ORIGINAL ARTICLE

Association of Red Blood Cell Transfusion with Mortality and Morbidity in Post Cardiac Surgery Patients

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ABSTRACT

Introduction: CAD accounts for 25% of mortality in Malaysia public hospitals. CABG is one of treatment for patients with CAD, but requires RBC transfusion, which is associated with morbidity and mortality. This study was to evaluate the association between RBC transfusion and morbidity and mortality in CABG patients at the National Heart Centre, Malaysia (IJN). **Methods:** Retrospective cross-sectional study performed using data from 434 patients who underwent CABG in 2013 and 2014. Subjects had systematic random sampling every fifth subject of the patients in the sequence of dates of the year. Data related to the relationship between RBC transfusion with mortality and morbidity, and the predicting factors captured. **Results:** 64.3% of CABG patients (n = 279) received RBC transfusion perioperatively. Age, gender, BMI, and EF, were factors that contributed for RBC transfusion. RBC transfusion was a contributor to longer intensive care unit length of stay (ICULOS) and hospital length of stay (HLOS). Multiple logistic regression revealed, for every 1 year increase of age, there is 3.5% higher chance of transfusion. Whereas an increase of 1 kg/m^2 of BMI and 1% of EF reduced the odds of RBC transfusion by 13.0% and 3.0% respectively. **Conclusions:** Age, gender, BMI, and EF determine the probability of needing RBC transfusion during CABG, and RBC transfusion will result in longer ICULOS, and HLOS. Probability of RBC transfusion will be higher in older patients and reduced in those with higher BMI and EF.

Keywords: CAD, CABG, RBC transfusion, Morbidity, Mortality

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INTRODUCTION

In 2012, estimated 17.5 million people died from CVDs worldwide. Of these deaths, an estimated 7.4 million were due to coronary artery disease (CAD) (1). Coronary artery bypass grafting (CABG) is an effective mode of treatment for patients with CAD. However, it is associated with high usage of blood products (2). Red blood cell (RBC) transfusion often is required during the procedure, which in turn is associated with morbidity and mortality.

The National Heart Centre, Kuala Lumpur (IJN) is the leading tertiary cardiac centre in Malaysia. Statistics from IJN for year of 2010 to 2016 revealed that 1200 to 1600 CABG procedures cases were performed each year, with 60.4 to 82% of patients receiving blood transfusion perioperatively (unpublished data of IJN, 2017).

The goals of this study were to assess the proportion of CABG patients who require RBC, compare the outcomes (intensive care unit length of stay (ICULOS), hospital length of stay (HLOS), infection complications, and death) of patients who did and did not receive RBC transfusion, and determine predictive factors (age, gender, body mass index (BMI), ejection fraction (EF) associated with RBC transfusion in CABG.

MATERIALS AND METHODS

Study design

This was a retrospective cross-sectional study that included data from 434 patients who underwent primary and elective CABG over a period of two years (2013 and 2014) at IJN. The inclusion criteria were as follows: Malaysian citizen; 18-70 years old; New York Heart Association Class 1 & II only; under IJN follow-up, pre-operation, and post-operation; and the CABG procedure must have been elective and for the first time. The exclusion criteria included co morbidities

such as morbid obesity stage III-IV, uncontrolled diabetes mellitus with HbA1C > 9%, chronic kidney disease and on renal replacement therapy and major haemoglobinopathy and bleeding disorders, as these co morbidities are highly associated with independent risk of infection, and possibility of need for blood transfusion.

From January 2013 through December 2014, 3,640 patients underwent CABG at IJN. Of the 2,545 patients who met the inclusion criteria 434 cases were chosen using systematic random sampling.

The study sample size required was 329. With the addition of 20% more samples to cover incomplete data, the final sample size was 394 samples. Thus, our data from 434 cases were more than sufficient to meet this requirement.

Data analysis

Statistical analysis (descriptive, statistical and multivariate) was performed using SPSS version 23.0 for Windows (SPSS, Chicago, USA). For the demographic data, number and percentage values were used for gender, and BMI, and the mean was used for age, EF, and cardiopulmonary bypass (CPB) time. For infection complication and death data, the Fisher's exact test was used, whereas ICULOS and HLOS data were compared using the, Man Whitney U test, as these factors were not normally distributed. To analyse age, BMI, and CPB time, independent t- tests were used, whereas the Pearson chi square test was used for gender. The associations between the five factors (age, gender, BMI, EF, CPB time) and RBC transfusion were analysed individually using simple logistic regression (univariate analysis). Only significant independent variables with p-value < 0.25 were analysed using multiple logistic regression.

RESULTS

Table I shows the patients' demographic data. The study population was predominantly male. Two hundred seventy nine patients received RBC transfusion when they underwent primary and elective CABG at IJN.

Table I: Demographic characteristics distribution of the patients

Characteristics	RBC transfusion	
	Yes	No
[a]Number of patients	279 (64.3)	155 (35.7)
[a]Gender		
Male	251 (90.0)	147 (94.8)
Female	28 (10.0)	8(5.2)
[b]Age (years)	57.80 ±7.0	55.00±7.3
[b]Body Mass Index (kg/m^2)	25.90±3.5	27.70±3.5

[a]Value expressed in number (percentage)
[b]Value expressed in mean (±SD)

Mean ages were similar between the transfused and non-transfused groups and most patients were male for both groups. The BMI and EF values for patients who required RBC transfusion were lower than that, of patients who did not require RBC transfusion.

Bivariate analysis revealed significant association between RBC transfusion and age (p =0.001), gender (p = 0.038), BMI (p < 0.001), and EF (p <0.001) (Table II). Significant associations for ICULOS and HLOS with RBC transfusion also were detected (p < 0.001). However, no significant association (p > 0.05) between RBC transfusion and infection complication or death was found (Table III).

Table II: Factors associated with RBC transfusion

Characteristics	RBC transfusion		T stat	Chi square value	p-value
	Yes	No			
[a]Age (years)	57.80 ±7.0	55.00 ±7.3	3.46		0.001*
[b]Gender				4.29	
Male	251 (90.0)	147 (94.8)			0.038*
Female	28 (10.0)	8(5.2)			
[a]Body Mass Index (kg/m^2)	25.90 ±3.5	27.70 ±3.5	5.02		< 0.001*
[a]Ejection Fraction (%)	53.20 ±10.7	56.10 ±9.9	2.63		0.007*
[a]Cardio-pulmonary bypass times (CPB) (minutes) (n = 379)	91.71 ±29.59	92.67 ±29.7	0.30		0.764

[a]Independent t test [b]Pearson Chi-square test *Significant at p < 0.05

Table III: Association between morbidity/mortality and RBC transfusion

Morbidity / Mortality	RBC transfusion		p-value
	Yes	No	
[a]Infection complication			
Yes	7 (2.5)	3 (2.0)	0.725
No	272 (97.5)	152 (98.0)	
[b]ICU length of stay (days)	1.00 (1.00, 10.00)	1.00 (1.00, 7.00)	< 0.001*
[b]Hospital length of stay (days)	7.00 (4.00,70.00)	6.00 (2.00,29.00)	< 0.001*
[a]Death			
Yes	2 (0.7)	2 (1.3)	0.460
No	277 (99.3)	153 (98.7)	

[a]Fisher's Exact test [b]Mann Whitney-U test
*Significant at p < 0.05

Factors that were significant in the bivariate analyses were analysed using multiple logistic regression to identify those that independently predict RBC transfusion in these patients. The final model showed that three factors (age, BMI, and EF) were independently associated with RBC transfusion among the CABG patients in this study (Table IV). A one year increase in age increased the odds of acquiring RBC transfusion by 1.04 times (p=0.021, adjusted odd ratio (AOR) 1.04 95% confidence interval (CI) 1.01-1.07). In contrast, increases of 1 kg/m2 of BMI and 1 unit of EF reduced the odds of requiring RBC transfusion by 0.88 and 0.97 times respectively. This final model explained 12.2% of the variability of RBC transfusion among CABG patients in this study (Nagerlkerke R2 = 0.122). Overall, 68.4% of all RBC transfusions among the CABG patients involved in this study could be predicted accurately by this model. There was no issue of multicollinearity or interaction between the significant predictors.

Table 4. Prediction model for RBC transfusion among CABG patients

Predictors	B	S.E.	Wald	df	p-value	Adjusted OR	95%CI for OR	
							Lower	Upper
Age	0.034	0.015	5.305	1	0.021*	1.035	1.005	1.066
BMI	-0.128	0.031	16.969	1	0.000*	0.880	0.828	0.935
EF	-0.027	0.011	6.717	1	0.010*	0.973	0.953	0.993
Gender	-0.757	0.451	2.813	1	0.094	0.469	0.194	1.136
Constant	4.281	1.493	8.226	1	0.004	72.302		

Backward Likelihood Ratio Method Hosmer and Lemeshow Test (p-value): 0.894
*Significant at p-value < 0.05

DISCUSSION

A variety of treatment options are available for CAD. CABG is a type of treatment for patients with CAD. Yusuf (1994) reported that CABG offered a better outcome than medical therapy for patients with left main or triple vessel disease (3).

Worldwide, CABG is one of the most common types of surgery performed in major cardiac centers. However, CABG is associated with a high rate of RBC transfusion, with reported values ranging from 7.8% to 92.8% (4). At IJN, 60.4% to 82% of them received RBC transfusion during the intraoperative and postoperative period (unpublished data of IJN, 2017).

Prevalence of RBC transfusion in CABG patients at IJN

Of the 434 cases of CABG from 2013 to 2014 analysed in this study, 279 patients (64.3%) received RBC transfusion. The 64.3% RBC transfusion rate is within the range of global blood transfusion practice in cardiac surgery; 27 to 92% in the USA2 and 3 to 88% in Scandinavian countries (5). The transfusion rate in cardiac centres worldwide is varies widely, as it is determined by several factors, including the presence of transfusion guidelines, the status of the centre as a bloodless surgery centre or a conventional centre, and the personal preference of the clinician involved (6, 7).

The significant association between gender (i.e., being female) and RBC transfusion observed in this study was consistent with many other studies showing that female gender was an important determinant factor for risk of requiring RBC (8-11).

Mean ages were 57.80 ± 7.0 and 55.00 ± 7.3 years for the transfused and non-transfused groups, respectively. In general, the risk of CVD increases with increasing age due to decline in the function and structure of the cardiovascular system (11,12).

Bower (2010) and Veenith (2010) also suggested that older patients who undergo operations have more co morbidities are not in the best clinical condition for major surgery, and therefore have higher blood transfusion rates during and after surgery (13, 14). In addition, older patients with CVD often are on medication, including anticoagulation medication. As a result, emergency surgery with suboptimal cessation of medication would lead to higher risk of bleeding (15).

Mean BMI of patients who required RBC transfusion was lower than that of patients who did not receive RBC (27.70±3.5kg/m2), meaning that lower BMI were associated with higher transfusion rate. Previous studies also reported that higher BMI was significantly associated with lower RBC transfusion rate (16-18). The "obesity paradox" postulated that heart disease patients who are overweight and mildly obese have better prognosis for long- term treatment outcome, including lower bleeding rate perioperatively (19-20). One potential explanation for this paradox is that patients with lower BMI (i.e., leaner body), may be cachetic and malnourished and have a higher chance of suffering from other associated illnesses. Low BMI also is indicative of low total blood volume as well, thus even minimum blood loss during surgery can be significant (21).

Mean EF of patients who received RBC transfusion was significantly lower than that of mean EF of patients who did not receive RBC transfusion. Patients with moderately to severely impaired EF can have generalized poor perfusion, which reduces blood supply to vital organs in the body (22). Patients with impaired EF also are more likely to have other co morbidities, and; low EF itself is an independent risk factor for perioperative morbidity and mortality (23).

Mean CPB time for patients who received RBC transfusion was slightly shorter than that of patients who did not receive RBC. However, other studies reported that longer CPB time was a main predictor of higher probability of needing RBC transfusion (24-26). The contradicting study as compared to others might be resulted by the small number of sample size in this study.

Outcome of CABG patients

HLOS and ICULOS were both significantly longer in

patients who received RBC transfusion than in those who did not. Numerous other studies reported similar findings. Galas (2013) found that cardiac surgery patients who received more than 3 units of RBC transfusion had median HLOS of 15 days, those who received 1– 3 units of RBC stayed for 10 days, and patients who never had RBC transfusion stayed for only 9 days. Veenith (2010) reported that both HLOS and ICULOS were directly associated with amount of RBC transfusion (14), with median of 1 day ICULOS for RBC transfusion of 0 to 2 units and 2 days ICULOS for RBC transfusion of more than 2 units (14).

The need for RBC transfusion might be, considered an indicator of perioperative difficulty, thereby resulting in higher morbidities that lead to longer ICULOS higher risk of infection, and ultimately longer HLOS (27). Bower (2010) reported that transfused patients in their study were significantly older and more ill, which contributed to higher chance of complications intraoperatively and postoperatively, and therefore RBC transfusion was more likely to be administered (13).

However, no significant associations between RBC transfusion and infection complication or death were detected in this study.

Ali (2004) stated that RBC transfusion did not increase the risk of infection, although of other studies reported that RBC transfusion was associated with increased infection complications (28). Hovrath (2013) found that the most common major infections following cardiac surgery were pneumonia, C. difficile colitis, and bloodstream infection, and the probability of infection was greater with higher number of RBC transfusions (i.e., a dose- related association) (29). Whitson (2010) reported that RBC transfusion of more than 5.5 units was an important predictor of infection complication, and Bower WF (2010) reported that non- cardiac surgery patients who received RBC transfusion suffered twice the risk of surgical wound infection (13, 30).

In this study, only four deaths occurred post CABG, and deaths all happened within 30 days of the surgery. Jakobsen (2012) and Engoren (2002) both reported that RBC transfusion was an important factor associated with long- term mortality after cardiac surgery; however, they agreed that RBC transfusion might not be significant in early mortality post cardiac surgery, as was found in this study (31, 32). Jakobsen (2012) suggested that early death post cardiac surgery can result from various factors, including surgical challenges and poor condition of the patients prior to surgery, and thus it may not be due solely to RBC transfusion (31).

Predictive factors for RBC transfusion in CABG

Single logistic regression (SLR) was performed for each factor - (age, gender, BMI, CPB time, and EF), and all factors except CPB time were found to be significant.

Multiple logistic regressions to analyse the likelihood of requiring RBC transfusion with CABG were conducted using these four independent variables (age, gender, BMI, gender and EF), and all but gender made a statistically significant contribution to the model ($p < 0.05$).

For age, the B value of 0.034 indicated that the chance of needing RBC transfusion was higher with increasing age. The OR for age showed that for every 1 year increase in age, the odds of having a RBC transfusion would increase by 1.04 times, when adjusted for BMI and EF ($p = 0.021$, OR 1.04, 95% CI 1.01–-1.07). Anaemia is more prevalent with increasing age, and Guralnik (2004) reported that about 11% of men and 10.2% of women older than 65 years old were anaemic (33). Dunne (2002) found that, the incidence of preoperative anemia (haematocrit < 36%) in elderly patients undergoing surgery was 34%, which increased the chance of needing RBC transfusion intra- and postoperatively (34).

In the patients in this study, higher BMI and EF appeared to be factors that prevented the need for RBC transfusion. For BMI, the B value of -0.128 indicated that higher BMI resulted in lower probability of RBC transfusion. For a person with an increase of 1 kg/m2 of BMI, the odds of needing a RBC transfusion would decrease by 0.88 times when adjusted for age and EF. Mongero (2016), Engstrum (2002), and Ellis (1996) also reported that higher BMI was a protective factor against bleeding in cardiac surgery (16-18). Patients in the low BMI category might be severely underweight and malnourished and, therefore more likely to have eventful perioperative and postoperative periods that, include bleeding (21).

The results also show that a 1% increase in EF value would reduce the odds of needing a RBC transfusion by 0.97 times when adjusted for age, gender, and BMI. Low EF indicates impairment of left ventricular function, which poses an extra surgical challenge to surgeons because it is associated with higher mortality and morbidity, including higher risk of transfusion (35). In general, patients with lower EF have a higher probability of having co morbidities, which in turn increase the chance of needing a RBC transfusion. Low EF itself is a known independent risk factor for perioperative morbidity and mortality (23, 36, 37).

In the simple linear regression analysis, female gender was significantly associated with RBC transfusion, but it became not significant once adjusted with other factors in multiple linear regression. This difference likely is due to the small sample size of female patients (only 36, or 8.3% of the total).

As age, BMI, and EF were the main predictors for patients to require blood transfusions during the CABG procedure, the predictor model for RBC transfusion requirement among CABG patients is:

RBC transfusion needed (z) = 3.665 + 0.034 (Age) –

0.133 (BMI) – 0.027(EF)

This final model explained 12.2% of the variability of RBC transfusion among CABG patients in this study (Nagelkerke R2= 0.122). In addition, 68.4% of all RBC transfusions among CABG patients involved in this study could be predicted accurately by this model.

CONCLUSION

The RBC transfusion rate in CABG patients at IJN was 64.3%. The significant factors that contributed to the need for RBC transfusion were older age, female gender, lower BMI, and lower EF. In addition, those who received RBC transfusion during CABG had longer ICULOS and HLOS, but no significant association between RBC transfusion and infection complications or death were detected.

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