and scale indicate improved wellness.

The assessment also included mortality rates in the ICU and the hospital. The tertiary outcomes were the quantity of red blood cell units transfused in the ICU, the minimum daily hemoglobin level, incidence of infections, transfusion-related problems, duration of mechanical ventilation, and duration of stay in both the ICU and the hospital.

estimation executed utilizing). On basis of a previous study ⁽²⁾, the mean \pm SD of average hemoglobin concentrations were 10.5 ± 6.1 g/dL for the liberal transfusion group of trauma patients with closed head injury, and 8.5 ± 7.0 g/dL for the restrictive transfusion group. The calculation was dependent on a 95% confidence interval, 95% study power, and a 1:1 group ratio. To mitigate dropout, 16 additional cases were comprised in each group, bringing the total number of patients to 250 per group.

Approval Code :(RC 23-10-2024)

Statistical analysis

IBM SPSS Statistics version 26 (IBM Corp., Chicago, IL, USA) was utilized for statistical analyses. Shapiro-Wilk

Patient characteristics

The cases mean ages are similar in both groups, with 49.7 years old in the Liberal group and 49.2 years old in the restrictive group. Regarding the gender distribution reveals that 73.6% of the Liberal group is male, compared to 65.2% in the Restrictive group as presented in table 1.

The investigation of the relevant medical history reveals that the rates of positive qualitative drug screens and blood ethanol screens are relatively comparable between the two groups. The prevalence of ischemic heart disease is 6% in the Liberal group and 7.6% in the Restrictive group, while previous traumatic brain injuries are reported in 18% of the Liberal cohort

testing and histograms were utilized for assessing the data distribution's normality. Parametric data were analyzed utilizing unpaired Student's t-tests and expressed as mean \pm standard deviation (SD) for comparing quantitative variables between groups. Mann-Whitney U tests were utilized to assess non-parametric data, which were then presented as median with interquartile range (IQR). When appropriate, Fisher's exact or Chi-square tests were employed to analyze the qualitative variables. The results were displayed as frequencies and percentages (%). Statistical significance is deemed as.

Results:

In all, 785 patients had their eligibility for our study evaluated. Of these, eighty patients declined to participate, and 205 patients were eliminated based on the criteria. Two groups of 250 patients each were randomly selected from the remaining eligible patients. Every patient who was enrolled was tracked down and included in the statistical analysis (Figure 1).

compared to 14.8% in the Restrictive group. The injury cause was varied the accidents involving pedal cycles, motorcycles, or all-terrain vehicles comprise 22.4% in the Liberal group and 21.6% in the Restrictive group while, motor vehicle collisions account for 16.8% in the Liberal group and 20.4% in the Restrictive group. Extracranial injuries were presented in about three-quarters of the cases in the Restrictive group (71.6%) in comparison with (63.6%) in the Liberal group. Additionally, there was an elevated Injury Severity Score of 32 ± 12 in the liberal group and 34 ± 12 in the Restrictive Strategy group. (Table 1)

Regarding GCS scores, the median GCS motor score in both groups was 4 (1-5) with most cases demonstrating 5 (localization) in both groups followed by 1 (no movement), then 6 (Obedience to commands).

A greater proportion of patients in the liberal-strategy group in comparison The lowest mean daily haemoglobin level during the ICU stay is depicted in (Figure 2).

The GOS-E score at six months was analysed utilizing sliding dichotomy revealed that 171 of 250 patients (68.4%) in the liberal-strategy group had an undesirable outcome, whereas 184 of 250 (73.5%) in the restrictive-strategy group did. These results held true even for patients with the worst, intermediate, and best-predicted prognoses (Table 2). The worst-

Secondary Outcomes

At 6 months, mortality was 26.8% in the liberal-strategy group and 26.4% in the restrictive-strategy group, with insignificant differences observed between the two groups. Among patients who survived 6 months, the Median score on Functional Independence Measure was comparable between groups regarding the overall, motor, and cognitive measures.

The quality-of-life assessments indicate notable differences between the Liberal and Restrictive treatment strategies across various measures. The median score on the EuroQol visual analogue scale is higher in the Liberal group (65, IQR 45-75) compared to the Restrictive group (55, IQR 35-70), suggesting better perceived health status among Liberal patients. Similarly, the median score on the EQ-5D-5L utility index is greater in the Liberal group (.72, IQR .43-.88) than in the Restrictive group (.61, IQR .36-.81). The Qolibri scale scores also favor the Liberal strategy, with a

with the restrictive-strategy group had a Marshall score of II, which indicates diffuse injury.

Moreover, hemoglobin levels at randomization are notably lower in the Liberal group. (Table 1)

Primary Outcom

prognosis group (GOS-E score ≤ 3) was the most prevalent between groups; the Restrictive group had a notably higher unfavorable outcome rate (81.8% vs. 75.9%). Overall, the Restrictive strategy appears to be linked to a greater prevalence of unfavorable outcomes across all prognosis categories. (Table 2)

median of 58 (IQR 38-69) compared to 49 (IQR 32-67) in the Restrictive group. Additionally, while the median PHQ-9 scores indicate mild depressive symptoms, the proportion of patients scoring ≥ 10 —indicative of moderate to severe depression—is higher in the Restrictive group (43.06% vs. 36.6% in the Liberal group). Table 2

Tertiary Outcomes

Regarding red-cell unit transfusions reveal significant differences between the Liberal and Restrictive treatment strategies. In the Liberal group, a total of 1,025 red-cell units were administered, with a median of three units per patient (IQR 2-5), compared to just 209 units in the Restrictive group, with a median of zero units per patient (IQR 0-1). Infection occurred in most patients, with 55.6% in the Liberal group and 52.4% in the Restrictive group, most commonly presenting as pneumonia. Both groups' median lengths of stay in the hospital and intensive care unit were comparable (Table 2).

Table 1: baseline patient characteristics

	Liberal Strategy (N=250)		Restrictive Strategy (N=250)	
	N	%	N	%
Age (years) mean± SD	49.7±16.3		49.2±17.1	
Male sex (no. (%))	148	73.6	163	65.2
Relevant medical history (no. (%))				
Positive qualitative drug screen	32	12.8	34	13.6
Positive blood ethanol screen	64	25.6	57	22.8
Congestive heart failure	2	0.8	5	2
Ischemic heart disease or myocardial infarction	15	6	19	7.6
Previous traumatic brain injury, including concussion	45	18	37	14.8
Chronic anemia	2	0.8	5	2
Cause of injury (no. (%))				
Motor vehicle collision	42	16.8	51	20.4
Pedal cycle, motorcycle, scooter, or other all-terrain vehicle collision	56	22.4	54	21.6
Vehicle–pedestrian collision	29	11.6	31	12.4
Assault	12	4.8	18	7.2
Other	124	49.6	112	44.8
Extracranial injury — no. (%)	159	63.6	179	71.6
Injury Severity Score	32±12		34±12	
Median GCS motor score (IQR)	4 (1–5)		4 (1–5)	
GCS motor (no. (%))				
1: No movement	65	26	82	32.8
2: Extension	17	6.8	14	5.6
3: Abnormal flexion	28	11.2	19	7.6
4: Normal flexion	54	21.6	59	23.6
5: Localization	67	26.8	63	25.2
6: Obedience to commands	55	22	43	17.2
Hypotension — no./total no. (%)	60	24	75	30
Hypoxemia — no./total no. (%)	67	26.8	70	28
Marshall injury classification based on CT (no. (%))				
I	4	1.6	9	3.6
II	128	51.2	131	52.4
III or IV	27	10.8	28	11.2
V or VI	93	37.2	83	33.2
Traumatic subarachnoid hemorrhage no. (%)	220	88	221	88.4
Epidural hematoma no. (%)	44	17.6	46	18.4
Glucose — mmol/liter	9.4±3.3		9.3±3.4	
Hemoglobin — g/dl	12.6±1.7		12.8±1.3	
Hemoglobin at randomization /dl	8.7±.8		9.2±.6	
Median time from injury (IQR)				
To first hospital admission — min	65(40-104)		64(41-99)	
To randomization— hr.	57(39-91)		58(37-85)	

Data are presented as median (IRQ), mean± SD or frequency (percentage). IQR: interquartile

Table 2: outcomes of both groups

	Liberal Strategy (N=250)		Restrictive Strategy (N=250)	
	N	%	N	%
Worst-prognosis group: GOS-E score ≤ 3	171/250	68.4	184/250	73.5
Intermediate-prognosis group: GOS-E score ≤ 4	63/83	75.9	72/88	81.8
Best-prognosis group: GOS-E score ≤ 5	55/82	67.07	59/85	69.4
Dichotomized as GOS-E score ≤ 4	53/85	62.3	53/77	68.8
Secondary outcomes	155/250	62	168/250	67.2
Death — no./total no. (%)				
In the ICU	43	17.2	39	15.6
In the hospital	58	23.2	54	21.6
At 6 months	67	26.8	66	26.4
Median score on Functional Independence Measure (IQR)				
Overall	120 (97-127)		116 (75-123)	
Motor	89 (72-92)		87 (51-91)	
Cognitive	33 (24-35)		31 (40-75)	
The median score on EuroQol visual analogue scale (IQR)	65 (45-75)		55 (35-70)	
Median score on EQ-5D-5L utility index (IQR)	.72 (.43-.88)		.61 (.36-.81)	
Median score on Qolibri scale (IQR)	58 (38-69)		49 (32-67)	
PHQ-9				
Median score (IQR)	5 (3-11)		6 (4-12)	
Score ≥ 10 — no./total no. (%)	52/142	36.6	59/137	43.06
	1025		209	
	3 (2-5)		0 (0-1)	
	139	55.6	131	52.4
Pneumonia	88	35.2	82	32.8
Bacteremia	16	6.4	18	7.2
Sepsis or septic shock	14	5.6	19	7.6
Ventriculitis, meningitis, or brain abscess	8	3.2	10	4
Transfusion reaction	4	1.6	18	7.2
Median duration of mechanical ventilation (IQR) — days	10 (6-15)		9 (5-15)	
Median length of ICU stay (IQR) — days	13 (8-20)		13 (8-20)	
Median length of hospital stay (IQR) — days	30 (15-50)		30 (20-52)	

Safety

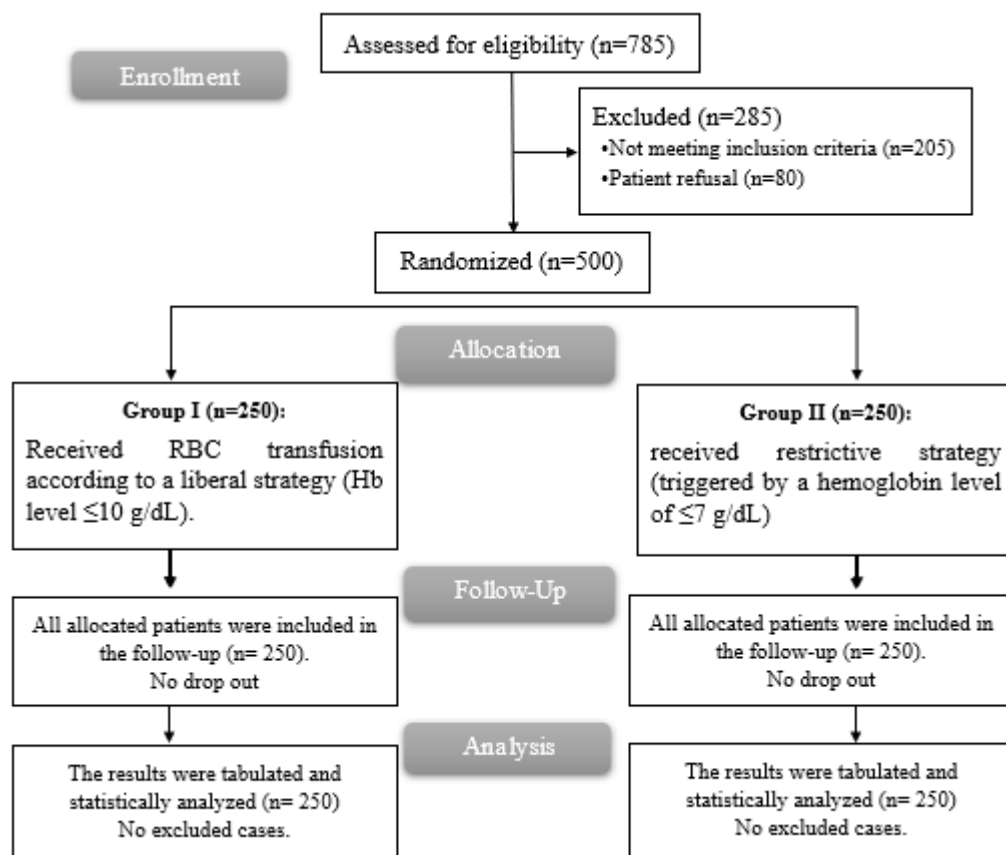
Safety outcomes indicate notable differences between the Liberal and Restrictive treatment strategies. In the Liberal group, there were 8 transfusion reactions (3.2%), compared to just 1 (0.4%) in the Restrictive group. Additionally, the Liberal strategy reported a higher rate of venous thromboembolic events, with 35 cases (14.0%), compared to 21 cases (8.4%)

in the Restrictive group. Acute respiratory distress syndrome occurred in 12 patients (4.8%) in the Liberal group versus 3 (1.2%) in the Restrictive group. Notably, there was only one serious adverse event in the Liberal group, which was deemed unrelated to the intervention, while the Restrictive group had two similar cases. Table 3

Table 3: Adverse effect of the studied groups

Outcome	Liberal Strategy (N=250)	Restrictive Strategy (N=250)
Transfusion Reactions	8 (3.2%)	1 (0.4%)
Venous Thromboembolic Events	35 (14.0%)	21 (8.4%)
Acute Respiratory Distress Syndrome	12 (4.8%)	3 (1.2%)
Serious Adverse Events	1 (unrelated to intervention)	2 (unrelated to intervention)

Data are presented as frequency (percentage).

**Figure 1:** The randomized trial flow diagram, comprising enrollment, intervention allocation, and analysis

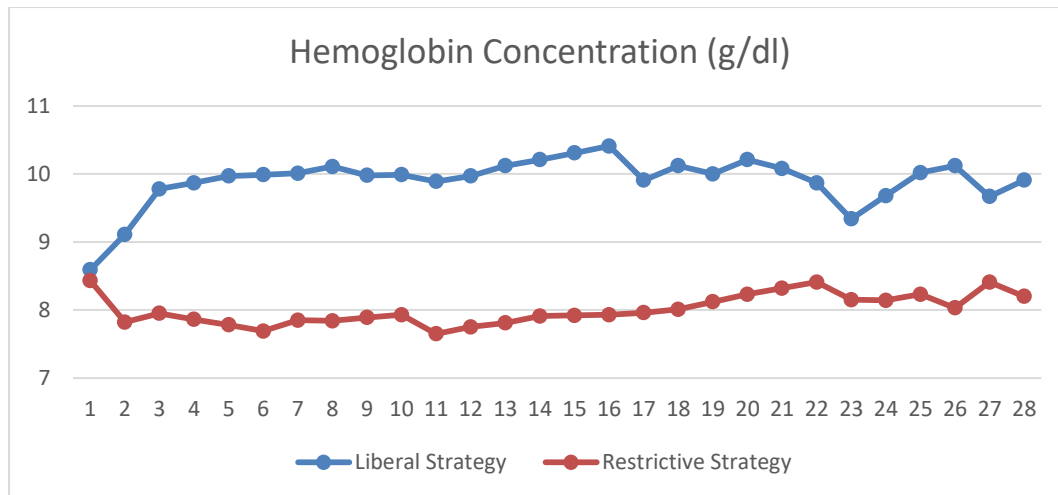


Figure 2: The Mean Daily Hemoglobin Level during the First 28 Days.

Discussion

In this trial of critically ill patients with moderate or severe traumatic brain injury and anemia, insignificant difference was observed between the liberal and restrictive transfusion strategies in terms of GCS motor scores or unfavorable neurologic outcomes at 6 months.

Among survivors at 6 months, a liberal transfusion strategy was linked to better scores in several areas of motor function and quality of life.

After TBI, certain brain areas may be more susceptible to hypoxia and shock that result from inadequate oxygen supply. Increased brain cell death due to this sensitivity may result in inferior functional outcome and greater mortality rates unless hemoglobin concentrations are kept above critical levels. Studies investigating at how anemia and transfusion impact TBI outcomes in animal models are scarce. Experimental brain damage, as shown by decreased cerebral autoregulation and the appearance of cerebral contusions⁽¹⁵⁾, becomes worse, according to these investigations, when combined with anemia caused by hemorrhage.

In a rat model free of hypotension and hypoxemia, Hare and colleagues⁽¹⁶⁾

investigated the impact of hemodilution on cerebral oxygen tension after unilateral TBI. Brain oxygen tension in the wounded hemisphere was significantly reduced after acute hemodilution to hemoglobin concentrations approaching 50 g/L, but this effect was not seen in the sham-injured rats or the contralateral cerebral hemisphere. The decrease in cerebral tissue oxygen tension was caused by impaired cerebral oxygen tension.

Minimal investigations regarding red-cell transfusion thresholds have investigated long-term neurological effects across any patient demographic, with only two trials focused explicitly on individuals with traumatic brain injury⁽¹³⁾. The more extensive experiment, done at two sites with 200 non-anemic patients, failed to demonstrate a distinction in hemoglobin levels across groups, so undermining the capacity to identify a clinically relevant difference in outcomes⁽¹³⁾.

Furthermore, that research demonstrated a heightened risk of venous thromboembolic events associated with a liberal transfusion

approach in contrast to a restricted strategy⁽¹³⁾.

Our findings concerning mortality align with the outcomes of prior randomized trials in other critically sick cohorts. While death is a significant factor, critically ill patients with traumatic brain injury and their caregivers may prioritize alternative, patient-centered outcomes, since the majority of survivors will endure profound neurological impairments and varying degrees of reliance⁽¹⁷⁾.

Recent research has shown how common anemia is when patients are admitted to the intensive care unit. The average hemoglobin concentration at ICU admission was 11.3 g/dL, according to a cohort study that included 3,534 patients from 146 Western European intensive care units with a range of case mixes (the ABC research; anemia and blood transfusion in critical care trial)⁽¹⁸⁾.

In a comparable study conducted in the USA, 4,892 ICU admissions were analyzed (the CRIT study; Anemia and Blood Transfusion in the Critically Ill: Current Clinical Practice in the United States)⁽¹⁹⁾.

In the TRICC study (Transfusion Requirements in Critical Care Trial), the average hemoglobin level. Moreover, 52% of patients had a hemoglobin concentration of ≤ 9 g/dL on their first day of ICU care, which increased to seventy-seven percent on the second day⁽²⁰⁾.

In a retrospective study of 166 mechanically ventilated COPD patients with type 2 respiratory failure, Nevins and Epstein identified anemia (mean hematocrit of 36) as a factor correlated with worse outcomes. Despite evidence indicating that anemia correlates with worse outcomes in mechanically ventilated patients, there is a lack of substantial research endorsing the transfusion of Packed Red Blood Cells (PRBC) to aid in the

weaning of patients off mechanical ventilation⁽²⁰⁾.

In this research by Manal et al.⁽¹⁾ on blood transfusion for anemia treatment, no significant difference was seen concerning blood transfusion and outcomes, using a hemoglobin threshold of 7 g/dL. In the research, 63 out of 165 patients did not get a blood transfusion, with 23 of them not surviving, representing 14% of the total. Conversely, a total of 102 participants received blood transfusions during their ICU stay, and 40 of these participants did not survive, representing 23.6% of the entire group. Our research is limited by the recruitment of only anemic patients, its single-center design, and the selection of a group with more severe TBI, which may account for the elevated baseline risk of an unfavorable outcome. The healthcare providers could not be blinded to the treatment allocations.

Conclusions:

A liberal transfusion strategy for critically ill patients with anaemia and traumatic brain injury did not reduce the likelihood of adverse neurological outcomes at six months.

Financial support and sponsorship:
Nil

Conflict of Interest: Nil

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To cite this article: Reham S. Mohamed, Zeyad M. Elbagoury, Ahmed I. Soubih. Liberal or Restrictive Transfusion Strategy in Patients with Traumatic Brain Injury. *BMFJ* XXX, DOI: 10.21608/bmfj.2025.369403.2346.

