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ORIGINAL ARTICLE

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ABSTRACT

Objective: To build a clinical predictive model to determine the need for transfusing blood and its products in coronary artery bypass grafting (CABG) procedures in South East Asian population.
Study Design: Analytical study.
Place and Duration of Study: Section of Cardiothoracic Surgery, Aga Khan University Hospital, Karachi, from January 2006 to October 2014.
Methodology: Information on pre-, intra- and postoperative variables were collected for all adult patients who underwent on-pump CABG. The patients grouped into those who received blood and its components, and those who did not. A univariate as well as multivariate logistic model was built to determine the predictors of transfusion.
Results: A total of 3,550 patients underwent CABG and males were dominant in both groups (75 vs. 93%). The transfusion rate was 56.4% (n=2001). Age (adjusted OR 1.03, $p < 0.001$), obesity (1.50, p=0.001), tobacco use (1.29, p=0.001), and male gender (4.51, $p < 0.001$) found to be a stronger predictor. Among preoperative comorbidities, diabetes (1.20, p=0.016), myocardial infarction (1.22, p=0.009), preoperative creatinine (1.12, p=0.033), and left main vessel disease of > 50% (1.49, $p < 0.001$) were independently associated with the outcome. Compared to elective cases, transfusion rates were high in urgent and emergent cases (OR: 1.93 and 3.36 respectively, $p < 0.001$ for both).
Conclusion: Age, male gender, obesity, tobacco use, diabetes, myocardial infarction, high creatinine, urgent and emergent cases were independent predictors of transfusion in CABG procedure. This model can be utilized for pre-operative risk stratification of patients and their management to improve the outcomes.

Key Words: *Adult. Blood component transfusion. Predictors of blood transfusion. Coronary artery bypass grafting.*

INTRODUCTION

Blood product use during coronary artery bypass grafting is an easy solution to the large volume of blood loss; however, there is growing evidence that this is associated with other complications as well.[1-6] Current transfusion trends for packed red blood cells average between 0 to 6.3 units per person.[1,2] This variation in transfusion rate exists due to a host of factors which range from preexisting comorbidities to use of anti-platelet agents, procedure related factors, and even institution-based variability.[7]

It would be correct to extrapolate from pre-existing European, North American and Middle Eastern data that a decrease in transfusion rate will assist in conserving resources and improving outcomes by controlling complications, some of which stem directly from transfusions. Some of these complications include renal failure, transmission of infectious diseases such as Hepatitis B and C, HIV, syphilis, transfusion associated lung injury, immune-modulation, and stroke.[2,3,5] Studies have shown that longer intubation time for patients who have been given packed red blood cells, has greater risk of re-intubation and longer postoperative stay.[4-6] Therefore, preventing the unnecessary use of blood and its products would provide substantial benefit to the patient and improve the overall outcomes.

To minimize the negative impact of blood product use, current practices include various techniques that have been adopted to reduce the need for allogeneic transfusion. These include preoperative autologous blood transfusion, use of intraoperative antifibrinolytic agents, intraoperative blood salvage techniques, and erythropoietin administration, which are beneficial however, they add a significant cost to an already expensive procedure and increase the burden on the patient.[7,8]

Therefore, to improve the outcomes it would require the ability to reduce the number of blood products used in patients, which can be done if we are able to predict who will and who will not require blood. Being able to correctly identify patients using a specific criteria, will assist not only in conservative blood banking and improved efficiency in blood product utilization but can also help to reduce related morbidity and mortality in patients undergoing CABG procedures.

However, of note is the fact that most available data is from the western hemisphere. Our analysis, therefore,

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aims not just to add pertinent variables that will be applicable to our South Asian population, but will also assist in drawing a prediction model that caters best for patients undergoing CABG in this part of the world. At the same time, it shall also highlight similarities as well as differences existing in our prediction tool as compared to those previously reported.[9,10]

The main objective of this study was to prepare a clinical predictive model to determine the need for transfusing various blood products in CABG procedures in local population.

METHODOLOGY

A retrospective analytical study was conducted at Section of Cardiothoracic Surgery, Aga Khan University Hospital from January 2006 to October 2014. It included all adult patients aged ≥ 18 years who underwent isolated on-pump CABG and had elective, urgent or emergent procedure and excluded all off-pump cases.

The information on blood product type and amount used that include whole blood, packed red blood cells (pRBC's), fresh frozen plasma, platelets and cryoprecipitate were extracted. To ensure reliability in recording the type of blood product and the amount being transfused, the hospitals, blood bank records were consulted in tandem with documented nursing orders confirming administration. The laboratory data which had been provided by the Aga Khan University Laboratory was accounted for and any work-up performed outside our institute was discounted for to ensure reliability.

Identification numbers were assigned to each participant to maintain confidentiality. Any of the participant's details were not used in these reports. This study was exempted by Ethical Review Committee (ERC) of the Aga Khan University Hospital.

The products (singly or in combination) used intra-operatively, postoperatively or both being allogeneic transfused to the patient considered blood product use (dependent variable). These include whole blood, packed red blood cells (pRBC's), platelets, fresh frozen plasma (FFP) or cryoprecipitate.

Data was analysed using Statistical Packaging for Social Sciences (SPSS) version 20. A p-value of < 0.05 was considered statistically significant. Histograms and Kolmogorov Normality test was performed to assess the distribution of the continuous variables. Frequencies and percentages for categorical variables, mean and standard deviation for normally distributed continuous variables, and median and interquartile range for non-normally distributed continuous variables were calculated.

Comparison of continuous and categorical variables between those who received blood products and those who did not, were evaluated through independent t-test or chi-square or Fisher's exact test, where appropriate. Independent predictors of blood transfusion were identified using univariate analysis and retained in the multivariable logistic model with an entry criteria of $p < 0.05$.

RESULTS

A total of 3,550 patients underwent isolated CABG during the specified period and 2,001 (56.4%) had received blood or its components. The participants of transfused group were elder than the non-transfused group (mean age 59.8 ±9.4 vs. 56.2 ±9.4 years). Male proportion in both groups was predominant (74.7 vs. 93.4%, Table I). The non-transfused participants were more obese compared to transfused participants, BMI (27.2 ±4.4 vs. 26.3 ±4.2). Diabetes, hypertension, myocardial infarction and chronic lung and presence of main left vessel disease of > 50% was more prevalent in the transfused group (p < 0.05 for all). Ejection fraction was low and creatinine was high in this group. However, proportion of family history of coronary artery disease and tobacco use was high in non-transfused group. Peri-

Table I: Comparison of patient's demographics, preoperative and intraoperative characteristics by transfusion and no transfusion, n=3550.

Variables	Transfused (n=2001)	Not transfused (n=1549)	p-value*
Age, mean ± SD (years)	59.8 ± 9.4	56.2 ± 9.4	< 0.001
Sex			< 0.001
Male, n (%)	1495 (74.7)	1447 (93.4)	
Female, n (%)	506 (25.3)	102 (6.6)	
BMI (Kg/m^2), mean ± SD	26.3 ± 4.2	27.2 ± 4.4	< 0.001
Current tobacco use, n (%)	778 (38.9)	804 (51.9)	< 0.001
Diabetes mellitus type-II, n (%)	1104 (55.2)	721 (46.5)	< 0.001
Hypertension, n (%)	1522 (76.1)	1065 (68.8)	< 0.001
Dyslipidemia, n (%)	1242 (62.1)	949 (61.3)	0.625
Myocardial infarction, n (%)	1109 (55.4)	702 (45.3)	< 0.001
Chronic lung disease, n (%)	65 (3.2)	32 (2.1)	0.037
Family history of CAD, n (%)	970 (48.5)	804 (51.9)	0.046
Ejection fraction, mean ± SD	46.7±14.4	50.4±12.4	< 0.001
Creatinine level, mean ± SD	1.2±0.8	1.1±0.7	< 0.001
Left vessel disease > 50%, n (%)	445 (22.2)	229 (14.8)	< 0.001
Initial hours. ventilated PO**	13 (7, 20)	8 (6, 14)	<0.001
IABP^ insertion, n (%)	255 (12.7)	51 (3.3)	< 0.001
Perfusion time (min), mean ± SD	106.8±48.6	98.6±43.3	< 0.001
Cross clamp time (min), mean ± SD	66.2±35.4	62.3±28.1	< 0.001
Lipid lowering therapy, n (%)	1309 (65.4)	962 (62.1)	0.041
Aspirin, n (%)	1576 (78.8)	1205 (77.8)	0.487
Mortality, n (%)	78 (3.9)	14 (0.9)	< 0.001
Type of surgery, n (%)			< 0.001
Elective#	1369 (68.4)	1270 (82.0)	
Urgent†	392 (19.6)	201 (13.0)	
Emergent‡	240 (12.0)	78 (5.0)	

* *Independent samples t-test for continuous and Pearson Chi-square or Fisher's Exact test for categorical variables where applied.*
** *PO=Post-operative; Median (25th, 75th centile), p value derived from Mann-Whitney-U test. BMI=Body mass index (kilogram/meter^2).*
^ *IABP= Intra-Aortic Balloon Pump.*
# *Any patient operated upon beyond the first 48 hours of being evaluated by the cardiothoracic services.*
† *Any patient operated upon between 12-48 hours from the time of admission.*
‡ *Any patient operated upon up to 12 hours from the time of admission.*

operative variables were statistically different among the groups. Intra-aortic balloon pump (IABP) requirement, perfusion and cross-clamp time was significantly high in transfused subset. The proportion of patient underwent elective procedure was higher in the non-transfused compared to the other group (82% vs. 68%); nevertheless urgent and emergent procedures were frequent in the transfused group (19.6 vs. 13.0% and 12.0 vs. 5.1% respectively, p < 0.001). More than 62% of patients were preoperatively using lipid lowering medicine and more than 77% were on Aspirin therapy in both groups (Table I). The mortality rate was high in transfused group (3.9% vs. 0.9%).

More women required transfusions compared to men included in the study (83% vs. 51%, Table I). Majority of patients n=1860, (93%) received packed red blood cells (pRBCs), while 24% received platelets, 21% received fresh frozen plasma, and only 1.3% received cryoprecipitate (Table II), while 24% (n=495) were recipients of more than one blood product.

Several conventional demographic and clinical risk factors were significantly associated at univariate level with increased need of transfusion. However, the ones that predicted best, the risk for blood product use had to be chosen. Therefore, all the univariate predictors with (p < 0.05) were taken to generate a multivariate parsimonious model.

A full multivariate model (Table III), adjusting for demographics, comorbidities, clinical and perioperative variables, shows a significant association with transfusions. Age {adjusted OR, (AOR) = 1.03, p < 0.001}, obesity (AOR=1.50, p=0.001), tobacco use (AOR= 1.29, p=0.001), while male gender emerged as a strongest predictor, (AOR= 4.51, p < 0.001) in this sample. Among preoperative comorbidities, diabetes (AOR=1.20, p=0.016), myocardial infarction (AOR= 1.22, p=0.009), preoperative creatinine (AOR=1.12, p=0.033), and left main vessel disease > 50% (AOR= 1.49, p < 0.001) were independently associated with the transfusion in CABG patients. Increasing ejection fraction showed a protective effect (AOR=0.99, p=0.002). Intraoperative intraaortic balloon pump (IABP) use had two times increased requirement of blood product use (AOR= 2.14, p < 0.001). A demographic adjusted model {age, gender, obesity (> 25 BMI Kg/m^2) and tobacco use} showed that those who were operated in urgent and emergent conditions had greater need of blood transfusions compared to elective procedures, (AOR: 1.93 and 3.36 respectively, p-value for both categories was < 0.001).

Table II: Break-up of type of blood products used, n=2001.

Type of blood products*	Number	Percentage (%)
Packed RBC	1860	93.0
Fresh Frozen Plasma	422	21.1
Platelets	481	24.0
Cryoprecipitate	27	1.3

**More than one blood product has been transfused*

DISCUSSION

The main aim of this study was to determine the factors that could predict the need of blood and blood product transfusions in patients underwent CABG surgery. This study results showed the transfusion requirement was up to 56.4% for all the patients which is comparable to other studies.[1,2,10]

These results demonstrated that conventional CVD risk factors such as age, obesity and tobacco use have an independent association with transfusion.[11] Male gender had the strongest association with the outcomes, although several studies had reported that females have greater rates of transfusion in CABG procedures, most likely because of their smaller circulating blood volume necessitating increased blood product use.[11,12] A number of comorbidities were independently associated with transfusion rates. Diabetes shows a significant effect as this high risk population makes CABG a highly demanded surgery.[13] Previous history of myocardial infarction, presence of left main vessel disease by > 50%, and high creatinine level showed independent

Table III: Crude and adjusted odds ratios and 95% CI for blood and blood product transfused in isolated CABG patients.

Variables	Crude OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
Age	1.04 (1.03, 1.05)	<0.001	1.03 (1.03, 1.04)	<0.001
Gender (male)	4.80 (3.84, 6.01)	<0.001	4.51 (3.54, 5.75)	<0.001
Current smokers	1.23 (1.08, 1.41)	0.002	1.29 (1.11, 1.50)	0.001
BMI > 25 (Kg/m^2)	1.35 (1.18, 1.56)	<0.001	1.50 (1.29, 1.75)	0.001
Diabetes mellitus type-II	1.41 (1.24, 1.62)	<0.001	1.20 (1.03, 1.39)	0.016
Hypertension	1.44 (1.25, 1.68)	<0.001	1.14 (0.97, 1.34)	0.117
Myocardial infarction	1.39 (1.21, 1.59)	<0.001	1.22 (1.05, 1.43)	0.009
Ejection fraction	0.98 (0.97, 0.99)	<0.001	0.99 (0.98, 1.00)	0.002
Creatinine level	1.25 (1.11, 1.40)	<0.001	1.12 (1.01, 1.25)	0.033
Left vessel disease	1.65 (1.38, 1.97)	<0.001	1.49 (1.23, 1.81)	<0.001
Perfusion time (min)	1.01 (1.00, 1.01)	<0.001	1.01 (1.00, 1.01)	<0.001
IABP	4.29 (3.15, 5.84)	<0.001	2.14 (1.48, 3.08)	<0.001
Initial hours ventilated PO	1.05 (1.04, 1.06)	<0.001	1.01 (1.00, 1.02)	0.001

**Adjusted for all variables in the model* associations as these factors are associated with significant morbidity and mortality in CABG procedures.[14] Association of hypertension showed a significant association with the outcome at univariate level; however, lost its significance after adjustments. High ejection fraction demonstrated a protective effect on the outcomes and reduced the transfusion requirements significantly. Similarly, intra- and postoperative variables such as IABP, perfusion time, and initial number of hours ventilated have demonstrated a significant association with blood product use. IABP insertion created twice demand of transfusions. This is due to the greater amount of time spent by the blood in contact with the artificial surfaces of the extra corporeal circulation, which in turn necessitates greater time; and subsequently, the bypass time itself can lead to an increased risk of transfusion.[15] Moreover, prolonged time on the bypass circuit can also lead to an inflammatory response with the release of large quantities of cytokines, particularly IL6, IL8, IL10, coupled with endotoxemia and ischemic reperfusion injury during and after bypass, all contributing to greater morbidity and mortality.[16] These cytokines along with oxygen derived free radicals and vessel constricting factors can all contribute to worsening of cardio-pulmonary function[17] and thus result in prolonged extubation time, length of CICU stay and chest outputs.

The type of surgery has shown to be a significant predictor and to be a pertinent variable reported in the literature.[10,18] Urgent and emergent cases were at greater need of blood transfusion with reference to elective ones. This can be attributed to the fact that in emergent cases due to the tenuous clinical status of the patient, there is frequently inability to wait for reversal of any anti-platelet agent; which leads to increased blood loss in the operative field and requires immediate need of transfusions.

Furthermore, it is also prudent to mention here the mortality rate in transfused group was thrice (3.9%) compared to non-transfused group (0.9%). Since the distribution of elective, urgent and emergent type of procedure was comparable in mortal cases and no significant association with the outcome was observed as other studies have reported;[19,20] however, these numbers cannot be ignored and a large sample size is required to derive a more direct cause and effect relationship between transfusion and mortality.

This is the first study to the authors' knowledge that has developed a predictive model from a large population that can preoperatively predict the risk of receiving blood and its products during or after the procedure on an individual basis. The importance of these tools lies in the fact that their clinical application will allow for the effective use of blood products since it will help to stratify those patients who require blood products from those who do not, which is a cost effective practice and will also help prevent the waste of this precious commodity. It will also facilitate to achieve penultimate goal of better outcomes for patients, since less and appropriately directed transfusions will mean a reduction in morbidity and mortality.

The results should be interpreted cautiously considering some limitations. Our model is developed at a single institution; therefore, it could not be generalized to whole population undergoing CABG surgery. A further multi-center study is required to get robust inferences. Only on-pump CABG patients were included; therefore, this model might not be applicable to the off-pump subsets. In addition, the effect of unknown confounders or variables which could not be explored due to retrospective design, cannot be disregarded completely due to limitation of the study design. A prospective study would provide precise and robust estimates.

CONCLUSION

In this study, age, male gender, obesity, tobacco use, diabetes, myocardial infarction, high creatinine and urgent and emergent cases were found to be independent predictors of blood and its components transfusion in CABG procedures. This model can be utilised for preoperative risk stratification of patients and their management to improve the outcomes.

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