RED BLOOD CELLS TRANSFUSION PRACTICE IN PAEDIATRIC CARDIAC SURGERY AT THE NATIONAL HEART INSTITUTE (IJN) OF MALAYSIA

BY

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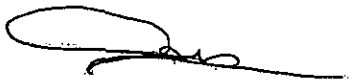
DISCLAIMER

I hereby declare that this research has been sent to Universiti Sains Malaysia (USM) for the degree of Master of Medicine (Transfusion Medicine). I certify that the work in this dissertation is my own except for the quotations and summaries, which have been duly acknowledged and I have no financial interest in the instrument or materials used in this study.



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LIST OF ABBREVIATIONS

RBC	Red blood cells
CHD	Congenital Heart Disease
HB	Haemoglobin
HCT	Hematocrit
IJN	Institut Jantung Negara
PICU	Paediatric Intensive Care Unit
RACHS-1	Risk Adjustment in Congenital Heart Surgery
ROTEM	Rotational Thromboelastometry
RAP	Retrograde autologous priming

LIST OF APPENDICES

ABSTRAK

Pengenalan: Pembedahan jantung pediatrik yang dilakukan dengan *"cardiopulmonary bypass"* (CPB) biasanya dikaitkan dengan insiden transfusi sel darah merah (SDM) yang tinggi. Transfusi SDM dikenalpasti berkemungkinan mengakibatkan kesan sampingan termasuk morbiditi selepas pembedahan. Kajian ini bertujuan untuk mengenal pasti faktor-faktor ramalan transfusi SDM dalam tempoh perioperatif dan mengkaji kaitan transfusi tersebut dengan komplikasi pasca pembedahan bagi memudahkan pengurusan pesakit dan membimbing doktor membuat keputusan transfusi darah yang efektif.

Kaedah: Kajian retrospektif rentas silang, yang dilakukan di IJN, merangkumi 243 pesakit pembedahan jantung pediatrik di bawah usia 18 tahun yang menjalani pembedahan CPB pada tahun 2018.

Keputusan: Sebelum pembedahan, 4.5% pesakit diberikan transfusi SDM didapati mempunyai haemoglobin (Hb) dengan nilai min 8.3 hingga 9.8 g/dL. Semasa pembedahan, kumulatif 99.2% pesakit menerima transfusi SDM dengan faktor ramalan berikut bagi subkumpulan penerima SDM isipadu yang tinggi; usia muda, berat badan rendah, skor RACHS-1 ≥ 3 dan mempunyai masa CPB terpanjang berbanding kumpulan lain. Status transfusi SDM sebelum dan semasa pembedahan didapati tidak mempengaruhi status transfusi SDM selepas pembedahan secara signifikan. Analisis kami menunjukkan bahawa 25.9% populasi yang dikaji menerima isipadu transfusi SDM yang rendah selepas pembedahan, sementara 11.5% yang lain menerima isipadu transfusi SDM yang tinggi. Tempoh CBP dan pembedahan adalah didapati jauh lebih panjang

dalam subkumpulan penerima transfusi SDM isipadu tinggi selepas pembedahan. Durasi bantuan pernafasan mekanikal yang panjang adalah signifikan dengan subkumpulan transfusi SDM isipadu rendah sebelum pembedahan, begitu juga dan faktor lain seperti berat badan yang lebih rendah dan tempoh masa CPB yang lebih lama adalah turut signifikan kepada morbiditi pasca pembedahan ini. Tempoh pesakit lebih lama tinggal di PICU, di dapati berhubungkait secara signifikan bagi transfusi SDM pasca operasi isipadu tinggi dan rendah, berat badan yang lebih rendah, skor RACSH-1> 2 dan jangka masa CPB yang lebih lama.

Kesimpulan: Faktor ramalan transfusi yang dikenal pasti berkaitan dengan waktu pembedahan adalah unik bagi setiap fasa. Kajian ini juga menyimpulkan bahawa transfusi SDM pada fasa perioperatif (sebelum, semasa dan 48 jam selepas pembedahan) menunjukkan hubungan yang signifikan dengan hasil pasca pembedahan terpilih, durasi bantuan pernafasan mekanikal dan tempoh pesakit tinggal di PICU.

Kata Kunci: *Pembedahan jantung pediatrik, penyakit jantung congenital, cardiopulmonary bypass, tranfusi sel darah merah (SDM), morbiditi pasca pembedahan.*

ABSTRACT

Introduction: Allogenic blood transfusion among paediatric cardiac surgery conducted under cardiopulmonary bypass (CPB) remains very frequent and is associated with potential adverse consequences, including postoperative morbidity. This study aims at identifying the predictive factors associated with perioperative red blood cells (RBC) transfusion and finding its association with postoperative outcomes, in order to promote patients' effective management and guide clinicians to decide on judicious blood transfusion.

Methods: This cross-sectional retrospective study, conducted in IJN, involved 243 paediatric patients with cardiac surgery less than 18 years of age who had CPB surgery done in 2018.

Results: Preoperatively, 4.5% of patients received RBC transfusion with significant predictor for transfusion; haemoglobin (Hb) with mean value of 8.3 to 9.8 g/dL. Intraoperatively, cumulative of 99.2% of patients received RBC transfusion with predictive factors for transfusion in high RBC transfusion subgroup; young age, low body weight, RACHS-1 scores of ≥ 3 and had longest CPB time compared to other groups. RBC transfusion status pre- and intraoperatively was found not to influence postoperative RBC transfusion status significantly. Our analysis showed that 25.9% of our studied population received low RBC transfusion during the postoperative period, while another 11.5% received high RBC transfusion. The CBP time and surgery duration were profoundly longer in the postoperative high RBC transfusion subgroup. Longest

mechanical ventilation is significantly associated with preoperative low RBC transfusion subgroup and other covariates like lower body weight and longer CPB time. Longer duration of PICU stay was correlated with low preoperative and high postoperative RBC transfusion, lower body weight, RACSH-1 score >2 and longer CPB time duration.

Conclusion: The predictive transfusion factors identified in relation to operative time were unique to each phase. This study also concluded that certain perioperative RBC transfusion status showed a significant association with selected postoperative outcomes, duration of mechanical ventilation and length of the PICU stay.

Keywords: *paediatric cardiac surgery, congenital heart surgery, cardiopulmonary bypass, RBC transfusion, postoperative morbidity.*

CHAPTER ONE: INTRODUCTION

1.1 Overview

This chapter covers an introduction to the background of the study on "Red Blood Cells (RBC) Transfusion Practice in Paediatric Cardiac Surgery, at the National Heart Centre (IJN) of Malaysia". This chapter will also discuss the literature review on RBC transfusion's predictive factors, including the risks and benefits of this therapy to paediatric cardiac surgery patients. It will also cover the discussion about available guidelines on RBC transfusion for paediatric congenital cardiac surgery patients and the local transfusion practice in IJN. Problem statements, as well as the objectives of the study, will also be highlighted in this chapter.

1.2 Background of study

Congenital heart disease (CHD), represents a significant global health burden, is one of the most major congenital abnormalities (Dolk H *et al.*, 2011). Worldwide, the prevalence of CHD is estimated at around 8 per 1000 live births (Bernier PL *et al.*, 2010). With the advancement of technology, especially the invention of cardiopulmonary bypass (CPB) technique, congenital heart disease has become a manageable disorder (Wu *et al.*, 2020).

As the number of the paediatric population with congenital heart disease requiring cardiopulmonary bypass (CPB) increasing, transfusion of red blood cell will continue to be a substantial practice of paediatric cardiac anesthesiology and clinicians handling the case (Guzzetta NA, 2011). In a review article, it was documented that red blood cells transfusion among children who underwent cardiopulmonary bypass (CPB) were high, estimated at around 79% of all procedures (Durandy Y., 2015). The decision of when

RBC transfusion should be administered to these patients is complex and are influenced by multifactorial (Guzzetta NA, 2011).

1.3 Literature review

1.3.1 Determinants and predictive factors for RBC transfusion in paediatric cardiac surgery patients

Several causes exposed paediatric population with congenital heart disease to the development of anaemia and bleeding during the perioperative period and subsequently result in the need for RBC transfusion.

The proportion of specific cases contributing to preoperative anaemia has not been extensively studied especially among paediatric cardiac surgery patients. The aetiology of anaemia preoperatively may be complex and multifactorial. Poor nutrition or malabsorption may result in nutritional deficiencies of iron, folate or vitamin B12. Certain drugs may also result into decrease in red cell production in the bone marrow. Other than that, the underlying diseases may cause activation of immune system and inflammatory cytokines including interferon-gamma (IFN-γ), tumour necrosis factor-alpha (TNF-α), and interleukins (IL)-1, -6, -8 and -10 may causes anaemia through their participation in a variety of pathophysiological mechanisms that decrease RBC's half-life and inhibit proliferation and differentiation of erythroid cells (Manuel M *et al.*, 2015).

Predictors that increased need for allogeneic red blood cells transfusion during heart surgery among children may be attributed by low age and body weight, presence of comorbidities, the urgency of the surgery, cardiopulmonary bypass time as well as haemostatic alteration induced by CPB (Eugeniu V *et al.*, 2017, Guzzetta NA, 2011).

Hemodilution is an inevitable consequence of cardiopulmonary bypass and often result

in the administration of RBC. Especially in the young age for example infants, the priming volume circuit may be as large as their circulating blood volumes, contributing to haemodilution (Guzzetta NA, 2011).

CPB is also emphasised as an important predictive factor that contributed to the occurrence of haemorrhage postoperatively resulting from haemodilution, consumption of coagulation factors, hypothermia and also due the inflammatory response (Eugeniu V *et al.*, 2017).

1.3.2 Benefits and risks of RBC transfusion in paediatric cardiac surgery patients

RBC transfusion known benefit is to increase blood oxygen-carrying capacity aiming to improve tissue oxygenation, improve haemostasis as well as to replace blood loss during acute haemorrhage (Guzzetta NA, 2011, Durandy Y, 2015). Among important consideration is also to maintain optimum on-bypass haematocrit as this will help to define the oxygen delivering capacity to tissues (Matte G *et al.*, 2019).

RBC transfusion intraoperatively, while patients are on CPB, may benefit in terms of increasing overall oxygen delivery in those who are with low haemoglobin due to blood loss (Iyengar *et al.*, 2013).

Nevertheless, red blood cells transfusion benefits in paediatric cardiac surgery patients must be balanced against its risks as in recent years, more evidence of adverse transfusion reaction has resurfaced.

Risks can be divided into several broad categories including those with human error, an immune-mediated reaction such as transfusion-related acute lung injury (TRALI) as well as non-immune mediated adverse reactions, for example, transfusion-transmitted infection, and transfusion-associated circulatory overload (TACO) (Slonim AD *et al.*, 2008, Guzzetta NA, 2011, Du Pont-Thibodeau *et al.*, 2013).

In addition, other studies have also suggested adverse consequences following increased RBC transfusions, such as prolonged duration of mechanical ventilation and hospital length of stay, as well as increased incidence of neurological deficit and infection (Iyengar *et al.*, 2013, Willems A *et al.*, 2013).

1.3.3 Practice of RBC transfusion for paediatric cardiac patients

The practice of RBC transfusion in paediatric cardiac surgery patients among clinicians is not standardised and still varies widely. Despite the existence of clinical transfusion guidelines developed based on recommendations from consensus conferences, a substantial gap still exists in the advice form or clinical practice by the medical community. Physicians may be reluctant to apply transfusion practice proposed by scientific work as the field of paediatric cardiac surgery is a subspecialty, and this subgroup of patients have specific needs (Durandy Y, 2015).

Analysis of blood transfusion practices and complications in children by Slonim et al. also suggested that physicians practice often deviated from the established transfusion clinical guidelines proposed for paediatric patients' age groups. Among factors identified that contribute to this phenomenon are scarce data describing the indications of blood products transfusion and limited high-quality studies, primarily randomised control trials (RCT) on the association of transfusion with its clinical outcomes. As a result, physicians tend to prescribe transfusion therapy, aiming to correct the abnormal laboratory values rather than to achieve a clinical goal (Slonim AD *et al.*, 2008).

1.4 Research justification

Founded in 1992, Institut Jantung Negara (IJN) has offered various types of surgery for simple and complex congenital heart disease to the paediatric aged group. With regards to transfusion practice for paediatric cardiac surgery, clinicians have established a local

guideline for blood ordering schedule for elective surgery according to types of procedures and weight of the patients (Appendix A). In the event of bleeding or anaemia during the perioperative period, the approach of clinicians towards transfusion practice may vary, but according to observation, the determinants for the decision of RBC depends on haemoglobin and haematocrit level, amount of blood loss and utilisation of physiologic and laboratory parameters, examples are heart rate, blood pressure, and level of oxygenation and lactate.

Due to the variability and sometimes uncertainty as to when is the best time to transfuse the patients; hence it is essential to have an audit. This may be a good platform for an evidence-based study to establish guidelines and recommendations for transfusion in paediatric cardiac surgery. Alternative other than RBC transfusion to manage anaemia perioperatively is to aim for a blood conservation strategy. This should be explored more to optimise paediatric cardiac patient's outcomes as well as reduce the RBC transfusion and aim for transfusion-free surgery if possible.

1.5 Research question

i. What is the prevalence of red blood cells (RBC) transfusion among paediatric congenital heart disease (CHD) patients undergoing surgery?

ii. What are the factors that determine transfusion of red blood cells (RBC) perioperatively, among congenital heart surgery paediatric patients?

iii. What are the association of perioperative red blood cells transfusion among paediatric congenital heart surgery patients with postoperative morbidity and mortality?

CHAPTER TWO: OBJECTIVES

2.1 General objective

To determine the practice of red blood cells (RBC) transfusion among pediatric congenital heart disease (CHD) patients who underwent surgery in Institut Jantung Negara (IJN).

2.2 Specific objectives

i. To determine the prevalence of red blood cells transfusion among paediatric congenital heart disease patients who underwent surgery.

ii. To determine the socio-demographic, clinical and laboratory variables which influence transfusion of red blood cells perioperatively, among paediatric congenital heart surgery patients.

iii. To determine the association of perioperative red blood cells transfusion among paediatric congenital heart surgery patients with selective postoperative morbidity assessed by length of mechanical ventilation and length of PICU stay.

2.3 Alternative hypothesis

H_{A1}: There is a significant association between selected predictive factors with incidence of perioperative red blood cells transfusion in paediatric cardiac surgery patients.

H_{A2}: There is a significant association between perioperative red blood cells transfusion with postoperative outcomes.

2.4 Null Hypothesis

H_{01}: There is no significant association between selected predictive factors with incidence of perioperative red blood cells transfusion in paediatric cardiac surgery patients.

H_{02}: There is no significant association between perioperative red blood cells transfusion with postoperative outcomes.

CHAPTER THREE: METHODOLOGY

3.1 Study background

This chapter covers the methodology and ethical issues regarding the study on "Red Blood Cells (RBC) Transfusion Practice in Paediatric Cardiac Surgery, at the National Heart Centre (IJN) of Malaysia".

3.2 Study design

We performed a cross-sectional retrospective review on 250 out of 971 patients admitted to the Paediatric & Congenital Heart Centre (PCHC) of Institut Jantung Negara (IJN), who underwent cardiac surgery with cardiopulmonary bypass (CPB) between 1st January to 31st December 2018. Of those initially enrolled, 7 participants had to be dropped out due to incomplete data.

3.3 Study area

This year-long study was conducted at Paediatric & Congenital Heart Centre (PCHC) of Institut Jantung Negara (IJN).

3.4 Study population

Patients were classified according to American Academy of Pediatrics; neonates (<28 days), infant/toddlers (>28 days to 2 years), childhood (2 years to 12 years), middle adolescence from (12 to 17 years of age) (Hardin AP *et al.*, 2017, WHO).

3.4.1 Reference population: congenital heart disease (CHD) patients below 18 years old in Malaysia.

3.4.2 Target population: congenital heart disease patients who were referred to Paediatric & Congenital Heart Centre (PCHC) of Institut Jantung Negara (IJN).

3.4.3 Source population/sampling pool: congenital heart disease patients who underwent cardiac surgery in Paediatric & Congenital Heart Centre (PCHC), Institut Jantung Negara (IJN).

3.4.4 Sampling frame: paediatric cardiac surgery patients who were registered with Paediatric and Congenital Heart Centre (PCC), Institut Jantung Negara (IJN).

3.5 Subject criteria

3.5.1 Inclusion criteria

Briefly, the inclusion criteria were as follows; all patients under 18 years of age who underwent cardiac surgery in IJN from January to December 2018 with cardiac diagnosis and procedures they had were defined by International Classification of Disease (ICD-10) code.

3.5.2 Exclusion criteria

Premature neonates of gestational age < 37 weeks, parental refusal for blood transfusion, impending brain death, reoperation and subjects requiring extracorporeal membrane oxygenator were excluded.

3.6 Sample size

i.To determine the prevalence of red blood cells (RBC) transfusion among paediatric cardiac surgery patients who underwent surgery	Single proportion : $n = (z/\Delta)^2 p (1-p)$ n = sample size z= z statistic for a level of confidence = 1.96 (95% confidence interval) p=expected prevalence or proportion (in proportion of one ; if 100%, p=1) Δ = precision (in proportion of one ; if 5%, Δ = 0.05) Where, n=calculated sample size

	z= 1.96 for 95% confidence interval p=expected prevalence of RBC transfusion = 0.82 (Mazine e*t al.*, 2009) Δ=0.05 (5%) $n=(1.96/0.05)^2 \times 0.82 (1-0.82)$ = 226 + 10% drop out = 248
ii) To determine the socio-demographic and predictive transfusion factors which influenced transfusion of red blood cell (RBC) perioperatively, among paediatric cardiac patients	Single proportion : $n = (z/\Delta)^2 p (1-p)$ n = sample size z= z statistic for a level of confidence = 1.96 (95% confidence interval) p=expected prevalence or proportion (in proportion of one ; if 100%, p=1) Δ = precision (in proportion of one ; if 5%, Δ = 0.05) Where, n=calculated sample size z= 1.96 for 95% confidence interval p=expected prevalence of RBC transfusion in paediatric age group >2years=0.046 (Slonim AD e*t al.*, 2008) Δ=0.05 (5%) $n=(1.96/0.05)^2 \times 0.046 (1-0.046)$ = 67 + 10% drop out = 74
iii) To determine the association of perioperative red blood cells transfusion with postoperative morbidity assessed by length of mechanical ventilation and length of PICU stay, among paediatric cardiac surgery patients.	Two proportions : $n=p1(1-p1) + p2(1-p2)/ (p1-p2)^2 (z\alpha + z\beta)^2$ n=sample size p1=proportion of the associated factor p2=proportion of the associated factor zα = 1.96 for α = 0.05 (two tailed) or 2.58 for α =0.01 (two tailed) zβ = 0.84 for 80% power or 1.28 for 90% power Where, n=calculated sample size p1=proportion of patient with transfusion packed red cell transfusion and LOS=0.28 (Slonim AD et

	al. 2008) p2=proportion of patient with no transfusion packed red cell transfusion and LOS=0.11 (Slonim AD *et al.* 2008) $z\alpha = 1.96$ for $\alpha = 0.05$ (two tailed) $z\beta = 0.84$ for 80% power $n= 0.28(1-0.28) + 0.11 (1-0.11)/ (0.28-0.11)^2 \times (1.96 + 0.84)^2$ n= 81 + 10% drop out = 89

The highest number of sample is 248 (rounded up to 250), according to specific objective no. 1 and thus this was chosen as the total number of sample for this study.

3.7 Sampling method and subject recruitment

For this study, systematic random sampling was used to choose out 250 of 971 paediatric patients with congenital heart disease who underwent cardiac surgery in the year of 2018 in IJN. The sampling interval was determined by dividing the total number of patients, with the number of cases needed for the study, using Microsoft Excel Spreadsheet. In this study, the interval was 971/250 = 3.9 (rounded up to 3). A subject for this study was taken from every three samples; example (2, 5, 8.....).

3.8 Research tool

Patient's PROFORMA for research : Red Blood Cells Transfusion Practice in Paediatric Cardiac Surgery, at the National Heart Institute (IJN).

Patient's ID	
Date of admission	
Date of discharge	
Patient's Detail: a) Age (year and month) b) Gender c) Race d) Body Weight (kg)	
Primary Diagnoses	
Secondary Diagnoses	
Preoperative laboratory investigations : a) Hemoglobin (g/dL) b) Hematocrit (%)	

Surgery related: a) Aortic cross-clamping time (minute) b) Duration of surgery (minute) c) Priming of CPB time (minute) d) Oxygenator type e) Lowest nasal temperature (°C)	
Intraoperative laboratory investigations : a) Hemoglobin (g/dL) b) Hematocrit (%)	
Postoperative laboratory investigations : a) Hemoglobin (g/dL) b) Hematocrit (%)	
The volume of blood loss: a) Intraoperatively (ml/kg) b) Postoperatively (ml/kg)- total blood loss volume in 48 hours postoperatively	
The volume of red blood cells (RBC) transfused and indication for transfusion. a) Preoperatively (ml/kg) b) Intraoperatively (ml/kg) c) Postoperatively (ml/kg) –early postoperative RBCs transfused (within 48 hours post-surgery)	
Outcome: a) Duration of mechanical ventilation (days) b) Length of PICU stay (days)	

3.9 Data collection method

A comprehensive patients' database including demographics, diagnostic, perioperative information example; physiologic, laboratory and RBC transfusion as well as administrative information including; days of mechanical ventilation and PICU stay were obtained from IJN IT system database, *TRACKCARE*©, *ICIPT*© and patient's manual record (PMR).

The type of cardiac lesions was widely heterogeneous as well as the complexity of the surgery among patients. Hence, for this study, the cardiac surgical procedures were classified using the Risk-Adjusted Classification for Congenital Heart Surgery, Version 1 (RACHS-1) method.

Preordering of blood and blood products preoperatively were done according to the available local blood ordering schedule, refer to Appendix A. Intraoperative variables

including CPB time (minute), aortic cross-clamp time (minute), the lowest nasal temperature while on CPB (°C), total blood loss (ml/kg) was obtained through the IT database and manual record as mentioned earlier. The miniaturised cardiopulmonary bypass devices utilised were Terumo Baby RX, and Terumo RX15 and this device were chosen based on the child's weight.

For the example of the postoperative outcome, mechanical ventilation duration was defined as the duration of time (days) from admission to the PICU after leaving the operating theatre until the date of successful extubation. Duration of PICU stay (days) was taken as duration of admission to PICU after surgery until discharged to the general ward.

The RBC transfusion administered to all patients were as per institutional, local blood bank, the oldest available red cells would be provided first, but not necessarily leucofiltered. Meanwhile, irradiated blood products were only given to selected patients, example those with Di George Syndrome.

Three exposure groups were defined based on RBC transfusion volume administered during pre-, intra- and postoperative period of cardiac surgery. Patients requiring no blood transfusion were categorised as a non-transfusion group. The low RBC transfusion group referred to patients who received ≤20 ml/kg of RBC, while for the high volume of RBC transfusion group of patients, they were administered with total RBC volume >20 ml/kg. Nadir haemoglobin was defined as the lowest haemoglobin concentration prior to RBC transfusion. Early postoperative red blood cells transfusion volume in this study was defined as the total RBC transfusion (ml/kg) administered during the initial 48 hours of post-cardiac surgery (Salvin J *et al.*, 2011).

3.10 Statistical analysis

Data were analysed using IBM SPSS Statistics V26, licensed under IBM Corporation, New York. Descriptive analyses were performed to assess the characteristics of the studied population and to study the distribution of variables. For descriptive statistics, continuous variables were presented as mean and standard deviation (SD), while categorical variables were presented as frequency (%). Relationship between demographic and clinical variables towards perioperative RBC transfusion was assessed by univariate analyses. Continuous data were analysed for normality, and the data considered normal were evaluated by One- way ANOVA; while categorical variables were assessed by the Pearson Chi-square Test (x2). The association of postoperative outcomes; length of mechanical ventilation and PICU stay with RBC transfusion was explored using multiple linear regression test. The results were corrected by adjusting for the demographic and clinical variable, as shown in the result section. Statistical significance value was set at 0.05 or less ($p < 0.05$).

3.11 Operational Definition

	Definition
Congenital heart defect	Congenital heart disease (CHD) is a problem in the heart structure that is present at birth. Congenital cardiac malformations may be classified in different ways; to highlight the underlying anatomy and pathophysiology, the diseases could be grouped as follows: (a) CHD with shunt between systemic and pulmonary circulation, (b) left heart CHD, (c) right heart CHD, (d) CHD with anomalous origin of great arteries, and (e) miscellanea (Mechelleti A, 2018).
Cardiopulmonary bypass	Cardiopulmonary bypass (CPB) is a device that is utilised in cardiac surgery. CPB incorporates extracorporeal circuit, as physiological support in which venous blood is drained from the patient to a reservoir, while oxygenated blood is sent back to the body via a pump (Sarkar M et al., 2017).
Preoperative	Occurring before a surgical operation (Merriam Webster).

Intraoperative	Occurring, carried out or encountered in the course of surgery (Merriam Webster).
Postoperative	Following a surgical operation (Merriam Webster).
Perioperative	Relating to, occurring in, or being the period around the time of a surgical operation (Merriam Webster).
Non transfused	Patients requiring no blood transfusion were categorised as a non-transfusion group.
Low RBC transfusion	Low RBC transfusion group referred to patients who received ≤20 ml/kg of RBC.
High RBC transfusion	The high volume of RBC transfusion groups of patients was administered with total RBC volume >20 ml/kg.
Nadir haemoglobin	Nadir haemoglobin is defined as the lowest haemoglobin concentration before RBC transfusion.
Early postoperative RBC transfusion	Early postoperative red blood cells transfusion volume in this study was defined as the total RBC transfusion (ml/kg) administered during the initial 48 hours post-cardiac surgery.
Terumo Baby RX and RX 15 oxygenator	Terumo Baby RX oxygenator is designed for neonates and infants while Terumo RX 15 oxygenator is intended for children and young adults. These oxygenators are minimised circuits designed for low prime volume, with high oxygen transfer capacity.

3.12 Ethical issues

We obtained ethical approval from the Human Ethics Committee at the Hospital University Sains Malaysia [ref no: *USM/JEPeM/19010049*], IJN Research Ethics Committee (IJNREC) [ref no: IJNREC/398/2019] and the Medical Research Ethics Committee, Malaysia in the Ministry of Health Malaysia (NMRR No:18-320-44772). The confidentiality of the participants was strictly protected.

The data were recorded as anonymous into the Microsoft Excel forms so that patients involved could not be identified directly or indirectly to the data collected. All data were made anonymous and entered into SPSS software for analyses. Only research team

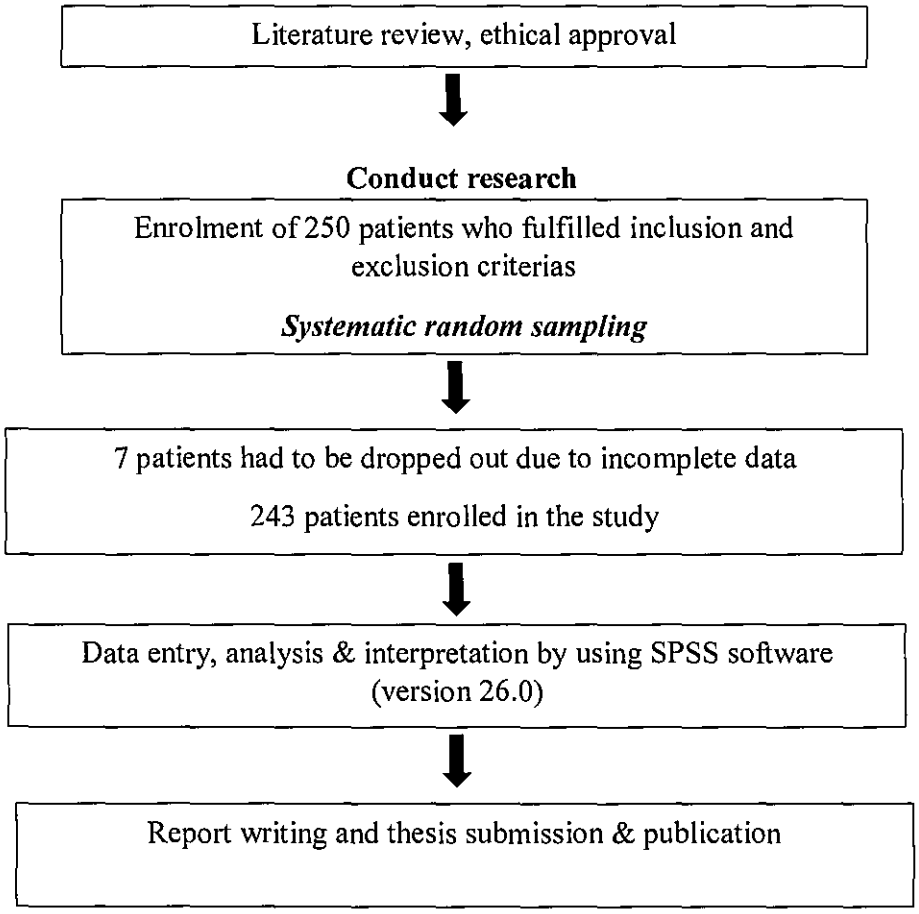
members could access the data.

The data was presented as grouped data and would not identify the responders individually. The study data would only be made available to the research team and the authorities of relevant bodies (i.e., USM/ IJN/ NMMR), however, it is not necessary to be disclosed to the individuals/subjects whose data are being studied and analysed.

The study data has been kept in the online storage device with an encrypted password, so the principal researcher and team can only access the data. The data will be stored until at least 7 years. Should the data is no longer needed to be stored, they will be permanently deleted from the online storage device. No data will be kept as hard copies or manually stored.

3.13 Study flowchart

Figure 1.1 Development of research proforma



CHAPTER FOUR: MANUSCRIPT

This section is prepared according to the journal "Malaysian Journal of Medicine and Health Sciences (MJMHS)" Author's guidelines. Instruction to Author is available in Appendix F.

This chapter is a stand-alone chapter. The introduction and methodology for this manuscript chapter should incorporate Chapter One, Chapter Two and Chapter Three.

Title Page

Red Blood Cells Transfusion Practice in a Paediatric Cardiac Surgery at the National Heart Institute (IJN) of Malaysia

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ABSTRACT

Introduction: Allogenic blood transfusion among paediatric cardiac surgery conducted under cardiopulmonary bypass (CPB) remains very frequent and is associated with potential adverse consequences, including postoperative morbidity. This study aims at identifying the predictive factors associated with perioperative red blood cells (RBC) transfusion and finding its association with postoperative outcomes, in order to promote patients' effective management and guide clinicians to decide on judicious blood transfusion.

Methods: This cross-sectional retrospective study, conducted in IJN, involved 243 paediatric patients with cardiac surgery less than 18 years of age who had CPB surgery done in 2018.

Results: Preoperatively, 4.5% of patients received RBC transfusion with significant predictor for transfusion; haemoglobin (Hb) with mean value of 8.3 to 9.8 g/dL. Intraoperatively, cumulative of 99.2% of patients received RBC transfusion with predictive factors for transfusion in high RBC transfusion subgroup; young age, low body weight, RACHS-1 scores of ≥ 3 and had longest CPB time compared to other groups. RBC transfusion status pre- and intraoperatively was found not to influence postoperative RBC transfusion status significantly. Our analysis showed that 25.9% of our studied population received low RBC transfusion during the postoperative period, while another 11.5% received high RBC transfusion. The CBP time and surgery duration were profoundly longer in the postoperative high RBC transfusion subgroup. Longest mechanical ventilation is significantly associated with preoperative low RBC transfusion

subgroup and other covariates like lower body weight and longer CPB time. Longer duration of PICU stay was correlated with low preoperative and high postoperative RBC transfusion, lower body weight, RACSH-1 score >2 and longer CPB time duration.

Conclusion: The predictive transfusion factors identified in relation to operative time were unique to each phase. This study also concluded that certain perioperative RBC transfusion status showed a significant association with selected postoperative outcomes, duration of mechanical ventilation and length of the PICU stay.

Keywords: *paediatric cardiac surgery, congenital heart surgery, cardiopulmonary bypass, RBC transfusion, postoperative morbidity.*

INTRODUCTION

Congenital heart disease (CHD) incidence reported was approximately 0.8%-1.2% of live births worldwide is one the most frequently diagnosed congenital disorder **(1,2)**. Generally, CHD is characterised as the abnormality of the heart and (or) great vessel (s) present at birth **(2)**. In another report, the overall global prevalence of CHD has significantly increased and is estimated to be 9 per 1000 live births, corresponding to 1.35 million in the last 15 years **(3)**.

Before the 1950s, nearly every severe CHD was considered an almost fatal disease. Fortunately, the introduction of cardiopulmonary bypass (CPB) in congenital cardiac disease surgery has transformed it into a manageable disorder **(2)**.

However, children undergoing cardiac surgery with CPB are often known to receive red blood cells (RBC) transfusion **(4,5)**. A study by Chambers et al. in 1996 reported that as high as 98% of paediatric cardiac surgery patients who underwent CPB received RBC transfusion. In a more recent review, researchers reported 38-74% of children who underwent cardiac surgery were administered RBC transfusions **(6,7)**.

In general, paediatric cardiac surgery is associated with a substantial risk of bleeding, hence no surprise that it requires frequent administration of allogenic red blood cell transfusion. Moreover, anaemia of different causes is also observed among paediatric cardiac surgery patients especially in neonates, and children may also be the reasons for blood transfusion. **(8)**.

The aetiology of preoperative anaemia among paediatric patients preoperatively may be complex and multifactorial **(8,9)**. Nutritional deficiency, commonly iron deficiency anaemia (IDA) followed by folate and vitamin B12 deficiency may be due to poor nutrition or malabsorption which may result in reduced RBC production. Other causes

may be due to activation of certain immune and inflammatory cytokines, e.g. interleukins (IL)-1,-6,-8,-10, interferon-gamma (IFN- γ) including tumour necrosis factor-alpha (TNF-α) **(9,34).** These inflammatory mediators are involved in different pathophysiological mechanisms which may contribute to dyserythropoietic; increase erythrophagocytsis; inadequate response to endogenous erythropoietin and pathological iron homeostasis through the action of hepcidin **(9).**

Other risk factors for anaemia identified in this population are haemodilution induced by cardiopulmonary bypass and fluid administration preoperatively; consumptive coagulopathy; anticoagulant effect by heparin as well as other causes; physiological disturbance and electrolytes imbalance namely hypothermia, acidaemia, hypocalcaemia and frequent phlebotomy **(8,9).**

Cardiopulmonary bypass (CPB) for paediatric cardiac surgery patients presents a unique challenge with regards to transfusion practice. The relatively large prime volume use in bypass circuit compared to the circulating blood volumes, especially in infant and young children lead to hemodilution, which is a strong predictive factor for RBC transfusion **(10).**

Besides, identifiable factors which predispose paediatric cardiac surgery patients to blood products transfusion are; smaller patient's size; the type and complexity of the procedure and the severity of illness **(10,11).** In a self-administered survey study, the researchers reported that the determinants considered by clinicians for RBC transfusion among paediatric cardiac patients were haemoglobin (Hb) level; patient stability; the presence of bleeding and parameters such as inadequate O_2 delivery (demonstrated by low SaO2/FiO2 and high lactate levels) and low blood pressure **(12).**

Of all the predisposing factors for RBC transfusion in paediatric cardiac patients, Hb

remains the most important determinant **(13).** Questions posed by many researchers, how much anaemia can these patients tolerate, and when the benefit of red blood cell transfusion outweighs their harm?

In general, red blood cell transfusion is deemed necessary to increase the oxygen-carrying capacity of blood as well as to improve tissue oxygenation in anaemic or bleeding patients who underwent surgery **(14,15,16,17,18).** Besides, RBC transfusion contributes to the improvement of homeostasis via a rheologic effect and promotes platelets' activation **(15).** In addition to that for patients undergoing cardiopulmonary bypass, blood products used for priming the CPB circuit has additional benefits besides delivering oxygen, which is also important for colloid pressure **(10).** The pathophysiological rationale behind red blood cell transfusion perioperatively is that anaemia has been correlated with postoperative morbidity and mortality in paediatric cardiac patients **(5).**

Despite their benefits and undisputedly life-saving potential during a bleeding event, RBC transfusion practise has been under scrutiny due to the more evidence of adverse events associated with their use being reported **(15).**

Risks or adverse transfusion reaction can be classified into several broad categories, including those associated with human error, an immune-mediated reaction such as transfusion-related acute lung injury (TRALI) and alloimmunisation to HLA and RBC antigens, a non-immune mediated adverse reaction such as transfusion-transmitted infection (TTI) as well as a transfusion-associated circulatory overload (TACO) **(11,13).**

Due to differences in age, body size and maturity of their physiology system, the paediatric cardiac surgery population may have different risk-benefit considerations compared to the adult population for red blood cells transfusion **(11,16).** During acute blood loss, adolescent and adults compensate for it by increasing their cardiac output. On

the other hand, small children have limited ability to increase cardiac contractility and therefore rely on increased heart rate to compensate for blood loss. Smaller children should be considered blood transfusion earlier, when there is a blood loss of 20-25% from total blood volume compared to the adult, 30-35% blood loss from total blood volume **(19).**

Risk of other postoperative serious morbidities such as neurologic events, renal failure, increased mechanical ventilation duration, and a longer stay in intensive care unit have also been associated with the transfusion of red blood cells in this patient population **(16,20).**

There is no standardization of the transfusion guideline in paediatric cardiac surgery **(21).** It is acknowledged that there is a substantial gap between published guidelines and recommendations for blood and blood products used in clinical practice. The variability of transfusion practise across different cardiac centres among clinicians is likely because the area itself is a subspeciality; with children of different age categories having their own specific needs **(22).** The transfusion practice in paediatric cardiac surgery, from deciding the transfusion indications and when clinicians should prescribe RBC transfusion varies among centres; an obvious example is lacking a commonly agreed safe lower limit of haemoglobin and haematocrit level applicable for cardiopulmonary bypass **(15,23).**

Founded in 1992, Institut Jantung Negara (IJN) the National Heart Centre of Malaysia provides cardiology and cardiothoracic surgery services for both adult and paediatric patients. Paediatric and Congenital Heart Centre (PCHC) of IJN, offers various types of surgery for simple and complex congenital heart disease to the paediatric aged groups. With regards to transfusion practice for paediatric cardiac surgery, clinicians have established local guidelines for blood ordering scheduled for elective surgery, based on