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Clinical outcomes of restrictive and liberal red blood cell transfusion strategies among septic patients with anemia in perpetual succour Hospital: A single-center cross-sectional analytical study

Eratosthenes S. Polito [1], Mercedes Mujeres[2*]

[1] MD, FPCP, DPSN Department of Internal Medicine, Perpetual Succour Hospital, Cebu City, Cebu, Philippines

[2] MD, FPCP, FPSMID Department of Internal Medicine, Perpetual Succour Hospital, Cebu City, Cebu, Philippines

Abstract

Background: Anemia is a common occurrence in the setting of sepsis. Red blood cell transfusion guidelines correctly promote a general restrictive transfusion approach for anemic hospitalized patients. Such recommendations have been derived from evaluation of specific patient populations, and it is important to recognize that engaging a strict guideline approach has the potential to incur harm if the clinician fails to provide a comprehensive review of the patient's physiological status in determining the benefit and risks of transfusion.

Objectives: To determine the difference in clinical outcomes between Restrictive and Liberal Red Blood Cell Transfusion strategies among septic patients with anemia and to provide local data on the incidence of sepsis, severe sepsis and septic shock as well as the incidence of anemia in these subgroups, and frequency of blood transfusion received in these groups of patients.

Study Design: Retrospective, single-center, cross-sectional chart review study

Participants: All admitted septic patients as defined by the Surviving Sepsis Guidelines 2013, with anemia (hemoglobin levels of ≤9g/dL) who received blood transfusion during their hospital stay.

Results: A total of 12,927 were admitted in Perpetual Succour Hospital last 2015, with 394 (3.05%) patients with sepsis syndrome. Of which sepsis accounts for 40.1%, severe sepsis, 8.4% and septic shock with 51.5%. Among these, only 55 (13.96%) patients had anemia and received blood transfusion with PRBC and were included in the study. Thirty-six percent (n=20) were identified in the restrictive group and 63.6% (n=35) in the liberal group. The mean hemoglobin level in the restrictive group was 5.9 mg/dL (3.01%) and 8.38 mg/dL (3.97%) in the liberal group with p-value 0.007. Transfusion with more than 5 units PRBC is high the restrictive group (40% versus 14.3%, p= 0.031). The use of vasopressors, utilization with mechanical ventilation and aid of renal replacement therapy were similar in the two intervention groups. No association of restrictive versus liberal transfusion in terms of acute lung injury, renal failure and coagulopathy.

Conclusion: This study suggests that there is no significant difference between the restrictive and liberal red blood cell transfusion strategies in terms of mortality and overall morbidity, number of blood units transfused and number of subjects being transfused.

Keywords: sepsis, severe sepsis, septic shock, restrictive blood transfusion, liberal blood transfusion

Introduction

Sepsis has been around since the dawn of time as far back as 100 BC, when Marcus Terentius Varro, the ancient Roman scholar and writer in 116 BC quoted, "Small creatures, invisible to the eye, fill the atmosphere, and breathed through the nose cause dangerous diseases". Progress has been made over the past half-century in identifying and treating sepsis however, it still remained as an ongoing challenge for clinicians around the world. Recent researches have reported a high population-based incidence in different countries with a worldwide incidence of approximately 19 million cases per year and an estimate of 240.4 cases per 100,000 per year according to American studies [1]. In the Philippines, however, national-level accounts on sepsis are scarce, to date, the only data obtainable was the prospective cohort observational study done in UP-Philippine General Hospital last 1999, to which they reported a high incidence of 24.8% related to hospital-treated sepsis [2].

Several factors have contributed to the high incidence and mortality, one of which is anemia. Anemia is a common feature during sepsis. It occurs due to iatrogenic blood loss, depression of serum iron levels and erythropoietin production, and a decreased lifespan of erythrocytes that take place in the setting of sepsis. Moreover, sequestration of fluids, renal failure and increase of intravascular space may additionally influence the change in hemoglobin concentration during intravenous fluid administration in the acute phase of sepsis.

The primary approach to septic patients is to optimize circulation and support organ perfusion by prompt administration of antibiotics, infection source control and resuscitation with intravenous fluids and vasopressor/inotropic drugs [3]. These interventions may be supplemented with blood transfusion in case of anemia and persistent hypoperfusion. Several recent, observational, multicenter studies reported that approximately one third of critically ill patients received a blood transfusion at one time or another, however, the benefits and harms of different hemoglobin thresholds for transfusion have not been established [4]. In a recent systematic review of 45 observational studies reporting the impact of transfusions on patient outcome (mortality, infections, acute respiratory distress syndrome) in populations of trauma, general surgery, orthopedic surgery, acute coronary syndrome, and ICU patients, Marik and Corwin identified RBC transfusion as an independent predictor of death [5].

Although the optimum hemoglobin concentration for patients with severe sepsis has not been specifically investigated, the Transfusion Requirements in Critical Care trial suggested that a hemoglobin level of 7 to 9 g/dL, compared with 10 to 12 g/dL, was not associated with increased mortality in critically ill adults. In addition, the Surviving Sepsis Guidelines advocate restricting RBC transfusion in adults with severe sepsis or septic shock until hemoglobin falls below 7.0 g/dL (restrictive transfusion strategy), and not transfusing above 9.0 g/dL (liberal transfusion strategy) if ischemic heart disease, severe hypoxemia, or active bleeding is not present.

Research Question

Is there a difference in clinical outcomes between Restrictive and Liberal Red Blood Cell Transfusion strategies among septic patients with anemia Perpetual Succour Hospital?

Operational Definition of Terms

Sepsis

Sepsis as defined by the Surviving Sepsis Guidelines 2013 is the presence (probable or documented) of infection together with systemic manifestations of infection.

Severe sepsis

Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion.

Septic shock

Septic Shock is defined by Surviving Sepsis Guidelines 2013 as sepsis-induced hypotension (systolic blood pressure (SBP) < 90mm Hg or mean arterial pressure (MAP) < 70mm Hg or a SBP decrease > 40mm Hg or less than two standard deviations below normal for age in the absence of other causes of hypotension) persisting despite adequate fluid resuscitation.

Restrictive Transfusion Strategy

It is a transfusion strategy with a transfusion threshold of less than or equal to 7 g/dl.

Liberal Transfusion Strategy

It is a transfusion strategy with a transfusion threshold of less than or equal to 9 g/dl.

Significance of the Study

This study aims to determine the difference in clinical outcomes of restrictive and liberal red blood cell transfusion strategies among patients with sepsis-induced anemia in a tertiary hospital.

According to the article by Global Health Journal Article in 2012 entitled, "Assessing Available Information on the Burden of Sepsis", there are no studies on the incidence, prevalence, mortality or case-fatality from sepsis in developing countries were found. To add, little is known regarding the epidemiology of sepsis in the Philippines. This, in turn, will provide clinical information based on the epidemiological data derived from our own patient population that will be incorporated in the clinical judgment regarding transfusion benefits and risks in our care plan.

This will also provide local data regarding incidence of sepsis, severe sepsis and septic shock, as well as anemia in a septic patients and frequency of blood transfusion received in these subgroups.

General Objective

To determine the difference in clinical outcomes between Restrictive and Liberal Red Blood Cell Transfusion strategies among septic patients with anemia in Perpetual Succour Hospital.

Specific Objectives

- To provide local data on the incidence of sepsis, severe sepsis and septic shock as well as the incidence of anemia in these subgroups, and frequency of blood transfusion received in these groups of patients.
- To establish patient demographics (Age, Sex, Co-morbidities, Hemoglobin levels on admission)
- To determine the primary outcome: mortality
- To determine intermediate outcomes (Use of life supports:
- Number days on vasopressors
- Number of days until the lysis of fever
- Use of oxygen supplementation
- Days on mechanical ventilation
- Assistance with renal replacement therapy (Hemodialysis)
- To identify clinically relevant factors
- Blood cultures and cultures from sterile sites
- Organs dysfunction
- Focus of sepsis
- Pulmonary
- Abdomen
- Genito-urinary tract
- Skin and soft tissue and others
- To identify number of patients with serious adverse reactions
- Allergic reaction
- Transfusion-associated acute lung injury (TRALI)
- Transfusion-associated circulatory overload (TACO)

Review of Related Literature

The Transfusion Requirement in Critical Care (TRICC) trial showed a significant increase in cardiac and pulmonary complications and a trend toward increased mortality in the liberal transfusion group during patients intensive care stay. In subgroup analysis, younger (less than 55 years old) or less critically ill (with APACHE II scores of less than 20) patients randomized to a liberal strategy had a statistically significant increase in mortality [6].

In 2002, Vincent et al. published a prospective observational study entitled, Anemia and Blood Transfusion in Critically Ill Patients (ABC) in 146 Western European Intensive Care Units, concluded that receipt of a blood transfusion increased a patients odds of dying and increased patients length of stay in the ICU [4].

Compared with liberal strategies, restrictive transfusion strategies were associated with a reduction in the number of red blood cell units transfused and number of patients being transfused, but mortality, overall morbidity, and myocardial infarction seemed to be unaltered. Restrictive transfusion strategies are safe in most clinical settings. Liberal transfusion strategies have not been shown to convey any benefit to patients.

Mirski, in 2015 on his paper, "Restrictive and Liberal Red Cell Transfusion Strategies in Adult Patients: Reconciling Clinical Data with Best Practice", concluded that the majority of clinical settings, a restrictive RBC transfusion strategy is cost-effective, reduces the risk of adverse events specific to transfusion, and introduces no harm [7].

In 2016, Lars Holst in the Danish Medical Journal construed that the transfusion practice has slowly moved towards a

more restrictive approach due to emerging trial data supporting still lower 'triggers' for transfusion of RBCs, subsequent revised clinical guidelines and increased focus on the concept of blood management. RBC transfusion is highly controversial because data from randomized clinical trials in different clinical settings are still lacking including patients with septic shock and practices are highly based on tradition and theory because of that [8].

Lastly, Laudico et al in 2000 on his paper, "Fluids for Resuscitation, Blood Transfusion, Assessment of Volume Resuscitation, Nutritional Support, Pharmacologic Cardiovascular Support", suggested that the criteria for PRBC transfusion should be based not only on the Hemoglobin level but to consider the patient's clinical condition and risk for inadequate oxygenation as well. Transfusion is rarely indicated when the hemoglobin concentration is greater than 10g/dl and is almost always indicated when it is less than 6g/dl. Between 6 and 10 g/dl, RBC transfusion should be based on the patient's risks for complications or inadequate oxygenation.

Scope and Limitations of the Study

This study aims to compare the two transfusion strategies (Restrictive group and Liberal group) categorized according to their hemoglobin level triggers or threshold among septic patients with anemia in Perpetual Succour Hospital. The outcomes were measured according to number of PRBC transfused, lung function measured as P/F ratio, acute kidney injury, coagulopathy, adverse reactions, assistance with mechanical ventilator, aid of renal replacement therapy, use of vasopressors, and supplementation with oxygen.

The current study has several limitations. The available census makes drawing conclusion difficult. Although this study was able to capture a robust amount of data involving septic patients with anemia in this institution, we cannot exclude the possibility of unaccounted or missing data, which may cause bias and undetected differences in baseline characteristics.

Methodology

Study Design and Setting

In this retrospective, single-center, cross-sectional, chart review design done in a tertiary hospital in Cebu City, Cebu, a general hospital database was used with the clinical information of all patients admitted with ICD code A41.9 or disease index for sepsis, who had an admitting hemoglobin level of at least 9 mg/dL and underwent blood transfusion with packed red blood cells obtained Medical Records Section was utilized.

Study Population and Data Collection

Inclusion Criteria

All admitted patients with anemia (hemoglobin levels of less than or equal to 9g/dL) with sepsis syndrome as defined by the Surviving Sepsis Guidelines 2013 who, received blood transfusion during their hospital stay.

Exclusion Criteria

- Patients who had history of previous serious adverse reaction with blood product
- Patients with life-threatening bleeding
- Patients with known hematologic diseases and malignancies

Data Collection

Retrieval of discharged charts of admitted patients in Perpetual Succour Hospital from January 2015 to December 2015 in the Medical Records Database was done using the query: Sepsis or ICD code A41.9. A total of 12,927 were admitted with 534 patients identified to have a diagnosis of sepsis. Fifty-eight (58) charts were excluded during the screening (26 charts were incomplete, 32 charts were considered lost). With further evaluation, only 394 patients were identified to have sepsis as defined by the Surviving Sepsis Guidelines 2013, and 55 had anemia and received blood transfusion with PRBC and were thus included in the study. Afterwards, patients were assigned into two study groups according to their pre-hemoglobin level transfusion threshold, the Restrictive Transfusion Threshold group and the Liberal Transfusion Threshold group.

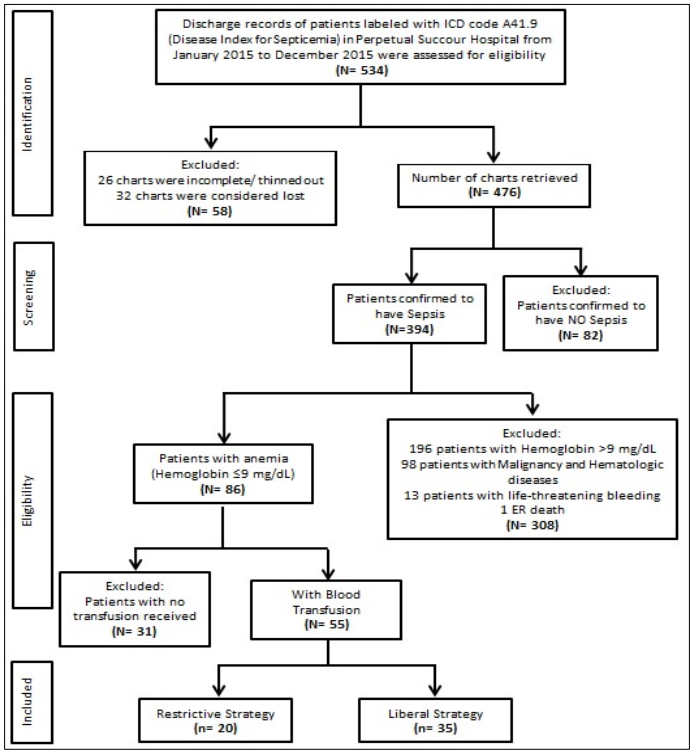

Fig 1: Flow diagram illustrating the details on how the study population was obtained.

Baseline demographic information collection was completed which includes the Age, Sex, Co-morbidities, and Hemoglobin levels on admission. In addition, primary outcome was determined, reported as death or discharge. Intermediate outcomes were also established with these parameters:

- Number days on vasopressors
- Number of vasopressors used
- Number of days until the lysis of fever
- If with oxygen supplementation at some point of hospital stay (answerable by Yes or No)
- Assistance with mechanical ventilation (answerable by Yes or No)
- Assistance with renal replacement therapy (answerable by Yes or No)

Moreover, identification of clinically relevant factors will be accomplished which includes:

- Blood cultures and cultures from sterile sites (Answerable by Positive or Negative)
- Assessment of organ dysfunction variables
- Lung function were measured as a ratio of partial pressure arterial oxygen and fraction of inspired oxygen (P/F ratio) from a sample of arterial blood gas
- Acute Kidney Injury, as measured by the change in the creatinine levels and/or urine output
- Coagulopathy was assessed, as measurement of prothrombin time (INR), activated partial thromboplastin time (aPTT) and platelet dysfunction
- Focus of sepsis were identified based on the history, physical exam and laboratory results
- Lung
- Gastrointestinal
- Genito-urinary tract
- Skin and soft tissue and others

Lastly, documentation on the number of patients with serious adverse reactions will be involved which comprises, gauged Allergic reactions, Transfusion-associated acute lung injury (TRALI) and Transfusion-associated circulatory overload (TACO).

Statement of Confidentiality

The data gathering of the study does not include the patient's name, any marks or personal information, description and the patient's privacy are being preserved. Other information that can affect the patient's financial status, or lead into social stigmatism or discrimination is not included. The researcher guaranteed that strict standards were observed in this paper. In addition, the researcher did not seek any financial support from any pharmaceutical companies and did not provide any financial assistance to the participants in the study.

Institutional Approval

The study was approved by the Institution Ethics and Review board (Level III).

Sample Size Determination

The PSH 2015 census reported 86 patients who are admitted to have sepsis syndrome as well as anemia to begin with. A sample size of 55 was determined using conservative capture rate of 50% estimated at 95% confidence level with ± 7.98 margin of error.

Statistical Analysis

All data retrieved was encoded in Microsoft Excel 2015. This study used frequency and percentage distribution in expressing all the categorical data. Likewise, mean and standard deviations will be utilized as well as indicators of continuous information. In comparing average age between the two groups, Mann Whitney U Test, a non-parametric test was used. For the rest of comparison of test of association, Chi-Square Test with 2x2 Fischer exact test adjustment was used. Any associated p-values lesser than 0.05 alpha were considered significant. IBM SPSS was used in processing the data for accuracy purposes of all computations.

Results

Study Population

A total of 12,927 were admitted in Perpetual Succour Hospital last 2015, with 394 (3.05%) patients with sepsis syndrome. Of which sepsis accounts for 40.1%, severe sepsis, 8.4% and septic shock with 51.5%. Among these, 86 had anemia on admission with a hemoglobin level of ≤ 9.0 mg/dL and only 55 (13.96%) patients received transfusion with PRBC and were thus included in the study. Table 1 is the summary of all patients included with their baseline demographic features.

Table 1: Baseline demographic features of the study population

	Total	**Restrictive Group**	**Liberal Group**	
Characteristics	**N=55**	**n=20**	**n=35**	**p-value**
Age mean years[sd]	65.8[16.99]	65.1[16.19]	66.2[17.66]	0.820
Sex				
Male	29[52.7%]	10[50%]	19[54.3%]	0.489
Female	26[47.3%]	10[50%]	16[45.7%]	
Sepsis Syndrome				
Sepsis	22[40%]	7[35%]	15[42.9%]	0.567
Severe Sepsis	4[7.3%]	1[5%]	3[8.6%]	0.624
Septic Shock	29[52.7%]	12[60%]	17[48.6%]	0.414
Comorbidities				
Hypertension	12[21.8%]	6[30%]	6[17.1%]	0.267
CHF	3[5.5%]	0[0%]	3[8.6%]	0.178
DM	11[20%]	2[10%]	9[25.7%]	0.161
BA	1[1.8%]	1[5%]	0[0%]	0.182
HPN+ DM	10[18.2%]	1[5%]	9[25.7%]	0.055
HPN+DM+BA	1[1.8%]	0[0%]	1[2.9%]	0.446
None	17[30.9%]	10[50%]	7[20%]	0.021
Hemoglobin Level				
mean[sd]	7.49[3.88]	5.9[3.01]	8.39[3.97]	0.007
#PRBC transfused				
1 unit	13[23.6%]	4[20%]	9[25.7%]	0.631
2 units	11[20%]	3[15%]	8[22.9%]	0.483
3 units	10[18.2%]	1[5%]	9[25.7%]	0.055
4 units	8[14.5%]	4[20%]	4[11.4%]	0.386
>=5 units	13[23.6%]	8[40%]	5[14.3%]	0.031

Abbrevations: CHF- Congestive heart failure; DM- Diabetes Mellitus; HPN- Hypertension; BA- Bronchial asthma; PRBC- Packed red blood cell.

With this table, 36% (n=20) were identified in the restrictive group and 63.6% (n=35) in the liberal group.

Sepsis occurs in all age groups however majority of the patients belonged to the elderly group with a mean age of 65.8 years, most were males with 29 (52.7%) and 26 (47.3%) females. Sepsis was high in the liberal group (42.8% versus 35%) but septic shock was more prevailing in the restrictive group (60% versus 48.6%).

Chronic comorbid medical conditions were common in majority; among these were hypertension (21.8%), type II diabetes mellitus (20%), and then hypertension with concomitant diabetes (18.2%). Fifty percent of the restrictive don't have any comorbidity compared to 20% in the liberal group with p-value 0.021.

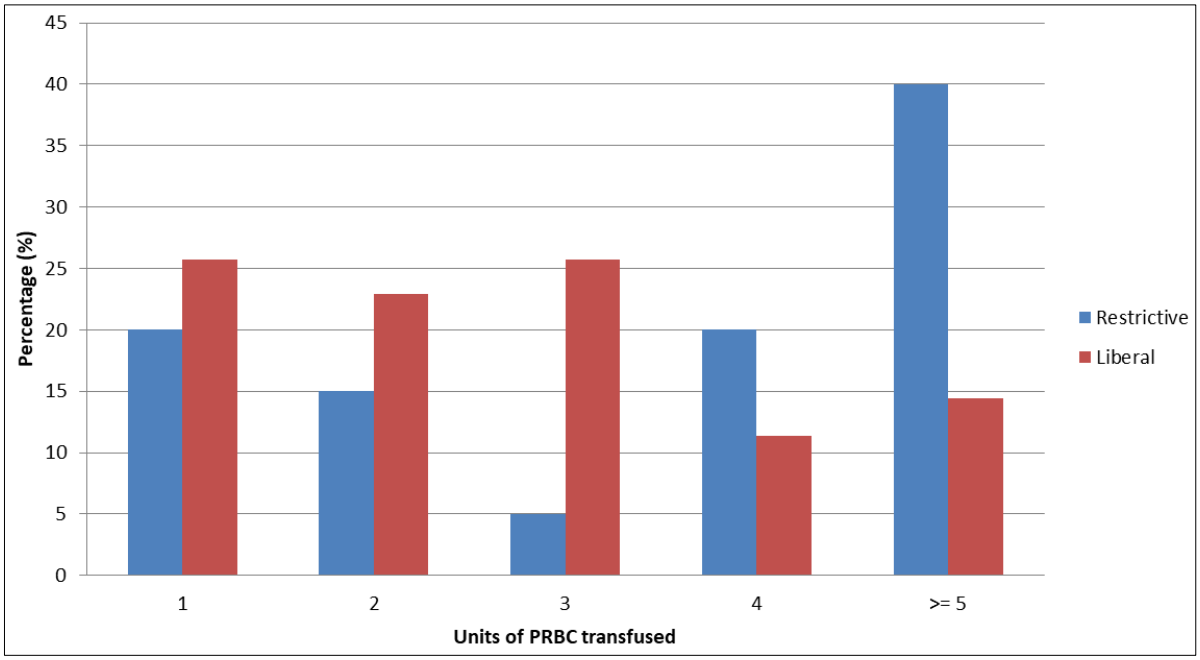

Fig 2: Amount of packed red blood cell (PRBC) transfused

Anemia in the setting of sepsis is not uncommon. Thirty-five patients (63.6%) have hemoglobin level of <9.0 mg/dL with a mean of 8.9 mg/dL while there are 20 (36.6%) patients have hemoglobin level of <7.0 mg/dL with a mean of 5.9 mg/dL. The decision to transfuse was driven by the triggers of hemoglobin levels. Transfusion with 1 to 3 units of packed red blood cell was predominant on the liberal transfusion threshold group but transfusion with 4 or more units was significantly more frequent in the restrictive group (40% versus 14.3%) with a p-value of 0.031 as shown in Table 1 and Figure 2.

Table 2: Admitting WBC and microbiologic features of the study population

Variables	Total	Restrictive Group	Liberal Group	
	N=55	n=20	n=35	p-value
White Blood Count				
mean[sd]	16.89[10.27]	16.39[9.44]	17.18[10.59]	0.180
<=5, 000	6[10.9%]	1[5%]	5[14.3%]	0.288
>= 10,000	46[83.6%]	18[90%]	28[80%]	0.335
Normal with 10% immature cells	[0%]	[0%]	[0%]	1.000
Normal with NO immature cells	3[5.5%]	1[5%]	2[5.7%]	0.911
Focus of Infection				
Lung	22[40%]	6[30%]	16[45.7%]	0.252
GI	5[9.1%]	1[5%]	4[11.4%]	0.425
GUT	6[10.9%]	1[5%]	5[14.3%]	0.288
SST	6[10.9%]	3[15%]	3[8.6%]	0.462
Lung+ GUT	4[7.3%]	1[5%]	3[8.6%]	0.624
Lung+ SST	[0%]	[0%]	[0%]	1.000
Lung+ SST+GUT	3[5.5%]	1[5%]	2[5.7%]	0.911
Lung+ Others	2[3.6%]	2[10%]	0[0%]	0.057
GUT+ SST	2[3.6%]	1[5%]	1[2.9%]	0.683
GUT+ Others	2[3.6%]	1[5%]	1[2.9%]	0.683
GI + SST	1[1.8%]	1[5%]	0[0%]	0.182
GI+ GUT	1[1.8%]	1[5%]	0[0%]	0.182
Others	1[1.8%]	1[5%]	0[0%]	0.182
Sepsis workup				
Blood	7[12.7%]	5[25%]	2[5.7%]	0.039
Urine	2[3.6%]	0[0%]	2[5.7%]	0.276
Sputum	3[5.5%]	0[0%]	3[8.6%]	0.178
Wound	2[3.6%]	1[5%]	1[2.9%]	0.683
Blood+ Urine	6[10.9%]	2[10%]	4[11.4%]	0.870
Blood+ Sputum	13[23.6%]	5[25%]	8[22.9%]	0.857

Blood+ wound	5[9.1%]	3[15%]	2[5.7%]	0.249
Blood+ Urine+ Sputum	7[12.7%]	1[5%]	6[17.1%]	0.194
Blood+Urine+ Wound	3[5.5%]	2[10%]	1[2.9%]	0.262
Blood +Urine+ Others	1[1.8%]	0[0%]	1[2.9%]	0.446
Blood+Sputum+Wound	1[1.8%]	0[0%]	1[2.9%]	0.446
Blood+ Others	1[1.8%]	1[5%]	0[0%]	0.182
Others	4[7.3%]	0[0%]	4[11.4%]	0.116

Abbreviations: WBC- White Blood Count; GUT- Genitourinary; SST- Skin and Soft tissues; GI- Gastrointestinal.

Clinical Characteristics

Table 2 shows the data of the microbiologic features of the study population. Majority of the two study groups have predominance of leukocytosis (83.6%) with a mean WBC count of 16,390 µL in the restrictive group and 17, 180 µL in the liberal group. Sepsis is not a random occurrence and is usually associated with direct introduction of microbes in to the bloodstream via several routes. Table 2 provides list of the focus of infection and sources of cultures taken during the course of hospital stay. The most common condition leading sepsis in this study was pneumonia (40%), urinary tract infection (10.9%), skin and soft tissue infections (10.9%), and gastrointestinal infections (9.1%). Forty-three percent of patients have multiple foci of infection.

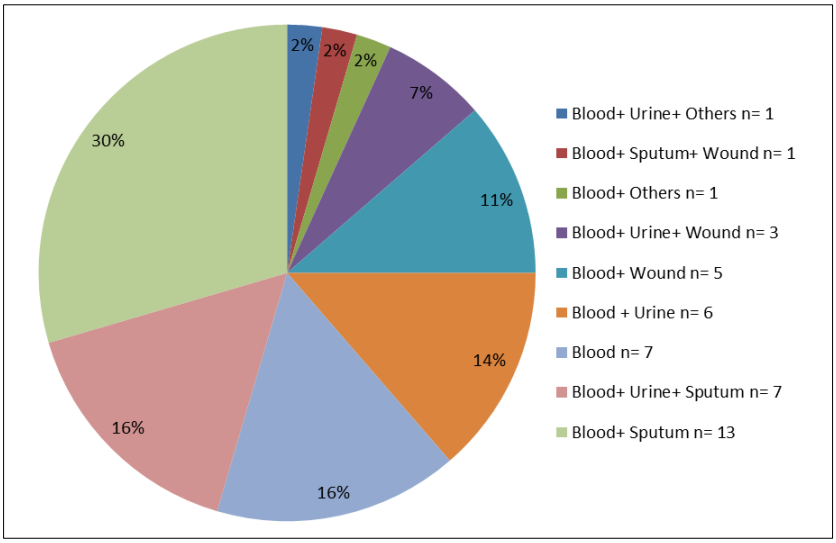

Fig 3: Distribution of the study population who yielded positive for blood culture and their corresponding sterile site/s, (n=44)

Blood cultures were obtained upon admission to facilitate isolation of a specific organism responsible for infection. There are 44 individuals (80%) that yielded positive in blood cultures while only 11 (20%) turned to be negative. Ninety-five percent and 83.3% of the population turned positive in the restrictive and liberal group, respectively. Figure 4 demonstrates the 44 subjects who came positive in their blood cultures with the most frequent sterile site involved were sputum 13 (30%), urine and sputum 7 (16%), urine 6 (14%) and lastly wound with a frequency of 5 (11%).

Organ Dysfunction

The ratio of partial pressure arterial oxygen and fraction of inspired oxygen (P/F ratio) from a sample of arterial blood gas was used to determine the degree of lung injury. Fifty percent of the subjects have a P/F ratio of less than 300, which is evident in the liberal group with a frequency of 19 (54.3%) compared to restrictive group with a frequency of only 9 (45%) as revealed in Table 3.

Table 3: Selected organ dysfunction variables involve in the setting of sepsis

Variables	Total	Restrictive Group	Liberal Group	
	N=55	n=20	n=35	p-value
Lung Function				
P/F ratio <=300	28[50.9%]	9[45%]	19[54.3%]	0.508
P/F ratio >300	17[30.9%]	8[40%]	9[25.7%]	0.270
Not taken	10[18.2%]	3[15%]	7[20%]	0.644
Acute Kidney Injury				
Increase of 0.3 mg/dL from the baseline creatinine	17[30.9%]	7[35%]	10[28.6%]	0.620
Increase of 50% from the baseline creatinine	17[30.9%]	6[30%]	11[31.4%]	0.912
Decrease in the urine output of 0.5cc/hr	6[10.9%]	4[20%]	2[5.7%]	0.102
None	15[27.3%]	3[15%]	12[34.3%]	0.122
Protime				
INR >1.5	16[29.1%]	8[40%]	8[22.9%]	0.178
INR <= 1.5	34[61.8%]	12[60%]	22[62.9%]	0.834
Not taken	5[9.1%]	0[0%]	5[14.3%]	0.076
aPTT				
Prolonged >30 sec from the control	4[7.3%]	4[20%]	0[0%]	0.006
Not Prolonged >30 sec from the control	30[54.5%]	12[60%]	18[51.4%]	0.539

Not taken	21[38.2%]	4[20%]	17[48.6%]	0.036
Platelet dysfunction				
Thrombocytopenia <150,000	14[25.5%]	6[30%]	8[22.9%]	0.559
No Thrombocytopenia	41[74.5%]	14[70%]	27[77.1%]	

Abbrevations: P/F ratio- ratio of partial pressure arterial oxygen and fraction of inspired oxygen; INR- international normalized ratio; aPTT- Activated partial thromboplastin time

Acute kidney injury (AKI) often accompanies sepsis. Forty (72.2%) individuals included in the study have some degree of kidney failure, measured as an increase of 0.3 mg/dL or increase to 50% from the baseline creatinine or a decrease in the urine output to less than 0.5 mL per hour. In the restrictive group 80.9% (n= 17) have AKI compared to 65.7% (n=23) in the liberal group.Coagulopathy, signaled by a mild elevation of the thrombin time or activated partial thromboplastin time (aPTT) or a moderate reduction in the platelet count, is extremely common. Twenty-nine percent have elevated prothrombin time, which is common in the restrictive group, with incidence of 40% compared to liberal group with only 22.9%. Prolonged aPTT to more than 30 seconds from the control is statistically high in the restrictive group. Thrombocytopenia is estimated to have occurred in only 25.5% of the individuals which are more apparent in the restrictive group.

Clinical Outcomes

Table 4 compares the outcome of the two groups. There was only one incidence of transfusion reaction lung injury noted in this study which is seen in the liberal threshold transfusion group. No documentation of transfusion-associated circulatory overload and allergic reactions were reported. The assistance of mechanical ventilator was only seen in 32.7% among the subjects which is predominant in the liberal group (40% versus 20%) but not statistically significant with a p-value of 0.110. Renal replacement therapy was noted only in 25.5% of the study population which is more evident in the restrictive group (30% versus 22.9%). The use of vasopressor was observed in 54.5%, fever for more than 3 days was noticed in 30.9% but all of the patients at some point of their hospital stay had oxygen supplementation.Of the 55 individuals who were included in the study, 18 (32.7%) patients died and 37 (67.3%) were discharged. Mortality is high in the restrictive group with 40% (n=8) compared to the liberal group with only 28.6% (n=10) but not statistically significant with a p-value of 0.282.

Table 4: Comparison of the primary and secondary outcomes of the two groups

Outcome Variables	**Total**	**Restrictive Group**	**Liberal Group**	
	N=55	n=20	n=35	p-value
Primary Outcome Discharged	37[67.3%]	12[60%]	25[71.4%]	0.282
Died	18[32.7%]	8[40%]	10[28.6%]	
Adverse reactions				
Allergic reaction	[0%]	[0%]	[0%]	1.000
TRALI	1[1.8%]	0[0%]	1[2.9%]	0.446
TACO	[0%]	[0%]	[0%]	1.000
None/ No response	54[98.2%]	20[100%]	34[97.1%]	0.446
Use of Mechanical Ventilator				
Yes	18[32.7%]	4[20%]	14[40%]	0.110
No	37[67.3%]	16[80%]	21[60%]	
Renal Replacement Therapy				
Yes	14[25.5%]	6[30%]	8[22.9%]	0.391
No	41[74.5%]	14[70%]	27[77.1%]	
Number of Vasopressors used				
0	25[45.5%]	8[40%]	17[48.6%]	0.539
1	17[30.9%]	4[20%]	13[37.1%]	0.186
2	10[18.2%]	5[25%]	5[14.3%]	0.322
3	3[5.5%]	3[15%]	0[0%]	0.018
Number of days on Vasopressor/s				
At day 5	21[38.2%]	6[30%]	15[42.9%]	0.345
At day 14	6[10.9%]	3[15%]	3[8.6%]	0.462
At day 28	2[3.6%]	2[10%]	0[0%]	0.057
None	26[47.3%]	9[45%]	17[48.6%]	0.799
Number of days febrile				
<= 3 days	36[65.5%]	11[55%]	25[71.4%]	0.218
>3 days	17[30.9%]	7[35%]	10[28.6%]	0.620
None	2[3.6%]	2[10%]	0[0%]	0.057
O2 supplementation				
Yes	55[100%]	20[100%]	35[100%]	1.000
No	0[0%]	0[0%]	0[0%]	
Surgery				
Emergency	13[23.6%]	6[30%]	7[20%]	0.401
Elective	8[14.5%]	2[10%]	6[17.1%]	0.470
None	34[61.8%]	12[60%]	22[62.9%]	0.834

Abbreviations: TRALI- Transfusion-related acute lung injury; TACO- Transfusion- associated circulatory overload; O2 supplementation- oxygen supplementation.

Discussion

Incidence of Sepsis and Sepsis-related Anemia

Perpetual Succour Hospital, a tertiary institution in Cebu City, Cebu that had a total admissions of 12, 953 last 2015 with 394 patients clinically diagnosed to have sepsis with a reported incidence of 3.04%, which is higher to the overall incidence of approximately 2% in the developed countries as accounted by Vincent JL et al., on his report, "Results on the SOAP Study", published by the Critical Care Medicine Journal in 2006. Sepsis accounts for 40.1%, severe sepsis, 8.4% and septic shock with 51.5%. Out of 394 patients, only 55 received blood transfusion due to sepsis-induced anemia with an incidence of 13.9%, which is lower compared to the incidence of 40%, reported by the CRIT Study published by the Critical Care Medicine Journal in 2004. The recommendations of the Surviving Sepsis Campaign 2013 regarding blood transfusion in patients with septic shock are complex and include a recommendation that transfusion threshold should be a hemoglobin level of less than 7 g per deciliter. Difference in the outcome may be due to the fact that there are limited data supporting these recommendations that causes many clinicians not to adhere on this guideline.

Transfusion Threshold Strategy

This study was designed specifically to determine the difference in the clinical outcomes between Restrictive and Liberal Red Blood Cell Transfusion strategies among septic patients with anemia. In the third world setting, where health resources are limited, it is important to cost-effectively allocate the resources available based on the epidemiological data derived from our own patient population.

Restrictive transfusion strategies were associated with increased in the number of red blood cell units transfused and number of patients being transfused. Transfusion with >=5 units of PRBC is significantly high in the restrictive group with 40% incidence versus 14.3% in the liberal group (p-value of 0.031). In contrast to the articles released by the British Medical Journal in 2015 entitled, "Restrictive Versus Liberal Transfusion Strategy for Red Blood Cell Transfusion: Systematic Review of Randomized Trials with Meta-Analysis and Trial Sequential Analysis", restrictive group was associated with reduced number of PRBC units transfused as well as the number of patients being transfused. For decades, it was considered that a hemoglobin concentration of 10g/dL, or a hematocrit of 30%, or the "10/30 rule", represented the lowest level acceptable. It was believed that hematocrit at around 30% or below this level, oxygen delivery and consumption were decreased in critically ill patients and mortality will be increased. This line of reasoning then led to the common practice of maintaining the "10/30 rule" as the standard and convenient "transfusion triggers" which may somehow explain why this study had a dissimilar outcome [14].

Intermediate Outcome

The use of vasopressors, utilization of life support with mechanical ventilation and aid of renal replacement therapy were similar in the two intervention groups. The analysis of this study showed no association of restrictive versus liberal transfusion in terms of adverse events such as acute lung injury, renal failure, and hemorrhage. We recorded only one serious adverse reaction to blood transfusion, but serious adverse reactions are rare events in general. When looking at the results of other studies, several problems were documented with RBC transfusions, such as infection, pulmonary complications such as TRALI and transfusion-associated circulatory overload (TACO), transfusion-related immunomodulation (TRIM) and multi-organ failure, and increased mortality, as conveyed in the articles, "Proceedings of a Consensus Conference: Towards an Understanding of TRALI" by Goldman M et al., in 2005, "Transfusion-Related Acute Lung Injury: Definition and Review" published by Critical Care Medicine Journal in 2005, as well "Report of the American-European Consensus Conference on Acute Respiratory Distress Syndrome: Definitions, Mechanisms, Relevant Outcomes, and Clinical Trial Coordination" released by the Journal of Critical Care last 1994. The result of this study may be opposing to the studies mentioned which is likely due the difference in methodology, inherent limitations of the retrospective study such as some data were not completely documented, as well as the big disparity in the number of target population.

Mortality

We did not find any association with mortality, when comparing restrictive transfusion strategies with liberal transfusion strategies (40% versus 28.6%, p-value 0.282), which is consistent with the data from the recent Transfusion Requirements In Septic Shock (TRISS) trial, which randomized 1005 patients with septic shock in the intensive care unit, in which there was no difference in mortality or morbidity with the use of pre-stored leucocyte reduced red blood cells at a transfusion trigger of 7 versus 9 g/dL. On the contrary, a review published in 2014 including 6936 patients from 19 trials assessing the impact of red blood cell transfusion with pooled data from three trials (2364 patients) using restrictive hemoglobin transfusion triggers of 7 g/dL showed reductions in in-hospital mortality. Differences in the outcomes are likely to be due to differences in the blood transfusions per se. Heightened awareness of the possible risks of blood transfusion have led to changes in blood preparation so that blood transfusions are perhaps safer today in terms of viral transmission than they were a decade ago. Leukodepletion, which may reduce some of the negative immunosuppressive effects of transfusions, has also been widely implemented. The leukocyte component of transfused blood has been implicated in some of the adverse effects associated with blood transfusion, including transfusion-related immunomodulation and transfusion-related acute lung injury.

Conclusion

This study concludes that there is no significant association between the two study groups, the restrictive and the liberal transfusion threshold group, in terms of mortality and overall morbidity, number of blood units transfused and number of people being transfused.

Recommendation

It is reasonably clear there is no clear cut hemoglobin trigger, and for the same level of hemoglobin, some patients will do well, whereas others will not. Thus, the decision to transfuse a patient should be individualized. Results may be not significant but whether we go restrictive or liberal, restrictive strategy will be cost effective and will reduce the risk of adverse events specific to transfusion.

The researcher primarily would like to recommend further multicenter and prospective design studies to establish firm

evidence to guide transfusion in subgroups of patients, specifically sepsis-induced anemia and to give efforts to include on the modifiable and non-modifiable clinical variables independently associated with mortality among septic patients have to be identified in order to provide guide to the physicians in providing optimum care.

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