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

By

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DECLARATION

I hereby declare that this research has been sent to Universiti Sains Malaysia for the degree of Masters of Medicine in Transfusion Medicine. It is not to be sent to any other universities. With that, this research might be used for consultation and can be photocopied as reference.

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List of abbreviation

AIS	Abbreviated injury scale
BP	Blood pressure
CaO_2	Arterial oxygen content
CBF	Cerebral blood flow
CT	Computed tomography
DVT	Deep vein thrombosis
DO_2	Oxygen delivery to the brain
GCS	Glasgow coma scale
GOS	Glasgow outcome scale
HUSM	Hospital Universiti Sains Malaysia
ICU	Intensive care unit
IQR	Interquartile range
ISS	Injury severity score
JEPeM	Human Research Ethics Committee
LIS	Lab information system
OR	Odd ratio
PbtO2	Brain tissue partial pressure of oxygen
PRBC	Packed red blood cell
RBC	Red blood cell
SaO_2	Arterial oxygen saturation
SD	Standard deviation
SLR	Simple linear regression
TACO	Transfusion associated circulatory overload
TBI	Traumatic brain injury
TRALI	Transfusion related acute lung injury
TRICC	Transfusion Requirement in the Critical Care trial (TRICC)
USM	Universiti Sains Malaysia
UTI	Urinary tract infection

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ABSTRAK

Pengenalan: Prevalensi anemia terhadap pesakit cedera otak berat (TBI) adalah tinggi. Walau bagaimanapun, tiada garis panduan transfusi yang tersedia di ICU mahupun di wad. Kajian ini bertujuan untuk menentukan prevalensi anemia dan praktis transfusi darah di kalangan pesakit TBI berat terpencil dan membandingkan dua strategi transfusi iaitu strategi transfusi liberal dan strategi transfusi restriktif. **Kaedah**: Kajian kohort retrospektif ini dilakukan di Hospital Universiti Sains Malaysia, Kelantan. Data daripada tahun 2012 hingga 2017 yang merangkumi demografi pesakit, variabel klinikal dan variabel hasil diambil daripada rekod perubatan, system informasi makmal (LIS) dan rekod transfusi darah (MyTransfusi) dicatat di dalam proforma pesakit. Subjek kemudian dibahagikan kepada dua kumpulan iaitu strategi transfusi liberal (kadar haemoglobin dikekalkan lebih daripada 10g/dL) dan strategi transfusi restriktif (kadar haemoglobin dikekalkan diantara 7-10g/dL) dan perbandingan hasil dilakukan. Untuk Analisa statistik, *Mann Whitney*, *independent t* dan *chi square* digunakan untuk perbandingan kedua-dua kumpulan. *Simple linear* dan *logistic regression* digunakan untuk menentukan hasil yang berkaitan. **Keputusan**: Sebanyak 146 rekod pesakit diambil untuk kajian ini. Anemia sederhana mencatatkan prevalensi tertinggi dengan 60.3% (n=88), diikuti dengan anemia ringan dengan 21.9% (n=32) dan anemia berat dengan 17.8% (n=26). Kesemua pesakit dengan anemia berat, 79.5% daripada anemia sederhana dan 34.4% daripada anemia ringan menerima transfusi darah merah. Strategi transfusi restriktif mencatatkan bacaan haemoglobin terendah (P=0.001) dan unit darah merah yang ditransfusi (P=0.008) adalah lebih signifikan rendah berbanding strategi transfusi liberal. Hemoglobin selepas transfusi darah (P<0.001, b=1.809, 95% CI -2.453, -1.17) juga mencatatkan bacaan yang signifikan dimana strategi transfusi restriktif mencatatkan bacaan lebih rendah berbanding strategi transfusi liberal. Walau bagaimanapun, tiada perbezaan signifikan dicatatkan berkenaan kematian dan morbiditi. **Kesimpulan**: Strategi transfusi liberal tidak menunjukkan hasil yang lebih baik berbanding strategi transfusi restriktif. Kajian prospektif yang merangkumi subjek yang lebih banyak diperlukan. **Kata Kunci**: TBI, anemia, transfusi, liberal, restriktif

ABSTRACT

Introduction: Prevalence of anaemia is high in severe traumatic brain injury (TBI). However, there is no clear transfusion guideline available in the ICU or ward settings. 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. **Methods**: This was a retrospective cohort conducted in Hospital Universiti Sains Malaysia, Kelantan. Data from 2012 to 2017 which comprised of patients' demography, clinical variables and outcomes were extracted from the medical records, Laboratory Information System (LIS) and blood bank record (MyTransfusi). Samples were divided into liberal transfusion strategy group (haemoglobin level maintained above 10g/dL) and restrictive transfusion strategy group (haemoglobin level maintained between 7-10g/dL) 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**: A total of 146 patients were included in this study. There were 21.9% (n=32) 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. 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. **Keyword**: TBI, anaemia, RBC transfusion, liberal, restrictive

Chapter 1:

INTRODUCTION

CHAPTER ONE

INTRODUCTION

1.1 Background of study

Traumatic brain injury (TBI) is a common diagnosis seen in emergency department. In 2009, the national trauma database found that 78.35% of major trauma cases presented to emergency departments of 8 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 (1).

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 (2). 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 (2). GCS score is widely used in patients with traumatic brain injury due to its reliability and validity. Meanwhile, isolated traumatic brain injury is defined as traumatic brain injury without significant injury of other organs (3). In another article, isolated TBI is defined as patients with head AIS $\geq$ 3 and excluding patients with AIS > 2 in any other body region (4).

Pathophysiology of traumatic brain injury generally can be divided into 2 stages. The first stage consists of direct tissue damage by the trauma sustained beforehand, disrupted autoregulation of cerebral blood flow as well as impaired metabolism. This mechanism which resembles ischemia will lead to the accumulation of lactic acid resulted from anaerobic glycolysis, increased cell membrane permeability, and successive oedema formation. Subsequently, the adenosine tri-phosphate (ATP) store will be depleted since the anaerobic metabolism cannot meet the demands of the brain to maintain cellular energy states. This will result in failure of the ATP-dependent membrane ionic pumps which are important in maintaining brain homeostasis. The second stage of TBI pathophysiology cascade is characterized by terminal membrane depolarization along with excessive release of excitatory neurotransmitters such as glutamate and aspartate. Besides, N-methyl-D-aspartate, a-amino-3-hydroxy-5-methyl-4-isoxazolpropionate and voltage-dependent Ca2þ- and Naþ-channels are also activated. Sodium and calcium influx due to its channel activation will later on activate lipid peroxidases, proteases and phospholipases which in turn increase the intracellular concentration of free fatty acids and free radicals. Progressive structural changes of membrane and the nucleosomal DNA together with increase free radicals and free fatty acids will lead to membrane degradation, necrosis or apoptosis (5).

TBI can be further classified into primary and secondary brain injuries. Primary brain injury occurs during the initial insult or direct damage to the brain tissue due to transfer of kinetic energy. Secondary brain injury occurs moments after primary brain injury as consequence of various factors such as hypoxemia, hypotension, hypo- or hyper-carbia, hypo- or hyperglycemia, hypo- or hyperthermia, and seizures which later can lead to cerebral edema, cerebral ischemia and death. Therefore, prevention of secondary brain injury is the primary concern of therapeutic interventions following TBI (6). Protocol-based management strategies which is the core of Brain Trauma Foundation guidelines published in 2016 emphasise on high quality care and improvements in outcome for patients with TBI (7). The basis of the management of TBI is the intensive care treatment of these patients which focus on airway, improving oxygenation and providing adequate hemodynamic support to avoid the secondary injuries that are associated with events such as hypoxia or hypotension (6).

The incidence of anaemia in severe traumatic brain injury is high. In a retrospective study done in University of New Mexico, United States, in 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% (8). An example from another study also measuring anaemia and outcome among TBI patients revealed that 78% of the sample had anaemia with haemoglobin concentration of less than 11g/dL (9). The causes of 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 (10).

Brain oxygenation or oxygen delivery (DO_2) is directly proportional to the cerebral blood flow (CBF) and arterial oxygenation content (CaO_2=Hb x SaO_2 x 1.39). Therefore, significant decrease in Hb can cause reduce in brain DO_2 and cause hypoxia or ischemia if the regulatory mechanism is not optimum for example in brain injury (11). In healthy individuals, Hb level that reduce to 5 to 6 g/dL will further drop the brain oxygen delivery as compensatory mechanism has reached the maximum capacity in that critical Hb level. Symptoms may manifest as fatigue and cognitive disorder (12, 13). In TBI patient, the maximum compensatory mechanism by vasodilation and increase CBF occurs at higher Hb level of 8 to 9 g/dL as cerebrovascular reserve is compromised and any further reduction in Hb below this threshold will contribute to further drop in cerebral DO_2 (14).

A study which was done in Missouri, United States in 2016 showed that TBI patients with anaemia had poorer outcome compared to TBI patients without anaemia (15). In the study, the outcome was classified by Glasgow outcome scale (GOS) score. GOS score of 1 (death), 2 (persistent vegetative state) and 3 (severe disability) were grouped as poor outcome while score of 4 (moderate disability) and 5 (good recovery) were grouped as good outcome. The lower haemoglobin group had lower percentage of patients with good outcome (GOS score 4 or 5). Group with haemoglobin level less than 10 g/dL, 9 g/dL, 8 g/dL and 7 g/dL had lower percentage of patients with good outcome with 64.5%, 61.6%, 59% and 54% respectively. On the other hand, non anaemic group had 93.6% patients with good outcome. The study also concluded that transfusion can be considered when haemoglobin less than 8 g/dL (15). Another study showed that no significant difference in outcome when the haemoglobin level was less than 12 g/dL (mild anaemia) in TBI patients (16). A study done by Carlson *et al* found that the outcome of GOS and Rancho Los Amigos score were worse in the subjects with lowest haematocrit (8). However, in a study done by Talving *et al*, haemoglobin level less than 8 g/dL showed no significant association with GOS (17).

Data from a study done in 1976 showed that mortality was more than 50 percent in the patients diagnosed with severe TBI (18). The percentage had decreased to 30-40 percent over period of time which indicated better results. In a systematic review of progress in mortality by Stein *et al* published in 2010, average mortality rates in severe TBI decline at a rate of 3% per decade from the late 1800s to 1930. Mortality rates steadied from 1930 to 1970, and decreased 9% per decade from 1970 to 1990. Mortality rate due to severe TBI has remained at 35% since (19). The improvement of mortality rate from 1930 to 1970 was due to great technical advances in the treatment of trauma in general and TBI in particular while in the period of 1970 to 1990, it was due to the introduction of CT scanning, ICP monitoring and the more aggressive approaches to TBI management (20, 21). The survivors of severe TBI consist of patients who had good recovery and patients who had permanent disability (22). The outcome post TBI showed continuous improvement until sixth month, and maintaining thereafter. If TBI patients were followed up for 1 year, 40% showed favourable outcome (23). In another study done in America, risk of mortality of severe and moderate TBI was 2.2 times more than control (24).

In traumatic brain injury, red cell transfusion is a common management to treat anaemia to maintain oxygen delivery to the brain and to prevent secondary brain injury (25). Traditionally, liberal transfusion strategy is practised with haematocrit and haemoglobin are maintained above 30% and 10g/dL respectively (26). However, there is no sufficient data to support this practise. On top of that, blood transfusions are known to cause adverse reactions to the recipient such as acute haemolytic transfusion reaction, febrile nonhemolytic transfusion reaction, allergic reaction, transfusion related acute lung injury, transfusion associated circulatory overload, transfusion related immunomodulatory and transfusion related sepsis (27). Hence, the risk and benefit of transfusion have to take into consideration to strategize the treatment to optimize patient's condition.

1.2 Problem statement

Head injury or severe TBI is a common presentation in emergency department in Malaysia. To date, there is no published data in Malaysia about incidence of anaemia and its severity in severe traumatic brain injury patients. Besides, there is also no published data regarding the transfusion practice in severe TBI patients in Malaysia. Without this data, improvement of transfusion service in the area of head trauma cannot be done optimally.

In addition, there is also no study available in Malaysia about the evaluation of the outcome of transfusion in 2 different study group; restrictive and liberal transfusion group. Liberal strategy means packed cell is transfused to maintain haemoglobin level more than 10 g/dL has been adopted for a long time ago. This practice causes high demand for red blood cell product and thus increase overall cost. This include cost from blood procurement, preparation and transfusion process. Higher transfusion rate also will increase the risk of adverse transfusion reaction which sometimes can be fatal.

OBJECTIVES

1.3 General objective

To study the red blood cell transfusion practice in severe isolated TBI patients in HUSM

1.4 Specific objectives

i. To determine the severity of anaemia (mild, moderate and severe) in patients with severe isolated TBI and prevalence of transfusion in each anaemia group

ii. To determine the type of transfusion practice (liberal or restrictive) in severe isolated TBI patients at HUSM and to compare the outcome between 2 groups of transfusion strategy; liberal transfusion strategy group and restrictive transfusion strategy group with post transfusion haemoglobin level, in-hospital mortality and morbidity (pneumonia, urinary tract infection, seizure and deep vein thrombosis).

iii. To determine the incidence of adverse transfusion reaction in severe isolated TBI patients in HUSM

- Haemolytic transfusion reaction
- Allergic reaction
- Febrile nonhaemolytic transfusion reaction
- Transfusion related acute lung injury
- Transfusion associated circulatory overload
- Transfusion associated sepsis

1.5 Alternative Hypothesis

Restrictive transfusion strategy has similar to better outcome compared to liberal transfusion strategy

1.6 Null hypothesis

Liberal transfusion strategy has better outcome compared to restrictive transfusion strategy

Chapter 2:

BODY (MANUSCRIPT)

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

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2.1 Abstract

Introduction: Prevalence of anaemia is high in severe traumatic brain injury (TBI). However, there is no clear transfusion guideline available in the ICU or ward settings in Malaysia. 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. **Methods**: This was a retrospective cohort conducted in Hospital Universiti Sains Malaysia, Kelantan among adult severe isolated TBI patients age above 18 years old. Data from 2012 to 2017 which comprised of patients' demography, clinical variables and outcomes were extracted from the medical records, Laboratory Information System (LIS) and blood bank record (MyTransfusi). Samples were divided into liberal transfusion strategy group (haemoglobin level maintained above 10g/dL) and restrictive transfusion strategy group (haemoglobin level maintained between 7-10g/dL) 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**: A total of 146 adult patients were included in this study. There were 21.9% (n=32) 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. 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 did not have better

outcome compared to restrictive transfusion strategy. Prospective study with larger sample is needed. **Keyword**: TBI, anaemia, RBC transfusion, liberal, restrictive

2.2 Introduction

Traumatic brain injury (TBI) is a common diagnosis seen in emergency department in Malaysia. 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 was responsible for 48.2% of death due to trauma in Malaysia (1).

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 (2). 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 (2). Isolated traumatic brain injury is defined as traumatic brain injury without significant injury of other organs (3). In another article, isolated TBI is defined as patients with head AIS $\geq$ 3 and excluding patients with AIS > 2 in any other body region (4).

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 (28). 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 (29). 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 optimal transfusion practice and haemoglobin threshold had not been established in critically ill patients (29). There were also concern regarding blood supply and safety (29). 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 (30).

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% (8). 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 (9). 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 (10).

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 (29). 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 (29). 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 (29). 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 (29).

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 (26). 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 (27). Hence, the risk and benefit of transfusion have to take into consideration to strategise the treatment to optimise 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.

2.3 Method

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, in neurosurgery. 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, pregnant at the time of the injury and were on antiplatelet or anticoagulant 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, injury severity score, 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 and mortality.

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 (31). 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.

2.4 Results

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).

Table 1 Prevalence of anaemia in TBI 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)

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.

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

In this study, certain 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. 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 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

There was no significant difference between procedures and types of brain injury with transfusion practice (Table 4).

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

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).

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

Independent Variables	Mean ± 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

Table 6 Association between transfusion practice and in-hospital 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: in-hospital mortality)

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

Table 7 Association between transfusion practice and in-hospital 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: in-hospital 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)	
Non RBCT group (Restrictive strategy)	35 (100.0)	0	0.326

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.

2.5 Discussion

Our study recruited 146 subjects. The data shows that majority of the severe isolated 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* in 2016 where 335 out of 756 anaemic patients had haemoglobin level of 7 to 10 g/dL followed by mild anaemia with 333 patients (15). 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 (10).

In terms of transfusion practice, our data recorded 72.6% of 146 patients were transfused with at least 1 unit of red cells. All of severe anaemia patients in this study received red cell transfusion, whereas 34.4% of mild anaemia patients and 79.5% of moderate anaemia patients received red cell transfusion. A study done by George *et al* in 2008 found that in severe isolated TBI patients with severe anaemia, 96% of them were transfused with red cells. As for patients with mild anaemia, 5% of them were transfused and 52% of moderate anemia patients were transfused (32). 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 (33). 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 (33). 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 (34). 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 (35). There was no severe adverse transfusion reaction 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% (35). 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 liberal transfusion to restrictive 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 (36). 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 where both groups showed improvement in post transfusion haemoglobin even though restrictive group had lower mean of post transfusion haemoglobin compared to liberal group. 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 (37). 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 (32). 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 (38).