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Transfusion associated in-hospital mortality and morbidity in isolated Coronary Artery Bypass Graft surgery

Research Article

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Abstract: Transfusion after cardiac surgery is very common. This rate varies between institutions and has remained high despite established transfusion guidelines. We analyzed our database of patients who underwent isolated CABG (Coronary Artery Bypass Graft) to determine the predictive factors of homologous transfusion and associated postoperative morbidity, mortality and resource utilization.All 14,152 patients who underwent first-time isolated CABG, with or without cardiopulmonary bypass (CPB) who had postoperative homologous transfusion between February 2002 and March 2008 in Tehran Heart Center, were evaluated retrospectively. Overall, 16.5% of patients received transfusion. Transfused patients demonstrated a significantly higher incidence of postoperative complications (cardiac, infectious, ischemic, reoperation) and mortality ($p<0.001$). Homologous blood transfusion effect on mortality, morbidity and resource utilization. By Multivariable logistic regression analysis adjusted for confounders: Homologous blood transfusion effect on Mortality (30-days) (OR=3.976, $p<0.0001$), Prolonged ventilation hours (OR=4.755, $p<0.0001$), Total ICU hours (β =14.599, $p<0.0001$), Hospital length of stay (β =1.141, $p<0.0001$), Post surgery length of stay (β =0.955, $p<0.0001$). We conclude that the isolated CABG patients receiving blood transfusion have significantly higher mortality, morbidity and resource utilization. Homologous blood transfusion is an independent factor of increased resource utilization, morbidity and mortality.

Keywords: *Transfusion • CABG • Mortality • Morbidity*

1. Introduction

The frequency of blood transfusion in patients undergoing Coronary Artery Bypass Graft (CABG) surgery is high; annually more than 3 million patients receive more than 11 million units of transfused blood in cardiac surgery in United States [1]. By increase in age and comorbidities among patients that refer to cardiac surgery, a higher blood transfusion rate is expected. The decision to transfuse patients is always done to amend hemostasis or improve the carrying capacity of oxygen in the blood [2]. Physicians make transfusion decisions based upon their past teaching and enculturation. As a result of the lack of evidence based medicine supporting the transfusion decision, transfusion during CABG surgery varies widely [3,4]. In other way, transfused patients in general are immunosuppressive [5,6] and unfortunately, these patients have been associated with postoperative infection in a dose-dependent model by blood units transfused [7]. The combined effect of postoperative transfusion on patients undergoing isolated CABG in terms of cumulative morbidity and perioperative mortality and their resource utilization [total intensive care unit (ICU) hours, duration of intubations, hospital length of stay (HLOS), post operation length of stay (PLOS)] is less known. The purposes of this study were [1] to identify preoperative risk factors that may be associated with blood transfusion, [2] to evaluate the effect of blood transfusion on 30 days mortality

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and morbidity in patients undergoing isolated CABG, and [3] to evaluate the effect of blood transfusion on resource utilization.

2. Material and Methods

2.1. Statistical methods and experimental procedures

This is a retrospective cross sectional study consisting of 14,152 patients who underwent first-time isolated CABG with or without cardiopulmonary bypass (CPB), between February 2002 and March 2008 in Tehran Heart Center. Patients who had valvular, carotid endarterectomy or other operation simultaneously with CABG and any operational mortality were excluded. In each analysis, we grouped the patients by those who transfused and those who did not. Homologous packed cell was used for patients in postoperation units: intensive care unit (ICU) and/or critical care unite (CCU). In our study, the main indication for transfusion was postoperative Hematocrit (Hct) less than 25% to 26 %. But in the elderly, patients with low ejection fraction, or patients with haemodynamic instability, the threshold of blood transfusion may decrease on the basis of surgeon and anesthesiologists' decision. We had missing data in our database about the amount of packed cell units used for each patient; thus, we did not incorporate these variables in our analysis. For all patients, data recorded consisted of information on patient characteristics and their preoperative comorbidities, operative and postoperative variables, resource utilization parameter, their morbidity (any complications that happened during this admission) and 30-day mortality (any death which happen during 30 days post operation). We categorized our patients' morbidity into four groups: 1) Infectious complications: deep-sternal infection, thoracotomy, leg infection, septicemia, urinary tract infection, pneumonia, 2) Ischemic complications: postoperative stroke for more than 72 hours, transient neurologic deficit, continuous coma for more than 24 hours, renal failure, acute limb ischemia, iliac/femoral dissection, 3) Cardiac complications: heart block, atrial fibrillation, cardiac arrest, tamponad, aortic dissection, inotrope use, pulmonary emboli, and 4) Reoperation: Reop-bleeding/tamponad, graft occlusion, other cardiac reoperation, other non-cardiac reoperation. Preoperative and operative risk factors were analyzed for their association with blood transfusion, mortality and morbidity. Resource utilization parameters were analyzed for their association with transfusion status. All data were prospectively entered into the database. The definitions of Society of Thoracic Surgeons were used for all entries in the database [8].

2.2. Statistical methods

Numerical variables were presented as mean±SD, while categorical variables were summarized by absolute frequencies and percentages. Continuous variables were compared using the Student's t test or nonparametric Mann-Whitney U test whenever the data did not appear to have normal distributions, and categorical variables were compared using chi-square or Fisher's exact test, as required. A multivariable stepwise logistic regression model for risk factors predicting blood transfusion was constructed. The associations of independent predictors with blood transfusion in the final model were expressed as odds ratios (OR) with 95% CIs. Model discrimination was measured using the c statistic, which is equal to the area under the ROC (Receiver Operating Characteristic) curve. Model calibration was estimated using the Hosmer-Lemeshow (HL) goodness-of-fit statistic (higher p values imply that the model fit the observed data better). Also, multivariable logistic regression models for comparing postoperative complications and mortality across the two groups of patients in presence of confounders were established and the associations were presented as odds ratios (OR) with 95% CIs. Multivariable linear regression models for comparing resource utilizations across the two groups of patients in presence of confounders were also established and the associations were presented as β with 95% CIs. Variables were included into the multivariable model if the p value was found to be less than or equal to 0.15 in the univariate analysis. For the statistical analysis, the statistical software SPSS version 13.0 for windows (SPSS Inc., Chicago, IL) and the statistical package SAS version 9.1 for windows (SAS Institute Inc., Cary, NC, USA) were used. All p values were 2-tailed, with statistical significance defined by $p \leq 0.05$.

3. Results

The demographic and clinical data are presented in Table 1. There were 14,152 patients who met the inclusion criteria. The number of males was significantly higher than females in the transfused group. The mean age of the patients was 58.6 ± 9.5 years. All patients underwent isolated CABG. In transfused patients, 98.8% had an on-pump and others had an off-pump procedure. Of all cases, 0.2% was considered as emergent and the others were urgent or elective. Overall, 16.5% of patients transfused. A Canadian Cardiac angina Score (CCS) greater than 3 was seen more (9.3%) in transfused patients ($p<0.001$). Additionally, those patients who received transfusions required longer total perfusion times ($p <0.001$). Table 2 details the items analyzed to

Table 1. Demographic, preoperative and operative characteristics of patients underwent isolated CABG.

Characteristics	Total	Transfused	Non-transfused	P-value
Preoperative risk factors				
Gender				<0.001
Male	10527/14106 (74.6%)	1634/2333 (70.0%)	8893/11773 (75.5%)	
Female	3579/14106 (25.4%)	699/2333 (30.0%)	2880/11773 (24.5%)	
Age	58.64±9.50	59.76±9.51	58.41±9.48	<0.001
BMI (kg/m²)	27.22±4.05	27.14±4.23	27.24±4.01	0.296
Smoke	5849/14048 (39.1%)	857/2319 (37.0%)	4632/11729 (39.5%)	0.022
Diabetes	4477/14086 (31.8%)	850/2331 (36.5%)	3627/11755 (30.9%)	<0.001
Dyslipidemia	9442/14067 (67.1%)	1530/2323 (65.9%)	7912/11744 (67.4%)	0.158
Family history	5139/13978 (36.8%)	879/2299 (38.2%)	4260/11679 (36.5%)	0.110
Hypertension	7406/14084 (52.6%)	1198/2329 (51.4%)	6208/11755 (52.8%)	0.225
Cerebrovascular accident (CVA)	897/14091 (6.4%)	192/2329 (8.2%)	705/11762 (6.0%)	<0.001
Peripheral vascular disease (PVD)	253/14085 (1.8%)	51/2328 (2.2%)	202/11757 (1.7%)	0.117
Renal failure (RF)	242/14106 (1.7%)	54/2333 (2.3%)	188/11773 (1.6%)	0.015
Chronic lung disease (severe)	10/14049 (0.1%)	2/2317 (0.1%)	8/11732 (0.1%)	0.674
Immunosuppressive therapy	220/14089(1.6%)	49/2329 (2.1%)	171/11760 (1.5%)	0.021
Previous cardiovascular intervention	776/14095 (5.5%)	142/2329 (6.1%)	634/11766 (5.4%)	0.171
Myocardial infarction (MI)	5516/14080 (39.2%)	949/2328 (40.8%)	4567/11752 (38.9%)	0.086
Congestive heart failure (CHF)	1648/14052 (11.7%)	300/2325 (12.9%)	1348/11727 (11.5%)	0.054
Angina	13781/14106 (97.7%)	2282/2333 (97.8%)	11499/11773 (97.7%)	0.678
Cardiogenic shock	103/14070 (0.7%)	15/2328 (0.6%)	88/11742 (0.7%)	0.587
Resuscitation	146/14077 (1.0%)	24/2328 (1.0%)	122/11749 (1.0%)	0.974
Arrhythmia	395/14051 (2.8%)	86/2329 (3.7%)	309/11722 (2.6%)	0.005
CCS >3	863/11872 (7.3%)	176/1890 (9.3%)	678/9982 (6.9%)	<0.001
Number of diseased vessels>2	10123/14075 (71.9%)	1796/2327 (77.2%)	8327/11748 (70.9%)	<0.001
Left main disease≥50%	1268/13803 (9.2%)	215/2263 (9.5%)	1053/11540 (9.1%)	0.571
Ejection fraction (%)	49.45±10.29	48.91±10.67	49.56±10.20	0.010
*PRL Hb	11.81±1.66	11.29±1.63	12.36 ± 1.67	<0.001
Operative risk factors				
Operative status				0.018
elective	12044/14036 (85.8%)	1954/2319 (84.3%)	10090/11717 (86.1%)	
urgent	1961/14036 (14.0%)	356/2319 (15.4%)	1605/11717 (13.7%)	
emergent	31/14036 (0.2%)	9/2319 (0.4%)	22/11717 (0.2%)	
Cardiopulmonary bypass (CPB)	13801/14106 (97.8%)	2304/2333 (98.8%)	11497/11773 (97.7%)	0.001
Intra aortic balloon pump insertion (IABP)	317/14095 (2.2%)	143/2332 (6.1%)	174/11763 (1.5%)	<0.001
Number of grafts	3.61±0.94	3.70±0.91	3.59±0.94	<0.001
Number of arterial grafts	1.11±0.36	1.10±0.37	1.11±0.35	0.303
Number of vein grafts	2.50±0.94	2.60±0.92	2.48±0.94	<0.001
Perfusion time (min)	72.48±22.25	78.73±27.08	71.20±20.67	<0.001

** PRL Hb, Preoperative Recorded Laboratory Hemoglobin (mg/dl)*

evaluate complications and resource utilization. The total complication rate was 11.4%. In those not transfused, the complication rate reached 24.5% which was not shown in Table 2. Transfused patients demonstrated a significantly higher incidence of postoperative infectious, ischemic complications and most illustrious cardiac and reoperation complications, as well as, mortality (p<0.001). The number of deaths occurred in the nontransfused was 0.4% as compared to 2.6% among those in transfused group (P< 0.001). Those who transfused had a higher rate of reintubation, total ICU hours, and total ventilation time (p<0.001). By multivariable analysis we showed the risk factors of transfusion in isolated CABG (Table 3). Some of predictive factors of mortality were

Table 2. Postoperative complications and resource utilization of patients underwent isolated CABG.

Complications	Incidence	Transfused	Non-transfused	P-value
Prolonged ventilation (hour)	290/14097 (2.1%)	161/2332 (6.9%)	129/11765 (1.1%)	<0.001
Reintubation	157/14091 (1.1%)	93/2325 (4.0%)	64/11766 (0.5%)	<0.001
Total ventilation time (hour)	10.12±0.19*	16.14±0.87*	8.93±0.15*	<0.001
Total ICU hours	42.61±0.34*	59.83±1.39*	39.19±0.29*	<0.001
PLOS (day)	7.69±4.76	8.89±6.30	7.45±4.35	<0.001
HLOS (day)	16.38±9.56	18.07±11.44	16.05±9.12	<0.001
Infectious complication	99/14090 (0.7%)	42/2330 (1.8%)	57/11760 (0.5%)	<0.001
Ischemic complication	208/14096 (1.5%)	96/2332 (4.1%)	112/11764 (1.0%)	<0.001
Cardiac complication	995/14083 (7.1%)	298/2330 (12.8%)	697/11751 (5.9%)	<0.001
Reoperation	234/14094 (1.7%)	116/2331 (5.0%)	118/11763 (1.0%)	<0.001
Mortality (30-day)	102/14106 (0.7%)	60/2333 (2.6%)	42/11773 (0.4%)	<0.001

** Data are presented as Mean±SE*
PLOS, Post surgery length of stay
HLOS, Hospital length of stay

Table 3. Factors associated with homologous blood transfusion in patients underwent isolated CABG.

Factors	OR	95% CI for OR	P-value
Age	1.015	1.009-1.020	<0.0001
Male gender	0.723	0.642-0.813	<0.0001
Diabetes	1.182	1.058-1.321	0.0068
Renal failure	1.606	1.135-2.273	0.0048
Hypertension	0.868	0.779-0.966	0.0107
CVA	1.342	1.085-1.660	0.0025
Immunosuppressant therapy	1.520	1.071-2.157	0.0184
CCS >III	1.278	1.063-1.536	0.0100
Number of diseased vessel >II	1.273	1.116-1.452	0.0017
Cardiopulmonary Bypass (CPB)	0.069	0.006-0.767	0.0049
Perfusion time	1.013	1.010-1.016	<0.0001
IABP insertion	3.032	2.315-3.970	<0.0001
Number of grafts	0.905	0.843-0.971	0.0069

CI, Confidence interval
Hosmer-Lemeshow goodness of fit test; p = 0.7917
Area under the ROC curve; c = 0.62273

Table 4. Homologous blood transfusion effect on mortality and morbidity in Multivariable logistic regression analysis adjusted for confounders.

Outcomes	OR	95% CI for OR	P-value
Mortality	3.976	2.443-6.469	<0.0001
Infectious complication	2.415	1.469-3.973	0.0005
Cardiac complication	1.947	1.650-2.296	<0.0001
Ischemic complication	3.054	2.154-4.331	<0.0001
Reoperation	3.648	2.643-5.035	<0.0001
Prolonged ventilation (hour)	4.755	3.595-6.290	<0.0001

CI, Confidence interval

determined as confounders in the coherence between blood transfusion and mortality in isolated CABG that consist of: Gender (p=0.001), Age (p<0.001), Diabetes (p<0.001), Smoking (p=0.006), Renal failure (p<0.001), Hypertension (p<0.001), Congestive Heart Failure (p<0.001), Arrhythmia (p<0.001), Left Main Disease (p<0.001), Ejection fraction (p<0.001), Operation status (p<0.001), Intra Aortic Balloon Pump insertion (p<0.001), Perfusion time (p<0.001), and Number of arterial grafts (p<0.001). We also determined any confounding factors in examining the effect of blood transfusion on each group of complications and resource utilization, but these

Table 5. Blood transfusion effect on resource utilization in Multivariable linear regression analysis adjusted for confounders.

Outcome	β	95% CI for β	P-value
Total ventilation (hour)	5.091	4.136-6.047	<0.0001
Total ICU hour	14.599	12.858-16.340	<0.0001
PLOS (day)	0.955	0.724-1.187	<0.0001
HLOS (day)	1.141	0.680-1.602	<0.0001

CI, Confidence interval
PLOS, Post surgery length of stay
HLOS, Hospital length of stay

results are not shown. Results of multivariable analysis for the independent effect of transfusion on mortality, morbidity and resource utilization are demonstrated in detail in Tables 4, 5.

4. Discussion

Transfusion after cardiac surgery is very common [9]. This rate is varying between institutions [10] and has remained high despite established transfusion guidelines [11]. We analyzed our database of patients who underwent isolated CABG to determine the predictive factors of transfusion and the association of postoperative morbidity and mortality and resource utilization with blood transfusion. We found a strong statistical association between blood transfusion and increased in-hospital morbidity, mortality and resource utilization. Some of the blood transfusion risk factors were instinctive and some were not. The transfusion rate was higher in male gender, diabetic and renal failure patients, smoker, patients with lower EF and urgent or emergent surgery. There are several previous studies that determine risk factors of preoperative and post operative transfusion on mortality and morbidity, but because of differing patient populations and methodologies, they are not comparable. In our multivariable analysis of preoperative risk factors associated with transfusion; age, male gender, diabetes, renal failure, hypertension, immunosuppressant therapy, CCS>III, history of a CVA, number of diseased vessel>II, on-pump CABG, increased perfusion time, number of grafts, need to IABP insertion were independent predictors of transfusion. Engoren *et al*. [12] found that transfused patients were older, and stayed longer in the hospital, and were more likely to be female and to have CVA, PVD, hypertension, higher New York Heart Association (NYHA) functional class IV symptoms, and to need intraaortic balloon pumps. Manoj Kuduvallia *et al*. [13] in their studies showed on-pump surgery, female sex, number of grafts, renal failure, increased number of diseased vessel and older age as risk factors for transfusion. In our study, we determined some of these risk factors (Table 3). Magovern *et al*. in their study revealed the perfusion time as independent predictor of blood transfusion [14]. In agreement with this study, we found that increased perfusion time is associated with increased risk of transfusion. However, patients with short perfusion times may be still at risk for receiving a blood transfusion [15]. Recognition of risk factors for blood transfusion may help identify patients at high risk for transfusion and facilitate decision-making to reduce perioperative blood transfusion [14]. In our study, we demonstrated that blood transfusion is associated with a higher rate of postoperative complications (Table 2). Leal-Noval *et al*. [16] showed in their study, administration of blood derivatives, in particular red blood cells, was associated with a development of severe postoperative infections (pneumonia). In addition to a higher incidence of postoperative pneumonia, blood transfusion has also been shown to be associated with deep sternal wound infection [17] and severe sepsis [18]. In agreement with these findings we demonstrated blood transfusion to be associated with a higher risk of infectious complication. The mechanism whereby transfusion influences adverse outcome has not been obviously understood. The systemic inflammatory response may play role in the negative impact of transfusion on outcome [19]. Patients undergoing cardiac surgery manifest a noninfectious inflammatory response reflected by increased concentrations of inflammatory mediators [20]. Moreover, transfusion affects the release of inflammatory mediators [21]. Taken together, these findings support the immunosuppressive effect of blood transfusion with corresponding susceptibility to bacterial infection. We demonstrated in our study that transfused patients may have more ischemic complication (4.1% vs 1.0%). This may be related to the fact that most of transfused patients receive stored blood. Red blood cells which stored for a period of time (28 days or longer) in the blood bank do not perform as fresh as fresh blood. They are fragile, non-distensible, depleted of 2, 3 diphosphoglycerate (DPG) and have a dramatically left-shifted oxy-hemoglobin dissociation curve [22,23]. Because the oxy-hemoglobin curve is so left-shifted in stored blood, it is attainable that bank blood may actually draw oxygen out of the tissues or microcirculation. Therefore, stored blood has major performance limitations in delivery of oxygen. Our study also show transfused patients have higher rate of cardiac complication and reoperation and resource utilization and these are non cost effective for patients and their families. These results are parallel with previous reports [24,25]. To date, because lack of real time monitor of oxygen supply and demand to the microcirculation of the whole body or individual organs to determine when patients need to transfused, Therefore, physicians make transfusion decisions based upon their past teaching and training. We are encultured to believe that giving blood saves lives, yet there is little data published to support such a conclusion. As a result of the lack of evidence based medicine supporting the transfusion decision, transfusion during CABG surgery varies widely [26]. A change in transfusion behavior by a large segment of physicians for CABG patients will be suitable. Such a reduction in transfusion utilization will save medical care costs by reducing resource utilization, increase the availability of blood, and finally improve outcome for our patients. Evaluating the specific causal relationship of transfusion and outcome is limited in this retrospective observational study and could be answered definitively by a prospective randomized trial of transfusion in a model that accounts for comorbidities.

Limitation: There are various limitations to our study. Firstly, being a retrospective database study, by its nature, it is only capable of showing association between variables and outcomes, and is unable to demonstrate cause and effect. Secondly, the retrospective nature of the study cannot account for uncollected or unknown variables affecting the outcome or transfusion bias. Thirdly, we had missing in our registered database about postoperation Hct, thus, we could not show exactly in tables what percent of patients meet our transfusion criteria. The fourth limitation is the fact that there was no strict transfusion policy post-operatively and the triggers for transfusion were dependent on the individual clinician treating the patient.

5. Conclusion

We conclude that the isolated CABG patients receiving blood transfusion have significantly higher mortality, morbidity and resource utilization. Homologous blood transfusion is an independent factor of increased resource utilization, morbidity and mortality.

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