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RED BLOOD CELL TRANSFUSION AND ASSOCIATED OUTCOMES IN SEVERE ISOLATED TRAUMATIC BRAIN INJURY AT HOSPITAL UNIVERSITI SAINS MALAYSIA

Jernih A.R.[1] , Hasmah H.[1*] , Sharifah Azdiana T.D.[1]

[1]Regenerative Medicine, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Bertam, 13200 Kepala Batas, Penang, Malaysia

***Correspondence Author:** Dr. Hasmah Hussin, Regenerative Medicine, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Bertam, 13200 Kepala Batas, Penang, Malaysia. Email: hasmah.hussin@usm.my*

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ABSTRACT

Background: Prevalence of anaemia is high in severe traumatic brain injury (TBI). However, there is no clear transfusion guideline available in the ICU or ward. This study aims to determine the prevalence of anaemia and transfusion practice in TBI patients and to compare two groups of transfusion strategies; liberal transfusion strategy and restrictive transfusion strategy.

Materials and methods: This was a retrospective cohort conducted in Hospital Universiti Sains Malaysia, Kelantan. Data from 2012 to 2017 were extracted from the medical records, Laboratory Information System (LIS) and transfusion record (MyTransfusi). Samples were divided into liberal transfusion strategy and restrictive transfusion strategy group and compared with the outcome. For statistical analysis, Mann Whitney, independent t-test and chi square were used to compare both groups. Simple linear and logistic regression were used to determine the association of the outcome.

Result: Out of 146 patients, 21.9% had mild anaemia, 60.3% had moderate anaemia and 17.8% had severe anaemia. All patients who had severe anaemia received red blood cell (RBC) transfusion. Whereas, in mild and moderate group of anaemia, about 34.4% and 79.5% received RBC transfusion respectively. Restrictive transfusion strategy had significantly lower value of lowest haemoglobin level (P=0.001) and unit of RBC transfused (P=0.008) as compared to liberal transfusion strategy. Post transfusion haemoglobin (P<0.001, b=1.809, 95% CI -2.453, -1.17) is significantly lower in restrictive transfusion strategy. There was no significant difference in mortality and morbidity.

Conclusion: Liberal transfusion strategy does not have better outcome compared to restrictive transfusion strategy. Prospective study with larger sample is needed.

Keywords: TBI, anaemia, RBC transfusion, liberal, restrictive

1.0 Introduction

Traumatic brain injury (TBI) is a common diagnosis seen in emergency department. In 2009, national trauma database found that 78.35% of major trauma cases presented to emergency departments of eight hospitals in Malaysia involved severe head and neck injury with abbreviated injury scale (AIS) $\geq$ 3. Road traffic accidents accounted for the 76.8% of the cases and 96.3% of all the injuries were due to blunt trauma. Head injury is responsible for 48.2% of death due to trauma in Malaysia (Jamaluddin et al., 2011).

Traumatic brain injury or head injury can be defined as injury due to external force that can alter the physiology of the brain with or without anatomical changes. Therefore, to diagnose as traumatic brain injury, there should be presence of external forces such as head hit by objects or head hit an object, acceleration/deceleration force to the brain without direct trauma, penetrating injury or other external forces such as explosions or other forces yet to be defined. Also, there should be alteration to the physiology of the brain, with or without anatomical changes of the scalp, face, skull and/or brain. TBI can be classified according to presenting Glasgow Coma Scale (GCS). While mild TBI is defined as TBI with GCS 13 to 15, moderate TBI is defined as GCS 9 to 12 and severe TBI with GCS 3 to 8 (Liew et al., 2017).

More than half of the patients admitted to intensive care unit (ICU) were anaemic and nearly one third of them were moderate and severe anaemia (Walsh & Saleh, 2006). Anaemia has always been the problem in ICU settings. One study reported that poor outcome was observed in critically ill patients due to anaemia irrespective of the underlying illness (Hebert et al., 1999). In view of this, red cell transfusion has been used to treat anaemia previously. Even though by transfusing packed red cell to patients with anaemia improved the haemoglobin level, the transfusion of blood product can cause significant complications or adverse events (Blajchman, 1999). Therefore, current restrictive transfusion strategy which uses less transfusion, is based on clinical needs and targeting lower acceptable haemoglobin and haematocrit levels without compromising clinical outcome (Audet & Goodnough, 1992).

The incidence of anaemia in severe traumatic brain injury is high. In a retrospective study which the objective was to determine the association of anaemia and the outcome among TBI patients, 69% of the patients were anaemic with the haematocrit level of less than 30% (Carlson et al., 2006). Example from another study measuring anaemia and the outcome among TBI patients found that 78% of the subjects had anaemia with haemoglobin concentration of less than 11g/dL (Sekhon et al., 2012). The causes of the anaemia are multifactorial. It can be due to blood loss from operation, multiple trauma to the other part of body, decrease haemoglobin and haematocrit concentration due to massive infusion of crystalloid or colloid during resuscitation and also unnecessary blood sampling (Kramer & Le Roux, 2012).

Restrictive transfusion strategy is a strategy to reduce the use of red cell transfusion. Red cell will be transfused only when haemoglobin level decrease below 7 g/dL and the haemoglobin level is maintained from 7 to 9 g/dL. On the other hand, liberal transfusion strategy is transfusion of red cell when haemoglobin level decrease below 10 g/dL and haemoglobin level is maintained within the range of 10-12g/dL. In a prospective study done to compare restrictive strategy and liberal strategy among critically ill patients in four ICU in Canada, restrictive strategy showed better results than liberal strategy in terms of the outcome and number of red cell transfused in all the critically ill patients except for acute ischemic heart disease. In the study, red blood cell transfusion used to increase the oxygen carrying capacity and oxygen delivery to the tissue did not increase patients' survival when haemoglobin level more than 7 g/dL. However, restrictive transfusion strategy should be used with caution in patients with acute myocardial infarct and unstable angina (Hebert et al., 1999).

In traumatic brain injury, red cell transfusion is commonly used to treat anaemia. Traditionally, liberal transfusion strategy is practised where haematocrit and haemoglobin are maintained above 30% and 10g/dL respectively (Winn, 2004). However, there is no sufficient study to support this practise. On top of that, blood transfusions carry risk to cause adverse reactions to the recipient such as acute haemolytic transfusion reaction, febrile nonhaemolytic transfusion reaction, allergic reaction, transfusion related acute lung injury, transfusion associated circulatory overload, transfusion related immunomodulatory and transfusion related sepsis (Sahu et al., 2014). Hence, the risk and benefit of transfusion have to be taken into consideration to strategize the treatment to optimize patient's condition.

Although current strategy is moving towards restrictive transfusion, more studies on brain injury need to be done to evaluate the advantageous and effectiveness of restrictive transfusion strategy as compared to liberal transfusion strategy. Therefore, this study aimed to provide insights on the severity of anaemia in severe isolated TBI patients and the transfusion strategy used in the local setting particularly HUSM besides to compare the outcome between the two transfusion strategies; liberal and restrictive.

2.0 Materials and methods

This was a retrospective cohort using patients' medical record review conducted in Hospital Universiti Sains Malaysia (HUSM) in Kelantan, which is a tertiary referral center for the east coast of Peninsular Malaysia, especially in neurosurgical and neurosciences. Retrospective data from 2012 till 2017 were retrieved from patients' medical record. Patients included in this study aged 18 years and above, admitted to ICU, had computed tomography of the brain (CT-brain), diagnosed as severe isolated traumatic brain injury and had haemoglobin concentration of less than 13 g/dL for men and 12 g/dL for women. Those who passed away or brain death in 24 hours of admission, any prior central nervous system and cardiovascular disease, penetrating injury to the brain, underlying chronic anaemia and pregnant at the time of the injury were excluded.

Data were extracted from the medical records, Lab information system (LIS) and blood bank record (MyTransfusi) and recorded in proforma. The proforma comprises of patients' demographic, types of brain injury, Glasgow Coma Scale score, head Abbreviated Injury Scale (AIS), Injury Severity Score (ISS), laboratory investigation (haemoglobin level on admission, lowest and post transfusion, lowest sodium level and highest glucose level), unit of red cell transfused, procedure performed, types of adverse transfusion reaction, inhospital morbidity (pneumonia, urinary tract infection, seizure and deep vein thrombosis) and mortality. The samples were then divided into two groups of transfusion strategies; liberal transfusion strategy and restrictive transfusion strategy

The sample size was calculated based on five percent precision and 95% confidence level with infinite population, using single proportion calculation where 9.48% of isolated TBI patients were transfused with packed red blood cells (Duane et al., 2008). A minimum sample size of 146 was required. Convenience sampling method was employed for targeted study population within the study period. The subjects were taken either consecutively or not based on available data registry, who meet the criteria of inclusion, until the required sample size is achieved. The subjects then grouped into restrictive transfusion group and liberal transfusion group based on transfusion practised.

Statistical analysis was performed using SPSS version 24.0 for window-software (SPSS, Chicago Illinois, USA). The severity of anaemia, red cell transfusion and incidence of adverse transfusion reaction among the subjects were analysed and presented descriptively. The categorical data were expressed as frequency (percentage) and numerical data as mean (SD). Mann Whitney and Independent t-test for continuous data and chi square test for categorical data were used to compare the general characteristics between liberal and restrictive transfusion strategy group. To determine the association of outcome (post transfusion haemoglobin) between liberal and restrictive group, simple linear regression was used. To determine the association of mortality and morbidity (pneumonia, urinary tract infection, seizure, deep vein thrombosis) with the two group, simple logistic regression was used.

The ethical clearance was obtained from Human Research Ethics committee (JEPeM) of USM. All subjects were anonymous. Data were presented as group data and did not identify the respondents individually. All the written research documents, including study data (demographic and clinical data) were protected by researcher. The investigators declared no conflict of interest.

3.0 Result

3.1 Prevalence of anaemia group and patients transfused with packed red blood cell

Table 1 Prevalence of anaemia group and patients transfused with packed red blood cell

Anaemia classification	**Patients, n (%)**	**Transfused with RBC, n (%)**
Mild anaemia (men: Hb 10.0 – 12.9 g/dL) (women: Hb 10 – 11.9 d/dL)	32 (21.9)	11 (34.4)
Moderate anaemia (Hb 7 – 10 g/dL)	88 (60.3)	70 (79.5)
Severe Anaemia (Hb (Hb <7 g/dL)	26 (17.8)	26 (100)

Within the study period, there were 312 patients had severe isolated TBI with 146 of them fulfilled the inclusion criteria. There were 21.9% (n=22) had mild anaemia, 60.3% (n=88) had moderate anaemia and 17.8% (n=26) had severe anaemia. All patients who had severe anaemia were transfused at least 1 pint of RBC during hospital stay. Whereas, in mild and moderate group of anaemia, about 34.4% and 79.5% respectively received RBC transfusion (Table 1).

3.2 Prevalence of adverse reaction among severe isolated TBI patients

Table 2 Prevalence of adverse reaction among severe isolated TBI patients

Type of adverse reaction	Number of patient, n (%)
Haemolytic transfusion reaction	0
Febrile non-haemolytic transfusion reaction	2 (1.4)
Allergic transfusion reaction	1 (0.7)
TRALI	0
TACO	0
Transfusion associated sepsis	0

There was low incidence of adverse transfusion reaction among severe isolated traumatic brain injury during or post transfusion. Only 1.4% had febrile non haemolytic transfusion reaction followed by 0.7% with allergic transfusion reaction. No other adverse reaction experienced by the patients (Table 2). Overall, there was 2% incidence of adverse transfusion reaction found in this study.

3.3 Comparison on the demographic and clinical variables between Liberal Strategy group and Restrictive Strategy group

Table 3 Comparison on the demographic and clinical variables between Liberal Strategy group and Restrictive Strategy group

Variables	Liberal strategy	Restrictive strategy		
	Median (IQR)/ Mean (SD)	Median (IQR)/ Mean (SD)	Z stat / T statistic	P value
Age	40 (33)	41 (34)	-0.218	0.828[a]
GCS on admission	7 (3)	7 (2)	-0.663	0.508[a]
Head AIS	3 (1)	3 (1)	-0.646	0.519[a]
Injury severity score	10 (7)	10 (8)	-1.093	0.275[a]
Systolic BP on admission	134 (34)	126.5 (38)	-1.201	0.230[a]
Lowest haemoglobin (g/dL)	8.9 (1.8)	7.8 (1.7)	-3.261	0.001[b]
Lowest sodium (mEq/ml)	136 (6)	135 (5.25)	-0.339	0.735[a]
Highest glucose (mmol/L)	9 (4.1)	8.15 (2.7)	-1.875	0.061[a]
Units RBC transfused	2 (4)	0 (4)	-2.674	0.008[a]

[a]Mann-whitney test; median (IQR)
[b]Independent T test; mean (SD)
p is significant at <0.05

Samples were grouped into two different transfusion strategies; liberal transfusion strategy and restrictive transfusion strategy which consist of 111 and 35 samples respectively. Demographics and clinical variables were selected to be analysed. The variables are age, GCS on admission, head AIS, ISS, systolic BP on admission, lowest haemoglobin, lowest sodium, highest glucose, units of RBC transfused, procedure and types of brain injury (Table 3 & Table 4). In comparison of the demographic and clinical variables between liberal transfusion strategy and restrictive transfusion strategy, there were significant differences in lowest haemoglobin (p=0.001) and unit of RBC transfused (p=0.008) (Table 3).

Table 4 Association between procedure and types of brain injury with transfusion practice

	Liberal strategy n (%)	**Restrictive strategy n (%)**	**p-value**
Procedure			
Decompressive craniectomy	46 (41.1)	14 (40)	
Tracheostomy	11 (9.9)	6 (17.1)	
Decompressive craniectomy and tracheostomy	32 (28.8)	8 (22.9)	0.8[b]
Other procedure	8 (7.2)	3 (8.6)	
No procedure	14 (12.6)	4 (11.4)	
Brain injury			
Subdural hematoma	65 (58.6)	15 (42.9)	0.121[a]
Epidural hematoma	36 (32.4)	14 (40)	0.421[a]
Subarachnoid haemorrhage	27 (24.3)	6 (17.1)	0.489[a]
Intracerebral haemorrhage	2 (1.8)	1 (2.9)	0.701[b]
Intraventricular haemorrhage	4 (3.6)	1 (2.9)	0.832[b]
Brain contusion	56 (50.5)	19 (54.3)	0.703[a]
Diffuse axonal injury	9 (8.1)	6 (17.1)	0.125[b]

Chi-square analysis
[a]Fischer's exact test
[b]Pearson Chi square
p is significant at <0.05

3.4 Association between liberal transfusion strategy and restrictive transfusion strategy with the outcome

3.4.1 Comparison between liberal transfusion strategy versus restrictive transfusion strategy (transfusion practice) with post transfusion haemoglobin

Table 5 Comparison between liberal transfusion strategy versus restrictive transfusion strategy (transfusion practice) with post transfusion haemoglobin

Independent Variables	**Mean $\pm$ SD**	**SLR[a]**	
		b* (95% CI)	P- value
Transfusion practice	10.81 (1.39)	-1.809 (-2.453, -1.165)	<0.001

[a] Simple linear regression (dependent variable: Post transfusion haemoglobin)
b*= crude regression coefficient

In terms of the association between liberal transfusion strategy and restrictive transfusion strategy with the outcome, haemoglobin post transfusion is significantly higher in liberal strategy group than restrictive strategy group. The mean of haemoglobin post transfusion is 1.809 times lower in restrictive group compared to liberal strategy (b=-1.809, 95% CI -2.453, -1.17, p=<0.001) (Table 5).

3.4.2 Association between transfusion practice and inhospital mortality

Table 6 Association between transfusion practice and inhospital mortality

Independent variable	**N (%) Yes**	**N (%) No**	**Crude OR (95% CI)**	**P-value**
Transfusion practice				
-Restrictive	5 (14)	30 (86)	1	
-Liberal	27 (24)	84 (76)	1.929	0.216

Simple logistic regression (dependent variable: inhospital mortality)

There was no significant difference between liberal and restrictive group with regard to mortality (p=0.216) (Table 6).

3.4.3 Association between transfusion practice and inhospital morbidity

Table 7 Association between transfusion practice and inhospital morbidity

Independent variable	**N (%) Yes**	**N (%) No**	**Crude OR (95% CI)**	**P-value**
Transfusion practice				
-Restrictive	6 (17)	29 (83)	1	
-Liberal	31 (28)	80 (72)	1.873	0.206

Simple logistic regression (dependent variable: inhospital morbidity)

Table 8 Association between transfusion practice and pneumonia

Independent variable	N (%) Yes	N (%) No	Crude OR (95% CI)	P-value
Transfusion practice				
-Restrictive	5 (14)	30 (86)	1	
-Liberal	27 (24)	84 (76)	1.929	0.216

Simple logistic regression (dependent variable: pneumonia)

Table 9 Association between transfusion practice and seizure

Independent variable	N (%) Yes	N (%) No	Crude OR (95% CI)	P-value
Transfusion practice				
-Restrictive	1	34	1	
-Liberal	1	110	0.309	0.411

Simple logistic regression (dependent variable: seizure)

Table 10 Association between transfusion practice and urinary tract infection

Group	Urinary tract infection		*P* value
	No, n (%)	Yes, n (%)	
RBCT group (Liberal strategy)	108 (97.3)	3 (2.7)	0.326
Non RBCT group (Restrictive strategy)	35 (100.0)	0	

Pearson Chi-Square Analysis

There was no significant difference between the transfusion strategy groups in terms of overall morbidity (p=0.206), pneumonia (p=0.216), urinary tract infection (p=0.326) and seizures (p=0.411) (Table 7-10). No patients had been diagnosed with deep vein thrombosis during the hospital stay.

4.0 Discussion

Our study recruited 146 subjects. The data shows that majority of the severe traumatic brain injured patients had moderate anaemia at any point of time from admission or during the stay in the hospital. This finding correlate with the finding from the study done by Litofsky *et al* where 335 out of 756 anaemic patients had haemoglobin level of 7 to 10 g/dL followed by mild anaemia with 333 patients (Litofsky et al., 2016). The causes of anaemia identified were blood loss from surgical intervention, daily blood sampling for laboratory investigation, anaemia of inflammation with prolong ICU stay and haemodilution due to massive volume resuscitation (Kramer & Le Roux, 2012).

In terms of transfusion practice, our data recorded 72.6% of 146 patients were transfused with at least 1 unit of red cells. This showed that the practice of transfusing blood is common in this cohort study regardless of the severity of anaemia. There were no transfusion protocol or transfusion guideline available in the ICU or in the ward for traumatic brain injury specifically. Therefore, decision to transfuse was solely dependent on the respective neurosurgeons or intensive care physicians. In a study done in the US, three specialty surgeons and intensivists (trauma surgery, neurosurgery, ICU) were given a survey regarding the transfusion practice in acute severe traumatic brain injury, neurosurgeons were more likely to use higher haemoglobin threshold (liberal transfusion strategy) compared to trauma surgeons and intensivists. The reason being that neurosurgeons were more concern regarding secondary brain injury due to anaemia while the trauma surgeons and intensivist considered the complications of blood transfusion in their decision to transfuse (Sena et al., 2009). Hence, the transfusion practices were more likely to be differ from one patient to another as there is no standard guideline or protocol as a baseline requirement for transfusion in severe traumatic brain injury, even between surgeon or physician in the same specialty.

Although adverse transfusion reaction is seldom, it is possible that transfusion can lead to severe reaction. In one study, 1.1% in the retrospective study population developed serious transfusion reaction such as TACO, TRALI, anaphylaxis and hypotensive reaction. This incidence was not detected in many institutions and probably due to underreporting (Hendrickson et al., 2016). In this study, mild adverse transfusion reaction occurred in 2% (n=3) of the group, two patients developed febrile non haemolytic transfusion reaction and one patient develop mild allergic reaction. In comparison, transfusion reaction occurred lower (0.71%) in a study done in Universiti Kebangsaan Malaysia Medical Centre and the low incidence was probably due to prophylaxis medication given prior to transfusion to some patients and also underreporting. No severe adverse transfusion reaction was reported to the transfused patients in this study. The incidence for haemolytic transfusion reaction which could lead to severe haemolysis, kidney failure and death are 0.003% (Rabeya et al., 2011). Even though overall incidence of adverse transfusion reaction is low and most are mild, severe transfusion reaction can occur if blood products are transfused liberally with no clear indication.

When comparing the demography and clinical variables between restrictive and liberal transfusion group, units of red blood cell transfusion were higher in the latter group. Besides the risk in terms of adverse transfusion reaction, blood transfusion also incurs high cost per unit. In a study done in the US to compare safety and cost efficiency between the two groups, liberal transfusion strategy had more patients who were transfused compared to restrictive group. One unit of packed red blood cell can cost up to $1183. After changing protocol from restrictive transfusion to liberal transfusion, any TBI patient can save almost $400 and in severe TBI patient, it can save nearly $2000. After calculation based on patients admission in the ICU, the university hospital can save in average $115000 annually (Ngwenya et al., 2017). Hence, institution that adopt liberal transfusion strategy to maintain desired level of haemoglobin in certain patients' population will have to allocate more budget compared to restrictive transfusion approach.

In our study, there were no significant differences among the outcomes of mortality and morbidity except for post transfusion haemoglobin. Almost similar findings were found in a multicentre randomized controlled trial involving sixty-seven patients from the Transfusion

Requirement in the Critical Care trial (TRICC) where no significant difference was found in all primary and secondary outcomes including mortality, length of stay and organ failure (McIntyre et al., 2006). Another retrospective study done where restrictive and liberal transfusion strategy were compared, red blood cells transfusion did not have significant difference towards mortality in studied patients whose haemoglobin level were 8-10 g/dL (George et al., 2008). Both of the study shows that liberal transfusion strategy was not better as compared to restrictive transfusion strategy in terms of the outcome of the patients. However, another randomized controlled trial comparing the two transfusion protocol were found that restrictive group had lower haemoglobin concentrations and received less red cell transfusion while liberal group showed better outcomes in mortality and neurological status at 6 months. Hospital mortality were significantly higher in restrictive group probably due to higher incidence of cerebral post traumatic vasospasm (Gobatto et al., 2019).

In terms of morbidity during ICU and hospital stay, there were no significant difference between the two groups even though liberal strategy had higher proportion of patients with pneumonia and urinary tract infections as compared to restrictive strategy. The findings were echoed by another study comparing anaemic transfused with anaemic not transfused group of TBI patients where anaemic transfused had higher number of getting pneumonia compared to anaemic not transfused although it had no significance different (Salim et al., 2008). In another study pneumonia and urinary tract infections seems to have no significant different between the two groups except for deep vein thrombosis where more patients in the liberal group had deep vein thrombosis as compared to restrictive group. This also could be due to longer ICU length of stay and use of paralytic drugs that can contribute to DVT (George et al., 2008).

Other than that, the haemoglobin post transfusion was significantly different due to the transfusion strategy, in which liberal transfusion strategy requires the haemoglobin to be maintained 10-12 g/dL while restrictive transfusion strategy requires the haemoglobin to be maintained 7-10 g/dL. The aim of management and treatment of severe TBI patients are to prevent secondary brain injury. Injured brain is vulnerable to ischaemia due to hypoxia and hypoperfusion. Therefore, transfusion is the treatment of choice to increase delivery of oxygen to the injured tissue. However, red cell transfusion was not the absolute answer to this. One study found that brain tissue partial pressure of oxygen (PbtO2) increase only temporarily after red cell transfusion and some patients actually had decreased PbtO2 (Leal-Noval et al., 2006; Smith et al., 2005). Other studies also found that local tissue oxygen delivery were not increased after red cell transfusion in patients admitted to ICU (Dietrich et al., 1990; Lorente et al., 1993). Transfusion may decrease cerebral blood flow and tissue perfusion by increasing the blood viscosity (Kramer & Le Roux, 2012). Besides, storage lesion due to old storage of red cell could reduce the efficacy of red cell where it increases the affinity of oxygen to red cell causing it difficult to release oxygen to tissue. Altered nitric oxide metabolism and microvascular obstruction due to reduced deformability of stored red cells also might be the other possibilities (Beutler & Wood, 1969; Chaudhary & Katharia, 2012; Kannan & Atreya, 2010; Valeri & Hirsch, 1969; Van de Watering, 2011; Wang et al., 2012).

To our best knowledge, this is the first local study which determined the prevalence of anaemic group, transfusion practice and comparison between restrictive strategy and liberal strategy in traumatic brain injury patients in Malaysia. However, there are few limitations that are identified. The limitations include the retrospective design of the study, lack of data on red cell transfusion prior referral to HUSM, the age of RBC and neurologic outcome post admission. More studies need to be done especially prospective design with larger sample size to include wider group of TBI patients including polytrauma. As concept of patient blood management is growing acceptance in Malaysia, the need to have more evidence-based studies are important. The concept of restrictive transfusion and patient blood management where less blood is used preferably while employing alternatives such as intravenous iron, erythropoietin and anti-fibrinolytic are quite new in Malaysia (Krishnamoorthy et al., 2017).

5.0 Conclusion and recommendation

From our study, liberal transfusion strategy does not have better outcome compared to restrictive transfusion strategy in severe isolated traumatic brain injury. Our result suggest that it is safe to use restrictive transfusion strategy in isolated severe traumatic brain injury. However, large randomized controlled trial is warranted to compare the two different transfusion strategies to further determine the optimal threshold for transfusion, its benefits and risks.

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Declaration

Authors declare that no competing interest in this study.

Authors contribution

Author 1: Study design, literature review, data collection and drafting manuscript
Author 2: Study design, advice and guidance during manuscript preparation
Author 3: Study design, advice and guidance towards publication of manuscript

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