DISSERTATION MANUSCRIPT

MASTER OF GENERAL SURGERY

UNIVERSITI SAINS MALAYSIA

Adverse Outcomes of Perioperative Red Blood Cell Transfusions in Coronary Artery Bypass Grafting in Hospital Universiti Sains Malaysia

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P-UM0039/16

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ABSTRAK

Latar belakang: Transfusi sel darah merah sewaktu pembedahan pintasan jantung mempunyai manfaat dan risiko yang tersendiri. Matlamat kami adalah untuk mengkaji hubungan antara transfusi sel darah merah dan kesan sampingannya terhadap pesakit yang menjalani pembedahan pintasan jantung.

Kaedah kajian: Ini adalah kajian rekod secara retrospektif bagi pesakit yang telah menjalani pembedahan pintasan jantung di Hospital Universiti Sains Malaysia, Kelantan, Malaysia dari 1 Januari 2013 hingga 31 Disember 2017. Data diperolehi daripada rekod perubatan pesakit dan perbandingan dibuat, terutamanya dari segi kesan sampingan selepas pembedahan pintasan jantung antara pesakit yang menerima transfusi sel darah merah dan pesakit yang tidak menerima transfusi darah.

Keputusan: Sebanyak 108 orang pesakit yang telah menjalani pembedahan pintasan jantung dimasukkan ke dalam kajian kami, 78 orang pesakit (72.2%) menerima transfusi sel darah merah sementara 30 orang pesakit (27.8%) tidak. Selepas pembedahan, didapati pesakit yang menerima transfusi sel darah merah mempunyai kebarangkalian yang lebih tinggi dalam keperluan sokongan ventilasi yang berpanjangan (21.8% vs 0%, $p = 0.003$), morbiditi jantung (14.1% vs 0%, $p = 0.032$), kemerosotan fungsi buah pinggang (28.2% vs 3.3%, $p = 0.005$) dan jangkitan yang serius (20.5% vs 3.3%, $p = 0.037$). Dengan setiap unit sel darah merah yang diterima oleh pesakit, terdapat peningkatan risiko yang jelas dalam keperluan sokongan ventilasi yang berpanjangan (adjusted odd ratio [AOR] = 1.45; 95% confidence interval [CI] = 1.20 - 1.77; $p < 0.001$), morbiditi jantung (AOR = 1.40; 95% CI = 1.01 - 1.79; $p = 0.007$), kemerosotan fungsi buah pinggang (AOR = 1.23; 95% CI = 1.03 - 1.45; $p = 0.019$) dan jangkitan yang serius (AOR = 1.31; 95% CI = 1.07 - 1.60; $p = 0.009$).

Kesimpulan: Transfusi sel darah merah dalam pesakit yang menjalani pembedahan pintasan jantung didapati berkait dengan peningkatan risiko kesan sampingan seperti sokongan ventilasi yang berpanjangan, morbiditi jantung, kemerosotan fungsi buah pinggang dan jangkitan yang serius.

ABSTRACT

Background: Perioperative red blood cell (RBC) transfusion in coronary artery bypass grafting (CABG) has both benefits and harms. Our aim was to study the association between perioperative RBC transfusion and its adverse outcomes in patients who underwent isolated CABG.

Methods: This was a retrospective record review of patients who underwent isolated CABG in Hospital Universiti Sains Malaysia, Kelantan, Malaysia from 1 January 2013 until 31 December 2017. Data were collected from medical records, and comparisons were made between patients who received perioperative RBC transfusions and those who did not with their adverse outcomes after CABG.

Results: A total of 108 patients who underwent isolated CABG were included in our study, and 78 (72.2%) patients received perioperative RBC transfusions while 30 (27.8%) patients did not. After CABG, patients who received perioperative RBC transfusions compared to those who did not, were significantly more likely to develop prolonged ventilatory support (21.8% vs. 0%, p = 0.003), cardiac morbidity (14.1% vs. 0%, p = 0.032), renal morbidity (28.2% vs. 3.3%, p = 0.005) and serious infection (20.5% vs. 3.3%, p = 0.037). With each unit of packed RBC transfusions, there was a significantly increased risk of prolonged ventilatory support (adjusted odds ratio [AOR] = 1.45; 95% confidence interval [CI] = 1.20 - 1.77; p < 0.001), cardiac morbidity (AOR = 1.40; 95% CI = 1.01 - 1.79; p = 0.007), renal morbidity (AOR = 1.23; 95% CI = 1.03 - 1.45; p = 0.019) and serious infection (AOR = 1.31; 95% CI = 1.07 - 1.60; p = 0.009).

Conclusion: Perioperative RBC transfusion in isolated CABG patients is associated with increased risks of developing adverse events such as prolonged ventilatory support, cardiac morbidity, renal morbidity and serious infection.

1. INTRODUCTION

1.1 Introduction

Coronary artery disease (CAD) is the leading cause of mortality worldwide and in Malaysia (1). According to the World Health Organization (WHO), in Malaysia, CAD accounted for 29,400 deaths in 2012, or equals to 98.9 deaths per 100,000 population. It also accounted for 20.1% of all mortalities in the country (2). CAD is one of the major burdens to the hospitals of the Ministry of Health (MOH). According to the hospital admission records and death certifications, it accounted for 6.99% of total hospital admissions and 23.34% of all hospital deaths in 2014 (1).

Treatments for CAD include pharmacological therapy and interventions such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). CABG has been the standard of care for revascularisation of patients with complex CAD since its introduction in 1968 (3). Current evidence has demonstrated a survival benefit with CABG over PCI in patient with 3 or more vessel coronary artery disease and complex coronary artery anatomy. Mohr *et al.* (4) randomised 1800 patients with left main coronary disease or three-vessel disease to either CABG or PCI. The 5-year study demonstrated a higher survival rate in the CABG group compared with the PCI group for patients with complex multivessel coronary artery disease.

According to 2014 European Society of Cardiology (ESC) /European Association for Cardio-Thoracic Surgery (EACTS) Guidelines on myocardial revascularization, the mortality rate associated with CABG is 1-2% and a 1-2% morbidity rate for each of the following events: stroke, renal, pulmonary and cardiac failure, bleeding and wound infections (5). 2011 American College of Cardiology Foundation (ACCF) /American Heart Association (AHA) Guidelines for CABG surgery reported that elderly, women, patients with diabetes mellitus, chronic obstructive pulmonary disease/respiratory insufficiency, end-stage renal disease on dialysis,

concomitant peripheral vascular disease, previous stroke and reoperative CABG are associated with higher rates of morbidity and mortality (6).

The 2011 ACCF / AHA Guidelines for CABG surgery had recommended blood conservation strategy in CABG surgery (6). Blood conservation practices in cardiac surgery were introduced in the 1970s because of the scarcity and cost of this limited resource, awareness of transfusion-borne infections such as hepatitis B and C and human immunodeficiency virus and increasing awareness of immunologic implications of this allogeneic exposure (7).

The rationale for perioperative red blood cell (RBC) transfusions is based on the observations that anaemia is an independent risk factor for morbidity and mortality after cardiac operations (8,9). However, numerous studies have demonstrated that perioperative RBC transfusions in patients undergoing cardiac operations including CABG have been associated with higher rates of morbidity and mortality (10-16). Perioperative blood transfusions have been linked to higher rates of post-operative renal dysfunction (17), neurologic, respiratory and cardiac complications (12-14,18), serious infection (7,19,20), prolonged ventilatory support (12-14), prolonged length of stay (21-23), short-term and long-term survival (24-31).

1.2 Literature Review

According to WHO's Global Health Observatory (GHO) data, CAD accounted for 98.9 deaths per 100,000 population in Malaysia in 2012, or 29,400 deaths in total. It occupied 20.1% of all deaths, make it the most common cause of deaths in the country (2).

CAD possess a major burden to the healthcare institutions in the country. A data from a review of coronary artery disease research in Malaysia 2016 showed that, in hospitals of the MOH, CAD accounted for 6.99% of total hospital admissions and 23.34% of all hospital deaths in 2014 (1).

CAD is a disease of high mortality rate. Based on the National Cardiovascular Disease Database, the in-hospital mortality rates of acute coronary syndrome remained consistent between 6 to 8% over a 5-year period from 2006 to 2010, with overall average of 7% (23).

CABG has been the standard of care for revascularization of patients with complex coronary artery disease since its introduction in 1968. Mohr *et al.* in 2013 have conducted a study on CABG vs PCI in patients with three-vessel disease and left main coronary disease. In this clinical SYNTAX trial, which took place in 85 centers in USA and Europe, 1800 patients were randomly assigned to CABG (n=897) or PCI (n=903), after 5 years' follow up, Kaplan-Meier estimates of Major Adverse Cardiac and Cerebrovascular Events (MACCE) were 26.9% in the CABG group and 37.3% in the PCI group ($p<0.0001$). Results of the SYNTAX trial showed that CABG remains the standard of care for patients with complex coronary lesions, driven by favorable rates of MACCE, cardiac death, myocardial infarction, and repeat revascularization in the CABG group compared with the PCI group (4).

Similar to other surgical interventions and procedures, CABG surgery carries its own risk of adverse outcome and mortality. 2014 ESC / EACTS Guidelines on myocardial revascularization reported that the early clinical outcome at 3 months after CABG is characterized by a 1–2% mortality rate and a 1–2% morbidity rate for each of the following

events: stroke, renal, pulmonary and cardiac failure, bleeding, and wound infections. The early risk period after CABG extends up to 3 months, is multifactorial, and depends on the interface between technical variability and patient comorbidity (5).

RBC transfusion in cardiac surgery including CABG is a common practice as seen in other surgical disciplines, the most common indications of perioperative RBC transfusion are preoperatively symptomatic anemia, intraoperatively excessive/life threatening bleeding or postoperatively low hemoglobin level. However, throughout the years, growing literatures have shown that RBC transfusions are associated with morbidity and with short-term and long-term mortality after CABG. Although RBCs may certainly have life-preserving value, the impact of smaller quantities in a non-emergent setting (i.e. asymptomatic anemia/bleeding) has not been well documented. These small-volume transfusions are more discretionary and therefore potentially avoidable. A common rationale for RBC transfusion is to increase oxygen delivery to organ tissues sensitive to ischemia in patients with haematocrit or haemoglobin levels below a predetermined and usually arbitrarily set lower limit. However, well-described changes in RBC morphology, and the significant depletion of 2, 3-diphosphoglyceric acid and nitric oxide levels that occurs during storage, are known to profoundly limit the capacity of these RBCs to carry and deliver oxygen to the tissues. Accumulation of immunomodulating bioactive substances released from leukocytes to the storage medium and transfusion of white blood cell-containing allogeneic RBC products has been associated with an increased risk of postoperative infection in cardiac surgery. Thus, all of these have call into question the benefit of many of these transfusions (15,20).

Several studies have demonstrated the adverse outcome associated with RBC transfusion in cardiac surgery and critically ill patients, but there is lack of study conducted in our country and in this region to evaluate the adverse outcome associated with transfusion of RBC in CABG. There is increasing evidence for independent relationships between RBC

transfusion and infectious complications, cardiac and respiratory morbidity, prolonged length of stay and mortality after cardiac surgery (1, 12-14).

Number of transfused RBC units is an independent risk factor for worse outcomes, including mortality. In a retrospective analysis of 11,963 patients who underwent isolated CABG surgery, Koch *et.al.* showed that perioperative RBC transfusion was associated with a dose-dependent increased risk of postoperative cardiac complications, serious infection, renal failure, neurologic complications, overall morbidity, prolonged ventilator support, and in hospital mortality (13).

In a similar retrospective study, Murphy *et.al.* showed that RBC transfusion was strongly associated with infection and postoperative ischemic morbidity, hospital stay, increased early and late mortality, hospital costs, and a strong dose-response relationship was present (14).

More and more evidences have shown that blood conserving strategy proved to be beneficial in cardiac surgery. As evidenced by a study conducted by Hajjar *et.al.* in 2010. The transfusion requirement after cardiac surgery (TRACS) randomized controlled trial randomly assigned 502 patients who underwent cardiac surgery to a liberal strategy of blood transfusion (to maintain a haematocrit $\geq$ 30%) or to a restrictive strategy (haematocrit $\geq$24%), the study result showed that among patients undergoing cardiac surgery, the use of a restrictive perioperative transfusion strategy compared with a more liberal strategy resulted in non-inferior rates of the combined outcome of 30-day all-cause mortality and severe morbidity (47).

CAD is a prominent disease in the country, and CABG as the main revascularisation surgery, it is therefore clinically useful if we can identify the risk factors of its morbidity and mortality and further to devise a preventive measure or protocol.

1.3 Rationale of Study

- High prevalence of CAD worldwide and in Malaysia, with its increasing incidence over the years which contributes to major healthcare burden in the country
- CABG is the main surgical intervention performed for CAD, hence it is clinically important to study the factors that influence its outcome, e.g., morbidity and mortality
- There have not been any local studies done regarding morbidity and mortality risk associated with RBC transfusion in CABG

2. STUDY PROTOCOL

2.1 Proposal Submitted for Ethical Approval

Jabatan Surgeri

Department of Surgery

Pusat Pengajian Sains Perubatan,

Kampus Kesihatan,

Universiti Sains Malaysia,

16150, Kubang Kerian,

Kelantan, Malaysia.

Date: 25th March 2018

Chairperson,

Human Research Ethics Committee USM (HREC)

Health Campus, USM,

Kubang Kerian, Kelantan.

Protocol Title: Adverse Outcomes of Perioperative Red Blood Cell Transfusions in Coronary Artery Bypass Grafting in Hospital Universiti Sains Malaysia

Principal Investigator: Chan Choon Hua

Dear Prof,

Thank you for considering my thesis proposal.

DISSERTATION PROPOSAL
MASTER OF GENERAL SURGERY
UNIVERSITI SAINS MALAYSIA

ADVERSE OUTCOMES OF PERIOPERATIVE RED BLOOD CELL TRANSFUSIONS IN CORONARY ARTERY BYPASS GRAFTING IN HOSPITAL UNIVERSITI SAINS MALAYSIA

Principal Investigator:
DR. CHAN CHOON HUA
P-UM0039/16

Supervisor:
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Co-Supervisor:
DR. AHMAD ZUHDI MAMAT

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KUBANG KERIAN,
KELANTAN, MALAYSIA.

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List of Abbreviations

ACCF	American College of Cardiology Foundation
ACS	Acute Coronary Syndrome
AHA	American Heart Association
AOR	Adjusted Odd Ratio
CAD	Coronary Artery Disease
CABG	Coronary Artery Bypass Grafting
CRC	Clinical Research Centre
CT	Computed tomography
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
GCP	Good Clinical Practice
HUSM	Hospital Universiti Sains Malaysia
IQR	Interquartile Range
KDIGO	Kidney Disease Improving Global Outcomes
MACCE	Major Adverse Cardiac and Cerebrovascular Events
MOH	Ministry of Health
MREC	Medical Research Ethics Committee
NCVD	National Cardiovascular Disease Database
NIH	National Institutes of Health
NMRR	National Medical Research Register
PCI	Percutaneous Coronary Intervention
RBC	Red Blood Cell
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
SYNTAX	SYNergy between PCI with TAXus and cardiac surgery
TRACS	Transfusion Requirement After Cardiac Surgery
USM	Universiti Sains Malaysia
WHO	World Health Organization

1. Background

1.1 Introduction

Coronary artery disease (CAD) is the leading cause of mortality worldwide and in Malaysia (1). According to the WHO, in Malaysia, CAD accounted for 29,400 deaths in 2012, or equals to 98.9 deaths per 100,000 population. It also accounted for 20.1% of all mortalities in the country (2). CAD is one of the major burdens to the hospitals of the MOH. According to the hospital admission records and death certifications, it accounted for 6.99% of total hospital admissions and 23.34% of all hospital deaths in 2014 (1).

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According to 2014 ESC / EACTS Guidelines on myocardial revascularization, the mortality rate associated with CABG is 1-2% and a 1-2% morbidity rate for each of the following events: stroke, renal, pulmonary and cardiac failure, bleeding and wound infections (5). 2011 ACCF / AHA Guidelines for CABG surgery reported that elderly, women, patients with diabetes mellitus, chronic obstructive pulmonary disease/respiratory insufficiency, end-stage renal disease on dialysis, concomitant peripheral vascular disease, previous stroke and reoperative CABG are associated with higher rates of morbidity and mortality (6).

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- CABG is the main surgical intervention performed for CAD, hence it is clinically important to study the factors that influence its outcome, e.g., morbidity and mortality
- There have not been any local studies done regarding morbidity and mortality risk associated with RBC transfusion in CABG

3. Study Objectives

3.1 General Objective

- To study the adverse outcomes (morbidity and mortality) of perioperative packed RBC transfusions in patients who underwent isolated CABG

3.2 Specific Objectives

1. To determine the association of adverse outcomes (morbidity – prolonged ventilatory support/ cardiac morbidity/ renal morbidity/ neurologic morbidity/ serious infection and mortality) with perioperative packed RBC transfusions in isolated CABG
2. To determine the association between number of packed RBC transfused perioperatively and adverse events in isolated CABG

4. Research Questions

- Is there any association between transfusions of RBC and adverse outcomes (morbidity and mortality) in CABG?
- Is there any quantitative association between unit of RBC transfused and adverse outcomes (morbidity and mortality) in CABG?

5. Research Hypothesis

- H_0 - Perioperative RBC transfusions is not associated with increased adverse outcomes (morbidity and mortality) in isolated CABG
- H_A - Perioperative RBC transfusions is associated with increased adverse outcomes (morbidity and mortality) in isolated CABG

6. Study's Outcomes

The outcomes of this study are prolonged postoperative ventilatory support, cardiac morbidity, neurologic morbidity, renal morbidity, serious infection and postoperative mortality among CABG patients who received perioperative red blood cell transfusions.

7. Operational Definitions

1. Perioperative RBC transfusion, defined as transfusion of RBC during preoperative, intraoperative and/or postoperative period.

2. Prolonged postoperative ventilatory support, defined as mechanical ventilatory support for more than 72 hours postoperatively.

3. Cardiac morbidity, defined as low cardiac index (1.8 L/min/m^2) despite adequate fluid replacement and high dose inotropic agents for >4 hours or a postoperative myocardial infarction.

4. Neurologic morbidity, defined as focal or global neurologic deficits (stroke), evidence by clinical or imaging (CT brain) findings.

5. Renal morbidity, defined as new onset renal failure requiring dialysis or acute kidney injury defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria:

- Increase in serum creatinine by 0.3mg/dL or more within 48 hours or
- Increase in serum creatinine to 1.5 times baseline or more within the last 7 days or
- Urine output less than 0.5 mL/kg/h for 6 hours

6. Serious infection, defined as sepsis syndrome, septic shock, pneumonia, mediastinitis, sternal or leg wound infection. In addition, the diagnosis of sepsis included organisms isolated from the cultures along with elevated temperature and white blood cell counts.

7. Mortality, defined as an in-hospital or 30-day mortality

8. Methodology

8.1 Study Design

This is a retrospective record review of patients who underwent isolated CABG in HUSM from 1st of January 2013 until 31st of December 2017. There will be 3 main phases in this study:

1. Preparatory phase:

Researcher gathers relevant information from extensive web search, specialists and consultant cardiothoracic surgeons. Data collection sheet and a master list will be created and subsequently verified by consultant cardiothoracic surgeons.

2. Conduct of Study:

Patients' data will be retrieved from record in operation theatre, case notes from record office/computer database after obtaining ethical approval from MREC of USM.

3. Data Analysis:

Collected data will be analysed using SPSS 24.0. All collected data will be analysed and reported. Results obtained will be shared with stakeholders.

8.2 Place of Study

Study will be conducted at HUSM, Kubang Kerian, Kelantan.

8.3 Study Population

The study includes all adult patients who underwent isolated CABG in HUSM from January 1, 2013 to December 31, 2017. The list of patients who underwent isolated CABG will be traced from the record in the operation theatre. The data collection will be started after ethical approval.

8.4 Sampling Frame

This is a single centre study done at Cardiothoracic Unit, Department of Surgery, HUSM. All patients that fulfilled the inclusion and exclusion criteria will be recruited.

8.4.1 Inclusion criteria:

- Patients who underwent isolated CABG in HUSM from 1st of January 2013 until 31st of December 2017 (5 years)

8.4.2 Exclusion criteria:

- Patients who underwent combination surgery (e.g. CABG and valve replacement)
- Patients who underwent isolated CABG with missing/incomplete data
- Patients younger than 18 years old

8.5 Sampling Method

This study utilizes non-probability, convenient quota sampling method.

8.6 Sample Size Calculation

Sample size calculation using Raosoft® calculator based on each adverse outcome:

1. Adverse outcome: Prolonged ventilatory support

- Accepted margin of error: 5%
- Confidence level: 95%
- Population size: 300 (based on HUSM statistical data, number of CABG per year x study years = 60 x 5 = 300)
- Response distribution: 9.14% (based on Koch *et.al. 2006* (13), percentage of prolonged ventilatory support in patients with transfused RBC is 9.14%, $p < 0.0001$)

Sample size = 90 + 20% drop out = 108 patients

2. Adverse outcome: Cardiac morbidity

- Accepted Margin of error: 5%
- Confidence level: 95%
- Population size: 300 (based on HUSM statistical data, number of CABG per year x study years = 60 x 5 = 300)
- Response distribution: 3.03% (based on Koch *et.al. 2006* (13), percentage of cardiac morbidity in patients with transfused RBC is 3.03%, $p < 0.0001$)

Sample size = 41 + 20% drop out = 49 patients

3. Adverse outcome: Neurologic morbidity

- Accepted margin of error: 5%
- Confidence level: 95%
- Population size: 300 (based on HUSM statistical data, number of CABG per year x study years = 60 x 5 = 300)
- Response distribution: 2.41% (based on Koch *et.al. 2006* (13), percentage of neurologic morbidity in patients with transfused RBC is 2.41%, $p < 0.0001$)

Sample size = 34 + 20% drop out = 41 patients

4. Adverse outcome: Renal morbidity

- Margin of error: 5%
- Confidence level: 95%
- Population size: 300 (based on HUSM statistical data, number of CABG per year x study years = 60 x 5 = 300)
- Response distribution: 1.81% (based on Koch *et.al. 2006* (13), percentage of renal morbidity in patients with transfused RBC is 1.81%, $p < 0.0001$)

Sample size = 26 + 20% drop out = 31 patients

5. Adverse outcome: Serious infection

- Accepted margin of error: 5%
- Confidence level: 95%
- Population size: 300 (based on HUSM statistical data, number of CABG per year x study years = 60 x 5 = 300)
- Response distribution: 5.03% (based on Koch *et.al. 2006* (13), percentage of serious infection in patients with transfused RBC is 5.03%, $p < 0.0001$)

Sample size = 63 + 20% drop out = 76 patients

6. Adverse outcome: Mortality

- Accepted margin of error: 5%
- Confidence level: 95%
- Population size: 300 (based on HUSM statistical data, number of CABG per year x study years = 60 x 5 = 300)
- Response distribution: 3.07% (based on Koch *et.al. 2006* (13), percentage of in-hospital mortality in patients with transfused RBC is 3.07%, $p < 0.0001$)

Sample size = 42 + 20% drop out = 50 patients

Total sample size required for this study is 108

Include the 20% of dropouts

The sample size is calculated based on the adverse outcomes – an assumption of minimum number of complications (prolonged ventilatory support, cardiac morbidity, neurologic morbidity, renal morbidity, serious infection and mortality) among CABG patients who received perioperative red blood cell transfusions. Giving a 20% drop-out rate of incomplete data retrieval, a minimum number of 108 patients is required to meet the study objective. This figure is derived using Sample Size Calculator for Prevalence Studies (Raosoft®), estimated using 95% confidence interval of ± 5% precision to detect a prevalence of respective percentage of complications for these patients. Highest number among calculated sample size for each adverse outcome is taken as the sample size for this study.