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Cent. Eur. J. Med. • 5(3) • 2010 • 308-314
DOI: 10.2478/s11536-009-0094-6

Central European Journal of **Medicine**

Preoperative anemia associated in-hospital mortality and morbidity in isolated coronary artery bypass graft surgery

Research Article

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Received 14 May 2009; Accepted 13 June 2009

Abstract: Anemia is an indisputable finding in patients scheduled for coronary artery bypass graft (CABG) that can occur any time preoperatively. In presence of severe coronary artery disease, anemia can dramatically affect surgical outcomes. Therefore, we conducted this study to determine the effect of low preoperative hemoglobin (Hgb) on postoperative outcome in patients who underwent coronary artery bypass graft (CABG). In all, 4432 patients who had undergone isolated CABG at Tehran Heart Center over the 2-year period from March 2006 to February 2008 were studied. All medical records of the aforementioned patients were derived from our hospital surgery data bank. After adjustment for confounders, the association of different preoperative levels of Hgb with risk of cardiac, pulmonary, infectious, and ischemic complications, and also with prolonged ventilation and resource utilization, were assessed in a multivariable model. After adjustment for confounders that may affect mortality and morbidities, we found that cardiac, infectious, ischemic, and pulmonary complications, as well as postoperative mortality, were significantly higher in anemic patients compared to those with normal Hgb levels. In addition, total ventilation time, total intensive care unit hour stay (ICU), hospital length of stay (HLOS), and post-surgery length of stay (PLOS) were significantly longer in anemic patients. We concluded that isolated CABG patients with preoperative anemia have significantly higher mortality and morbidity, and use more health care resources. Preoperative anemia is an independent variable for increased resource utilization, morbidity, and mortality.

Keywords: *Anemia • Hemoglobin • Coronary artery bypass grafting • Postoperative complication • Mortality*

1. Introduction

Anemia is an frequent finding in patients scheduled for coronary artery bypass graft (CABG) surgery; it can happen anytime in the preoperative period. In presence of severe coronary artery disease, it can dramatically affect the outcome of surgery [1-6]. Patients who are candidates for CABG usually have severe defects in the coronary arteries that make them vulnerable to the effects of low hemoglobin (Hgb) [4,5,7,8]. Although several studies have described the effect of anemia on postoperative mortality and morbidity [9-15], it is still not clear whether these effects result only from low Hgb *per se*, or whether the association with other risk factors is the cause of these complications. Also, existing studies have not described in detail the exact relationship between the level of preoperative anemia and adverse outcomes in CABG patients [4]. In addition, the major factors predictive of preoperative anemia are still not fully established, especially in patients who are

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candidates for CABG [14,15]. Lack of this information makes it difficult to distinguish at-risk patients according to Hgb level, while understanding of detailed risk factors provides helpful information for optimizing the management of preoperative anemia. We conducted this study to evaluate whether different levels of Hgb can be an independent risk factor for postoperative CABG in-hospital mortality, cardiac, and non-cardiac complications. We also examined the confounding effect of preoperative risk factors on the relationship between preoperative anemia and postoperative complications. Finally, we determined which preoperative risk factors can be a predictive factor for preoperative anemia in patients who were candidates for a CABG operation.

2. Material and Methods

In total, 4432 patients who had undergone isolated CABG at Tehran Heart Center over a 2 year period from March 2006 to February 2008 were studied. All medical records of the aforementioned patients were derived from our hospital surgery data bank. Preoperative risk factors included age, body mass index (BMI), smoking, diabetes, dyslipidemia, opium addiction, a positive family history for cardiovascular disease, renal failure (creatinine level 2 mg/dL or higher), last creatinine clearance level, hypertension, cerebrovascular accident, infectious endocarditis, chronic lung disease, and peripheral vascular disease. Among previous surgical procedures, carotid surgery, cardiovascular intervention, CABG, valve procedures, percutaneous coronary angioplasty (PTCA), and coronary stent replacement are risk factors. Prior occurrences of thrombolysis, a history of myocardial infarction (MI), congestive failure (CHF), cardiogenic shock, and atrial fibrillation are preoperative risk factors as well. Postoperative occurrences measured were in-hospital complications (within 30 days), including cardiac complications: heart block, atrial fibrillation, valvular dysfunction, tamponade, and perioperative MI (0–24 hours post operation). Infectious complications measured included deep sternal infection, septicemia, and urinary tract infection. Ischemic complications included stroke (>72 hours), transient ischemic attack (TIA, <24 hours), continuous coma (≥24 hours), acute limb ischemia, and anticoagulation therapy. Pulmonary complications included pneumonia, and pulmonary embolism. Other post-surgery complications measured were prolonged ventilation (>24 hours), ICU stay (hours), total ventilation (hours), hospital length of stay (HLOS) (days), and post-surgery length of stay (PSOL) (days). All of the above pre -and post-operative factors are described according to the STS adult cardiac database [16]. The World Health Organization (WHO) has defined three Hgb levels: severe anemia as <10 g/dL, moderate anemia as 10 to 12 g/dL, and normal as >12 g/dL [17]. Patients with preoperative and intraoperative transfusion were excluded.

2.1. Statistical methods

Results are presented as mean ± SD (standard deviation) for numeric variables, and are summarized by absolute frequencies and percentages for categorical variables. Continuous variables were compared using one-way analysis of variance (ANOVA) or the non-parametric Kruskal-Wallis test whenever the assumption of equal variances was violated across the three categorized hemoglobin (Hgb) groups. Categorical variables were compared using the chi-square test or Mantel-Haenszel chi-square test for trends across the three predetermined groups. Multivariable logistic regression models were established for assessing the preoperative Hgb effect (categorized as <10, 10–11.99, and ≥12 g/dL) on mortality and morbidity in presence of potential confounders. The reference group against which other levels of Hgb were compared was normal (Hgb ≥12 g/dL). The association of Hgb with mortality and morbidity was expressed as odds ratios (OR) with 95% CI. Multivariable linear regression models for evaluating preoperative Hgb effects (categorized as <10, 10–11.99, and ≥12 g/dL) on resource utilization in presence of potential confounders were also established. Again, Hgb ≥12 g/L was the reference group. Resource utilizations were logarithmically transformed to reduce skewness. The association of Hgb with resource utilizations was presented as β with 95% CI. As a secondary objective, a multivariable stepwise logistic regression model for factors associated with Hgb <12 g/d was constructed. The association of independent predictors with Hgb in the final model was expressed as odds ratios with 95% CI. 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 mean that the model fit the observed data better). Variables were incorporated into the multivariable model if the *p* value was ≤0.15 in 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 $p \leq 0.05$.

Table 1. Patient characteristics (n= 4432) by preoperative Hgb classification.

p Value	normal (Hgb ≥12g/dl)	moderate (Hgb 10-11.99g/dl)	severe (Hgb <10g/dl)	variables
	3782(85.3)	581(13.1)	69(1.5)	Number of patients
				Noncardiac risk factors
<0.001	2961(78.3)	292(50.3)	36(52.2)	Male
<0.001	59.22±9.15	61.41±9.18	59.64±8.5	Age (year)
0.735	27.46±3.96	27.60±4.57	27.56±4.58	BMI (mg/dl)
<0.001	1544(40.8)	145(25.0)	17(24.6)	Smoking
<0.001	1179(31.2)	268(46.1)	33(47.8)	Diabetes
0.56	2761(73.0)	397(68.3)	48(69.6)	Dyslipidemia
0.685	1688(44.6)	266(45.8)	28(40.6)	Family history
<0.001	56(1.5)	44(7.6)	10(14.5)	Renal failure
<0.001	1881(49.7)	372(64.0)	41(59.4)	Hypertension
0.011	117(3.4)	31(5.3)	3(4.3)	CVA
0.991	172(4.5)	29(5.0)	2(2.9)	Chronic lung disease
0.024	87(2.3)	24(4.1)	2(2.9)	PVD
<0.001	1.20±0.32	1.34±0.98	1.52±1.58	Last creatinin (mg/dl)
				Cardiac risk factors
0.454	261(6.9)	48(8.3)	4(5.8)	Prior cardiac intervention
0.141	11(0.3)	5(0.9)	0(0)	CABG
	2(0.1)	2(0.3)	0(0)	Valve surgery
0.547	208(5.5)	36(6.2)	4(5.8)	PTCA
0.360	110(2.9)	22(3.8)	2(2.9)	Coronary stent
0.815	79(2.1)	12(2.1)	2(2.9)	Thrombolysis
0.099	1641(43.4)	232(39.9)	27(39.1)	MI
<0.001	311(8.2)	84(14.5)	9(13.0)	CHF
0.001	31(0.8)	12(2.1)	2(2.9)	Cardiogenic shock
0.665	173(4.6)	24(4.1)	3(4.3)	Arrhythmia

For categorical variables data are presented as number (%). For numeric variables, data are presented as mean ± SD, Hgb <10 is severe anemia, 10-11.99 is moderate anemia, and ≥12 is normal.
BMI, body mass index; CVA, Cerebrovascular accident; PVD, peripheral vascular disease; CABG, coronary artery bypass graft; PTCA, percutaneus transluminal coronary angioplasty; MI, myocardial infarction; CHF, congestive heart failure

Table 2. Factors associated with Hgb less than 12 g/dl in patients underwent isolated CABG.

	Multivariate*			Univariate		Variables
P-value	95% CI	OR	P-value	95% CI	OR	
<0.0001	1.007-1.027	1.017	<0.0001	1.015-1.034	1.024	Age
<0.0001	0.257-0.378	0.312	<0.0001	0.238-0.335	0.282	Male gender
0.0244	0.633-0.969	0.783	<0.0001	0.398-0.581	0.481	Smoking
<0.0001	1.171-1.684	1.404	<0.0001	1.608-2.254	1.904	DM
<0.0001	4.370-9.855	6.562	<0.0001	4.107-8.848	6.028	RF
0.0118	1.084-1.858	1.419	<0.0001	1.454-2.389	1.863	CHF
<0.0001	1.829-7.091	3.601	0.0026	1.409-5.035	2.664	Cardiogenic shock

DM, diabetes mellitus; RF, renal failure; CHF, congestive heart failure; OR, odds ratio; CI, confidence interval.
** Hosmer-Lemeshow goodness of fit test; χ^2= 8.8985, p-value= 0.3509, Area under the ROC (Receiver operating characteristic) curve; c= 0.71201.*

3. Results

Of 4432 patients, 1.5% had severe anemia, 13.1% had moderate anemia, and 85.3% had normal preoperative Hgb levels. The mean age of the patients with severe anemia was 59.64±8.5, with moderate anemia 61.41±9.18, and with normal Hgb levels 59.22±9.15. All patients underwent isolated CABG. We compared preoperative risk factors between three groups of patients according to Hgb level, and used the previously

Table 3. Postoperative outcomes by preoperative Hgb classification*.

P-value	Normal (Hb ≥ 12 g/dl)	Moderate (Hb 10-11.99 g/dl)	Severe (Hb < 10 g/dl)	Variables
<0.001	266 (7.0)	73 (12.6)	11 (15.9)	Cardiac complication
<0.001	47 (1.2)	18 (3.1)	3 (4.3)	Infectious complication
<0.001	40 (1.1)	21 (3.6)	4 (5.8)	Ischemic complication
<0.001	34 (0.9)	17 (2.9)	4 (5.8)	Pulmonary complication
<0.001	85 (2.2)	58 (10.0)	6 (8.7)	Prolonged ventilation
<0.001	10.85 ± 0.30	27.28 ± 5.18	45.66 ± 22.96	Total ventilation time (hour)†
<0.001	44.63 ± 0.63	73.29 ± 7.61	121.16 ± 31.27	Total ICU hour†
<0.001	16.21 ± 8.59	19.70 ± 11.76	21.42 ± 13.67	HLOS (day)
<0.001	7.35 ± 3.96	9.32 ± 9.45	11.15 ± 11.34	PLOS (day)
<0.001	35 (0.9)	21 (3.6)	5 (7.2)	Mortality

** Data are presented as mean ± SD or n (%).*
† Expressed as mean ± SE.
PLOS, post surgery length of stay; HLOS, hospital length of stay.

Table 4. Preoperative Hgb effect on mortality and morbidity in multivariable logistic regression analysis adjusted for confounders.

P-value	95% CI	OR	Variables
			Mortality
0.0228	1.204-11.902	3.785	Hgb < 10 g/dl
0.0240	1.099-3.810	2.046	Hgb 10-11.99 g/dl
–	–	Reference	Hgb ≥ 12 g/dl
			Cardiac complication
0.0208	1.134-4.624	2.290	Hgb < 10 g/dl
0.0022	1.181-2.146	1.592	Hgb 10-11.99 g/dl
–	–	Reference	Hgb ≥ 12 g/dl
			Infectious complication
0.0807	0.873-10.499	3.028	Hgb < 10 g/dl
0.0316	1.058-3.425	1.909	Hgb 10-11.99 g/dl
–	–	Reference	Hgb ≥ 12 g/dl
			Ischemic complication
0.0119	1.390-14.253	4.451	Hgb < 10 g/dl
0.0014	1.457-4.774	2.637	Hgb 10-11.99 g/dl
–	–	Reference	Hgb ≥ 12 g/dl
			Pulmonary complication
0.0004	2.506-23.818	7.726	Hgb < 10 g/dl
0.0006	1.633-5.952	3.118	Hgb 10-11.99 g/dl
–	–	Reference	Hgb ≥ 12 g/dl
			Prolonged ventilation
0.0121	1.292-8.040	3.224	Hgb < 10 g/dl
<0.0001	2.655-5.653	3.875	Hgb 10-11.99 g/dl
–	–	Reference	Hgb ≥ 12 g/dl

Hgb, Hgb; CI, confidence interval; OR, odds ratio.

mentioned definitions for our study variables. Among these risk factors, female gender, diabetes, renal failure, hypertension, cerebrovascular accidents, history of congestive heart failure (CHF), history of cardiogenic shock, older age, and higher last creatinine clearance level before the surgical procedure were significantly more prevalent at lower Hgb levels (p<0.001), while a history of smoking had a significantly higher rate in normal and severe Hgb levels (p<0.001) (Table 1). Upon univariate and multivariate analyses, we determined the preoperative risk factors for Hgb level <12 in isolated CABG to be older age, diabetes mellitus, renal failure, congestive heart failure, and cardiagenic shock to be positive predictors of preoperative anemia, whereas male gender, and smoking were negative predictors (Table 2). Table 3 shows short-term postoperative outcomes by

Table 5. Preoperative Hgb effect on resource utilization in Multivariable linear regression analysis adjusted for confounders*.

P-value	95% CI for β	β	Variables
			Total ventilation time
0.0010	0.087-0.346	0.217	Hgb < 10 g/dl
<0.0001	0.120-0.218	0.169	Hgb 10-11.99 g/dl
_	_	Reference	Hgb ≥ 12 g/dl
			Total ICU hour
<0.0001	0.186-0.498	0.342	Hgb < 10 g/dl
<0.0001	0.063-0.181	0.122	Hgb 10-11.99 g/dl
_	_	Reference	Hgb ≥ 12 g/dl
			HLOS
0.0011	0.062-0.248	0.155	Hgb < 10 g/dl
<0.0001	0.071-0.142	0.107	Hgb 10-11.99 g/dl
_	_	Reference	Hgb ≥ 12 g/dl
			PLOS
<0.0001	0.091-0.272	0.182	Hgb < 10 g/dl
<0.0001	0.044-0.112	0.078	Hgb 10-11.99 g/dl
_	_	Reference	Hgb ≥ 12 g/dl

** Resource utilizations were logarithmically transformed to reduce skewness.*
Hgb, Hgb; HLOS, hospital length of stay; PLOS, post surgery length of stay; CI, confidence interval; OR, odds ratio.

WHO Hgb ranges. The mortality rate among persons with severe and moderate anemia was 7.2%, and 3.6%, respectively, while it was 0.9% in the normal Hgb group. Before adjustment for confounders, cardiac, infectious, ischemic, and pulmonary complications, prolonged ventilation, and mortality were significantly higher in patients with lower Hgb levels. Also, total ventilation time, total intensive care unit (ICU) stay hours, hospital length of stay (HLOS), and post-surgery length of stay (PLOS) were significantly longer in anemic patients. In a multivariable analysis, after adjustment for all previously mentioned preoperative risk factors, cardiac, infectious, ischemic and pulmonary complications, and mortality as well, were significantly higher in anemic patients compared to that in patients with normal Hgb levels (Table 4). Also, total ventilation time, total ICU hour, hospital length of stay, and post surgery length of stay were significantly longer in anemic patients (Table 5).

4. Discussion

In cardiac surgery, anemia can be related to many adverse occurrences, but it is not yet clear if a lower Hgb level is an independent predictor for mortality, morbidity and longer resource utilization among patients undergoing CABG [18-20]. In many studies, preoperative anemia has been shown to play an indispensable role [7,8,18]. Although many studies have shown the association between preoperative anemia and adverse post-surgery outcomes, these studies did not exclude the influence of interoperative transfusion [4,21]. Kulier's review found that worse outcomes after coronary artery bypass surgery in anemic patients could be a result of other comorbidities in these patients, rather than anemia *per se*; the precise interaction between anemia and comorbidities that produce worse outcomes are still unclear [22]. Conflicting evidence remains between different studies concerning the exact effect of preoperative anemia and post-operative outcomes. The study by Zindrou et al. showed a significant relationship between preoperative Hgb and mortality [5]. Van Straten et al. found anemia to be a risk factor for early and late mortality after CABG [23]. However, in the study of Weber et al., there was no association between preoperative anemia and increased surgical site infection [24]. Other studies found a non-significant relationship, or one with a smaller odds ratios [25,26]. The Kulier et al. study showed a significant relationship between preoperative low Hgb and non-cardiac—but not cardiac—complications [1]. Although most studies suggest that mortality in surgical patients is related to low Hgb levels, the exact effect of anemia on survival is not yet clear [27,28]. Carson et al. found that the mortality risk increases in patients with Hgb levels lower than 11 g/dL [4]. However, in two smaller studies, there was no significant relationship between levels of Hgb and mortality [29,30]. This finding in these two studies may be a result of a lack of statistical power: both groups had an increased risk because they had some level of anemia.

Very few studies have described the association of anemia with morbidities and resource utilization [2]. In one study, there was a strong correlation between

mortality and anemia in nontransfused patients [4]. However, other studies revealed no association between anemia and complications of surgery [2]. In the present study, we retrospectively analyzed 4432 patients who had undergone isolated CABG to determine the predictive factors of preoperative anemia, and the association of postoperative morbidity, mortality, and resource utilization with preoperative anemia. We found a strong statistical association between preoperative anemia and increased in-hospital morbidity, mortality, and resource utilization. This finding can be explained by the vulnerability of anemic patients with cardiovascular problems to increased complications because compensatory mechanisms in anemic patients without cardiac problems, such as tachycardia and increased cardiac output, can not be tolerated well in these patients [15]. This decreased compensatory tolerance in cardiovascular patients can result in the tissue hypoxia, cellular death, and end organ failure that can occur during the postoperative course of CABG [17]. We also found that older age, diabetes mellitus, renal failure, congestive heart failure, and cardiogenic shock are preoperative risk factors for anemia, while male patients and those who smoked had higher levels of Hgb. These data can be a result of anemia of chronic disease in patients with previously mentioned risk factors. In the study by Anker et al., patients with diabetes mellitus, of female gender, older age, and post-MI heart failure and also patients with history of smoking had higher Hgb levels [31]. In the study of Milman et al., smokers of both genders had significantly higher mean Hgb than non-smokers. Smoking increases the CO level in blood, which binds more readily with Hgb than oxygen. This CO-induced hypoxemia can cause an erythropoietic response and a higher level of Hgb [32]. We suggest that management of preoperative anemia will benefit patients who are candidates for CABG by decreasing operative complications, and will lower the cost of medical care by reducing resource utilization.

4.1. Limitations of the Study

Being a retrospective study based on data base information, this study can show only an association between variables and outcomes. Although we were able to find the range of Hgb effect on outcomes, we did not find an exact level at which Hgb begins to have an effect on postoperative complications. Also, we did not have any follow-up period to assess long-term complications and mortality. Other controlled clinical trials studies should be done to find the optimal cause and effect relationship between long-term complications and preoperative anemia.

5. Conclusion

We concluded that isolated CABG patients with preoperative anemia have significantly higher mortality, morbidity, and use more health care resources through longer HLOS and PLOS. Preoperative anemia is an independent risk factor for increased resource utilization, morbidity, and mortality.

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