Clin. Cardiol. 30 (Suppl. II), II-35–II-43 (2007)

Impact of Acute Blood Loss Anemia and Red Blood Cell Transfusion on Mortality after Percutaneous Coronary Intervention

PETER KIM, M.D., SIMON DIXON, M.B.CH.B., A. BRADLEY EISENBREY, M.D., BARBARA O'MALLEY, M.D., JUDY BOURA, M.S., WILLIAM O'NEILL, M.D.*

Division of Cardiology, Department of Internal Medicine and Department of Clinical Pathology, William Beaumont Hospital, Royal Oak, Michigan; *Leonard M. Miller School of Medicine, University of Miami, Miami, Florida, USA

Summary

The clinical impact of increasing levels of blood loss has been shown to increase morbidity and mortality after percutaneous coronary intervention (PCI). The impact of red blood cell (RBC) transfusion for severe bleeding is unknown.

We systematically collected baseline and 8-h postprocedure hematocrit (HCT) values on patients undergoing PCI. The incidence of adverse events, including death and recurrent myocardial infarction, was correlated to increasing blood loss.

A total of 6,799 patients undergoing PCI (January 2000 to April 2002) had serial HCT levels. Negligible, mild, moderate, and severe blood loss occurred in 43, 25, 25, and 8% of patients, respectively. In-hospital mortality was 0.3, 0.5, 1.4, and 5.7% ($p < 0.0001$) with increasing severity of blood loss. Blood transfusion was independently associated with mortality (relative risk [RR] 2.03, $p = 0.028$).

A case-controlled analysis of 146 transfused patients versus 292 nontransfused patients with severe bleeding found an independent association between RBC transfusion and increased risk of 1-year mortality (RR 2.42, $p = 0.0045$). Patients receiving blood >35 days old had significantly worse 1-year survival rates compared with patients receiving blood <35 days old and patients not transfused (36 vs. 24 vs. 10%, $p < 0.0001$).

In a general PCI population, increasing levels of blood loss are associated with an increased incidence of major adverse cardiac events and in-hospital mortality. RBC transfusion in the setting of severe bleeding is associated with an increased risk of 1-year mortality. Transfusion of aged RBCs may also be detrimental in this setting.

Key words: anemia, blood transfusion, coronary disease, hemoglobin, hematocrit, percutaneous coronary intervention

Clin. Cardiol. 2007; 30 (Suppl. II): II-35–II-43.

Introduction

Percutaneous coronary intervention (PCI) is the most common coronary revascularization procedure performed worldwide, with an estimated 1.1 million PCI procedures performed annually in the United States alone.[1] Most PCIs are performed using a femoral artery approach, with systemic anticoagulation. Since vascular access is guided only by palpation and visualization of bony landmarks, a variety of vascular complications can occur. Inguinal hematoma, retroperitoneal bleeding, arteriovenous fistula, and femoral pseudoaneurysm are only a few potential causes of post-PCI blood loss. Systemic antithrombotic and antiplatelet therapy also increases the risk of gastrointestinal, genitourinary, and intracranial bleeding. As a result, red blood cell (RBC) transfusion has been reported in up to 3–9% of cases.[2,3] Consequently, tens of thousands of patients undergo RBC transfusion every year after PCI.

The Thrombolysis in Myocardial Infarction (TIMI)[4] and Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO)[5] trial groups have quantified the incidence and severity of bleeding risks after thrombolytic therapy for acute myocardial infarction (MI). In addition, Moscucci and Rao quantified the

Address for reprints:
Peter Kim, M.D.
Division of Cardiology
William Beaumont Hospital
3601 W. 13 Mile Road
Royal Oak, MI 48073, USA
e-mail: pskim@beaumont.edu

Received: June 18, 2007
Accepted: June 19, 2007

Published online in Wiley InterScience
(www.interscience.wiley.com).
DOI:10.1002/clc.20231

incidence and risk of bleeding in the acute coronary syndrome (ACS) population.[6,7] While major bleeding after acute MI has adverse consequences, the prognostic impact in a PCI population is not well established.

For these reasons, we prospectively collected timed hematocrit (HCT) values on patients undergoing PCI at our institution. The aim of this study was to report the incidence and consequences of acute blood loss anemia and to determine the impact of RBC transfusion on survival after severe blood loss anemia.

Methods

Since 1993, all PCI patients at William Beaumont Hospital undergo prospective reporting of baseline and post-PCI (at 8 h and as clinically indicated) measurements of laboratory values that include HCT, blood urea nitrogen, creatinine, and cardiac biomarkers. These measurements, all demographic and procedural variables, and in-hospital outcomes are prospectively recorded in a dedicated quality assurance database.

Patient Population

For this study, we reviewed the outcomes for the 9,927 patients undergoing PCI from January 1, 2000 to April 30, 2002. Only the most recent admission was analyzed in the 2,168 patients with multiple admissions for PCI. In addition, 960 patients were excluded because they lacked serial HCT measurements. Therefore, a total of 6,799 patients were analyzed. Permission was obtained from the Human Investigation Committee of William Beaumont Hospital to conduct this study.

Definitions

Nadir HCT levels were defined as the lowest value obtained either at the postprocedure blood draw or at any other time during the hospitalization. Renal failure was defined as an increase in serum creatinine ≥ 1 mg/dL, or new need for hemodialysis. In order to quantify blood loss, baseline and nadir HCT levels were recorded on all study patients. The level of blood loss was defined as (1) negligible (HCT drop $<4\%$); (2) mild (HCT drop 4.0–5.9%); (3) moderate (HCT drop 6–10%); or (4) severe (HCT drop $>10\%$).

Blood Banking

All RBC transfusions at William Beaumont Hospital, Royal Oak, are obtained from the American Red Cross Blood Services, Southeastern Michigan Region, and the Community Blood Center, Appleton, WI. All RBC products distributed by our blood bank have been leukocyte-reduced by the respective blood suppliers since March 2000. All blood products are stored in full compliance with the United States Food and Drug Administration (FDA) regulations, American Association of Blood Banks Standards, and Standards of the College of American Pathologists (Northfield, IL.)

Blood units are selected for issue based on compatibility and the oldest units in the inventory are issued first to prevent outdating of banked units. Only 37 units out of 35,792 RBC units entered into the inventory expired (outdated) in 2004. Outdated percentages range from 0.1 to 1.0% from 1983 to 2004, with an average of 0.2%, compared with a national average of approximately 4%.[8,9]

Statistical Analysis

Demographic variables, laboratory values, procedural events and adverse events during hospitalization were compared for patients with varying degrees of HCT loss. Categorical variables were examined using Chi-squared test, or Fisher's Exact Test when expected frequency was $\leqslant 5$. Continuous variables were examined using a Kruskal–Wallis test. A stepdown regression analysis was completed to determine the independent predictors of in-hospital death.

To analyze the impact of RBC transfusions, we analyzed those patients with severe blood loss. Given an expected baseline HCT of 40, an absolute drop of 10% would yield a HCT of 30. This is the level at which operative mortality has been shown to increase in cardiac patients who decline RBC transfusion.[10] A total of 567 patients with HCT loss greater than 10% were identified. Of these, 146 patients received RBC transfusions. To further isolate the impact of transfusions and minimize gender and age differences, we performed a case-control analysis where all index patients had 2 age-(± 5 years) and sex-matched control patients who had a HCT drop $>10\%$, but who did not receive a RBC transfusion. Therefore, 146 transfused and 292 case-control patients had outcomes analyzed.

All patients in the subgroup analysis had a detailed chart review to independently verify outcome measures. In addition, all study patients were contacted to identify vital status at 1 year. There were 30 patients lost to follow-up. The social security death registry was used to ascertain vital status for these patients. Patients' records were further cross-referenced with our blood bank to obtain details of transfusion amount, blood typing, and age of RBCs that were transfused.

Transfused patients were compared with case controls for demographics, cardiac risk factors, angiographic data, and in-hospital events. Categorical variables were examined using a Chi-square test where appropriate (expected frequency >5), otherwise, a Fisher's Exact Test was used. Continuous variables were examined using a Wilcoxon Rank Test. A propensity score for receiving a transfusion was determined using stepdown

TABLE 1 Baseline clinical characteristics

	HCT loss				
	<4%	4–6%	6–10%	>10%	p-Value
No. of patients	2,858	1,711	1,669	561	NA
Age (years)	64 ± 12	65 ± 12	67 ± 12	69 ± 12	<0.0001
Female gender (%)	729 (26)	496 (29)	596 (36)	266 (48)	<0.0001
Hypertension (%)	1,920 (67)	1,202 (70)	1,182 (71)	391 (70)	0.024
CRF (%)	96 (3.4)	63 (3.7)	88 (5.3)	54 (9.6)	<0.0001
History CHF (%)	431 (15)	249 (15)	245 (15)	135 (24)	<0.0001
PVD (%)	422 (15)	284 (17)	272 (16)	94 (17)	0.28
Prior PCI (%)	1,379 (48)	876 (48)	693 (42)	211 (38)	<0.0001
Creatinine (mg/dL)	1.2 ± 0.9	1.2 ± 0.9	1.2 ± 0.7	1.4 ± 0.7	0.11
HCT	39 ± 5.1	41 ± 4	41 ± 5	42 ± 4	<0.0001
Nadir HCT	37 ± 5	36 ± 4	34 ± 5	27 ± 6	<0.0001
Elective (%)	1,546 (54)	940 (55)	735 (44)	129 (23)	<0.0001
Pre-PCI heparin (u) (%)	685 (24)	407 (23)	489 (29)	241 (43)	<0.0001
Post-PCI heparin (u) (%)	50 (1.8)	35 (2.1)	91 (5.5)	107 (19)	<0.0001
Heparin dose (u) (%)	6,179 ± 3,679	6,163 ± 3,724	5,984 ± 3,857	5,684 ± 3,857	0.0001
GP IIb/IIIa use (%)	1,476 (52)	953 (56)	972 (58)	329 (59)	<0.0001
Recent MI (%)	254 (14)	169 (16)	255 (24)	145 (41)	<0.0001

Abbreviations: CHF = congestive heart failure; CRF = chronic renal failure; GP IIb/IIIa = glycoprotein receptor antagonists; HCT = hematocrit; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease.

logistic regression analysis. All variables with $p<0.10$ were included in the first step. This score was then included, along with receiving a transfusion and other covariates, in a stepdown logistic regression analysis to determine the most significant predictors of death at 1 year. All analysis used SAS (Cary, NC) version 9.1.

Results

From January 2000 to April 2002, 6,799 patients undergoing PCI at our institution had timed, serial Hgb/HCT levels obtained. Of these patients, 2,858 (42%) had negligible, 1,711 (25%) had mild, 1,669 (25%) had moderate, and 561 (8%) had severe blood losses. Demographic features associated with worsening blood loss included older age, female gender, lower weight, renal insufficiency, and hypertension (Table 1). The presence of peripheral vascular obstructive disease did not impact bleeding risk, and previous PCI appeared to protect against blood loss. Patients with moderate and severe bleeding were more likely to present for urgent PCI. In addition, they were more likely to have received pre- and postprocedure heparin and more likely to have suffered a recent MI.

Periprocedural events and clinical outcomes are shown in Table 2. Cardiac ischemic events, renal failure, and stroke were more likely in patients with moderate or severe bleeding. Patients with severe blood loss had significantly more procedural complications, particularly shock and intra-aortic balloon pump use (IABP). Similarly, the postprocedure hospital course was more complicated, with more severe cardiac, renal, and cerebral ischemia as reflected by a higher incidence of MI, renal failure, and stroke.

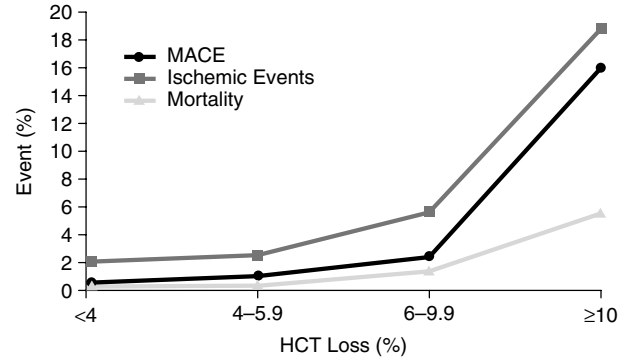

FIG. 1 Major in-hospital events with increasingly severe levels of blood loss. *Abbreviations:* HCT = hematocrit; MACE = major adverse cardiac events.

The consequences of moderate and severe blood loss are apparent (Fig. 1). In particular, patients with a HCT drop >10% have markedly more complicated catheterization procedures, along with major adverse cardiovascular events and mortality. Since severe blood loss is associated with a greater incidence of cardiac, cerebral, and renal parenchymal ischemia, the 20-fold increase in mortality compared with patients with negligible blood loss is not surprising. The presumption that transfusion of packed RBCs may ameliorate cardiac and systemic ischemia led to the use of packed RBCs in 26% of patients with severe bleeding.

TABLE 2 Procedural events and outcomes

	HCT loss				
	<4%	4–6%	6–10%	>10%	p-Value
No. of patients	2,858	1,711	1,669	561	NA
CPR (%)	1 (0.03)	5 (0.3)	10 (0.6)	11 (2)	<0.0001
Shock in laboratory (%)	2 (0.07)	3 (0.2)	2 (0.1)	8 (1.4)	<0.001
IABP (%)	19 (0.7)	21 (1.2)	55 (3.3)	89 (16)	<0.0001
Post-PCI events					
Angina (%)	44 (1.5)	28 (1.6)	60 (3.6)	62 (11)	<0.0001
Renal failure (%)	16 (0.6)	19 (1.1)	25 (1.5)	34 (6.1)	<0.0001
Stroke (%)	2 (0.07)	3 (0.2)	3 (0.2)	8 (1.4)	<0.0001
ECG changes (%)	12 (0.4)	7 (0.4)	20 (1.2)	26 (4.6)	<0.0001
Transfusion (%)	42 (1.5)	35 (2.1)	73 (2.1)	146 (26)	<0.0001
CABG (%)	3 (0.1)	0	5 (0.3)	50 (8.9)	<0.0001
MI (%)	8 (0.3)	9 (0.5)	14 (0.8)	18 (3.2)	<0.0001
Death (%)	9 (0.3)	9 (0.5)	24 (1.4)	32 (5.7)	<0.0001
MACE (%)	18 (0.6)	18 (1.1)	42 (2.5)	91 (16)	<0.0001

Abbreviations: CABG = coronary artery bypass graft; CPR = cardiopulmonary resuscitation; ECG = electrocardiogram; HCT = hematocrit; IABP = intra-aortic balloon pump; MACE = major adverse cardiovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 3 Independent predictors of in-hospital mortality

Variable	p-Value	Odds ratio	95% CI
Age >60 years	0.0027	2.82	1.44–5.67
Female gender	0.037	1.75	1.03–2.95
Recent MI	0.0003	2.91	1.62–5.21
Creatinine	0.025	1.13	1.02–1.26
Not elective	0.0043	4.2	1.56–11.3
CHF	0.028	1.85	1.07–3.21
PVD	0.014	2.11	1.16–3.84
Bleed with overt source	0.0002	4.42	2.04–9.57
Renal failure	0.042	2.33	1.03–5.23
Stroke	<0.0001	15.90	4.59–55.3
Postprocedure angina	0.0008	3.56	1.70–7.47
IABP	<0.0001	6.18	3.3–11.6
pRBC transfusion	0.028	2.03	1.00–3.83

Abbreviations: CHF = congestive heart failure; CI = confidence interval; IABP = intra-aortic balloon pump; MI = myocardial infarction; pRBC = packed red blood cells; PVD = peripheral vascular disease.

To ascertain which variables were independently associated with higher in-hospital mortality for the overall patient population, we performed a logistic regression analysis. Factors independently associated with higher mortality are presented in Table 3. Severity of blood loss was not independently associated with mortality, whereas blood transfusion was.

We attempted to ascertain what impact transfusions had after severe bleeding. To this end, we studied the 562 patients with severe blood loss. To minimize the impact of gender and age, we chose 292 sex- and age-matched (±5 years) case-control patients with severe bleeding who were not transfused, and compared them with the 146 patients with severe bleeding who underwent RBC transfusion.

Comparison of clinical characteristics (Table 4) demonstrates that patients who receive RBC transfusions appear to have more systemic illnesses, such as a history of cancer, renal dysfunction, and lower baseline HCT. In addition, the fall in HCT was greater in the transfused patients. Combined with the lower baseline HCT, the greater blood loss resulted in a significantly lower nadir HCT. Although heparin dosage was similar in the lab, the use of pre- and postprocedure heparin was more frequent in patients requiring transfusion. Interestingly, the use of glycoprotein receptor blockade was similar in the two groups. Balloon pump use and emergency procedures were more frequent in the transfused group.

Transfusion appears to have been prompted largely by the degree of HCT drop and vascular bleeding (Table 5). Since manifestations of ischemic changes (angina, ST-T changes, or a need for recatheterization) were similar, it appears clinicians were not prompted by overt ischemia to initiate transfusions. Rather, they appeared to have reacted to vascular events such as hematoma, retroperitoneal bleed, or need for vascular surgical repair, as well as obvious bleeding sources, such as upper gastrointestinal hemorrhage. Consequently, transfused patients had a markedly higher mortality rate during their hospitalization.

In order to determine the impact of transfusion on long-term survival, patients with severe bleeding were followed for a minimum of 1 year. Kaplan–Meier survival curves (Fig. 2) demonstrate a highly significant reduction in 1-year survival (74 vs. 90%, $p < 0.0001$) for transfused patients. This was particularly striking in

TABLE 4 Baseline characteristics in patients with severe blood loss anemia (transfused vs. case-controls)

	No transfusion	Transfusion	p-Value
No. of patients	292	146	
Age (years)	72 ± 10	72 ± 11	0.66
% Female	55	55	1.00
BSA	1.85 ± 0.26	1.84 ± 0.25	0.40
Diabetes	31%	35%	0.39
Hx Cancer	14%	25%	0.0049
Hypertension	74%	71%	0.49
Hx CRF	7.9%	15%	0.019
Hx CHF	25%	32%	0.13
COPD	19%	18%	0.73
Hx PVD	19%	18%	0.86
Prior PTCA	36%	38%	0.67
Prior CABG	22%	27%	0.23
Hx CVA	13%	15%	0.63
Baseline creatinine (mg/dL)	1.2 ± 0.8	1.3 ± 0.7	0.0061
Baseline HCT%	42 ± 4	39 ± 4	<0.0001
Lowest HCT%	28 ± 7	24 ± 3	<0.0001
HCT difference	14 ± 6	15 ± 4	<0.0001
Elective	27.1%	16.4%	0.022
Urgent	55.8%	58.9%	0.022
Emergent	17.1%	24.7%	0.022
Preheparin	42%	53%	0.03
Postheparin	15%	29%	0.0005
Heparin dose (u)	5,194 ± 3,177	5,506 ± 3,349	0.49
Prethrombolytics	6.5%	9.6%	0.25
GP IIb/IIIa agents	61%	64%	0.53
One vessel	32.2%	26.7%	0.24
Multivessel	67.8%	73.3%	0.24
In lab intubation	2.4%	5.5%	0.09
IABP use	11%	23%	0.001
In lab CPR	1.4%	2.1%	0.69
In lab shock	0.3%	1.4%	0.26
No reflow	2.7%	4.8%	0.27

Abbreviations: BSA = body surface area; CHF = congestive heart failure; CRF = chronic renal insufficiency; COPD = chronic obstructive pulmonary disease; CPR = cardiopulmonary resuscitation; CVA = cerebral vascular accident; GP IIb/IIIa = glycoprotein receptor antagonists; HCT = hematocrit; Hx = history of; IABP = intra-aortic balloon pump; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease.

patients undergoing urgent or emergent heart catheterization, with a 16% absolute reduction in 1-year survival (71 vs. 87%, p = 0.0004). To assess the impact of the age of the transfused RBCs on 1-year survival, patient survival was stratified by the age of the oldest unit of RBCs. Patients who received blood older than 35 days had a significantly lower 1-year survival, compared with patients transfused with blood younger than 35 days and nontransfused patients (36 vs. 24 vs. 10%, respectively, p<0.0001; Fig. 3).

We analyzed the impact of nadir HCT on 1-year outcomes in the subgroup with severe blood loss (Table 6). There is clearly a higher mortality with a lower nadir HCT level. Surprisingly, mortality was higher only for transfused patients and appeared to worsen with lower HCT levels.

To further examine the relationship between transfusions and survival in the severe bleed subgroup, a

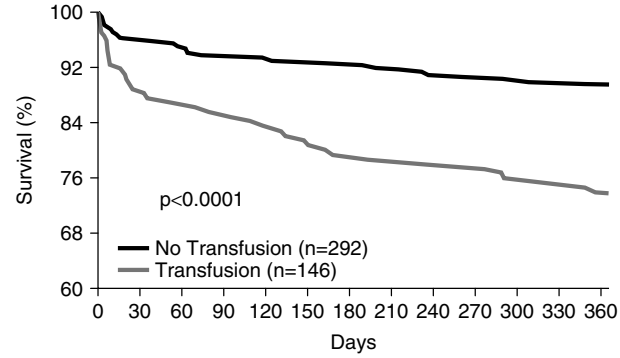

FIG. 2 Kaplan–Meier survival curves demonstrate a highly significant reduction in 1-year survival (74 vs. 90%, p< 0.0001) for transfused patients.

TABLE 5 In-hospital events

	No transfusion	Transfusion	p-Value
No. of patients	292	146	
Angina	13%	14%	0.62
Reocclusion	2.4%	2.7%	1.00
ST-T changes	5.8%	7.5%	0.49
Recatheterization	5.5%	6.9%	0.57
Re-PCI	7.9%	8.9%	0.71
CABG	7.2%	4.1%	0.21
Stroke	1.4%	1.4%	1.00
Renal failure	3.4%	14%	<0.0001
New dialysis	0%	3.4%	0.0039
Hematoma	25%	51%	<0.0001
Retroperitoneal bleed	0.7%	11%	<0.0001
Vascular repair	1%	5.5%	0.0081
Other bleed	3.8%	19%	<0.0001
Death	3.1%	11%	0.0008

Abbreviations: CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

propensity score for receiving transfusions was developed. All variables in Tables 4 and 5 with p<0.10 were included. The least significant variable was dropped at each step until only those with p< 0.05 remained in the final model. The model C-statistic was 0.85. The formula is as follows: propensity score − 5.4149 − (0.1420* baseline HCT) − (0.0720* Nadir HCT) − (0.5385* preheparin) − (0.7487 * postheparin) − (0.7536* smoke <6 months) + (1.5730* renal failure) + (1.5948* groin hematoma) + (3.6442* retroperitoneal hematoma) + (1.4781* systemic bleed) + (0.7493* IABP).

Univariate analysis was then completed to determine predictors of death. All variables with p <0.10 were included in a stepdown multivariate logistic regression analysis to determine predictors of death at 1 year. The least significant variable was dropped at each step until only variables with p <0.05 remained in the final model (Table 7). Propensity score quickly fell out as an independent variable. The final model is robust with a C-statistic of 0.81.

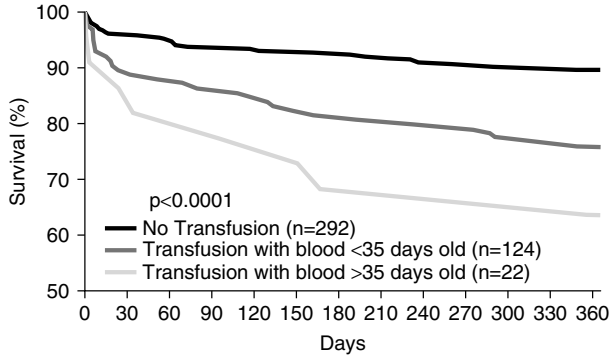

FIG. 3 Patients who received blood >35 days old had a significantly lower 1-year survival rate compared with patients transfused with blood<35 days old, and nontransfused patients (36 vs. 24 vs. 10%, respectively, p< 0.0001).

Discussion

We observed an overall 1.1% mortality rate in a large community-based PCI population. Mortality rates varied dramatically with increasing levels of blood loss. Our data suggest that mortality risk significantly rises with HCT loss >6%. Future clinical trials should consider routine postprocedure HCT determination to determine the safety of new antithrombotic or vascular occlusive strategies. Since older, more acutely ill patients with multiple comorbidities are more likely to have blood loss, it is difficult to isolate the impact of acute anemia in this setting. Intuitively, acute blood loss of moderate or severe degree requires volume replacement to prevent hypovolemic shock. Whether acute replacement of RBCs will improve oxygen delivery and outcome is unproven.

Transfusion of packed RBCs is common after PCI. Moscucci[3] reported an 8.9% incidence and Kinnaird[2] a 5.4% incidence. The use of glycoprotein IIb/IIIa receptor blockers in the elderly may further increase the incidence of blood transfusion to as high as 10%.[11] Given the 2.3 million PCI procedures performed worldwide in 2004, tens of thousands of patients received RBC transfusions. The liberal use of transfusions may be related to concern for the deleterious effect of anemia in coronary heart patients and the lack of evidence indicating a harmful effect of transfusion in this setting.

Weiskopf[12] demonstrated that healthy human volunteers could tolerate isovolemic anemia as low as 5.0 g/dL. The prevalence of obstructive coronary stenosis dramatically raises the threshold for ischemia. It has been shown in experimental models with fixed coronary stenosis that ischemic dysfunction occurs at hemoglobin levels <10 g/dL.[13,14] Carson[10] has shown that patients with cardiovascular disease who decline transfusions for religious reasons began to have increased mortality at hemoglobin levels <10 g/dL. Similarly, mortality is increased in anemic patients who undergo PCI.[15–17] The risk of chronic anemia appears to be highest in patients presenting with acute MI, whether they are treated conservatively[18] or with emergency PCI.[17]

The risk of anemia in patients with coronary artery disease may be attenuated by RBC transfusions. Wu reported improved survival after transfusion in elderly acute MI patients with baseline HCT <30%.[18] Similarly, Hébert suggested that a restrictive transfusion policy might be detrimental to intensive care unit patients with acute MI or unstable angina.[19] Conversely, Rao reported a higher mortality in patients with ACS who are transfused when they present with hematocrit levels >25%.[20] In addition, Kinnaird reported a higher in-hospital and 1-year mortality for PCI patients who are transfused.[2] Koch

TABLE 6 One year mortality

	Nadir HCT			
	<24 (n = 119)	24–30 (n = 202)	>30 (n = 117)	p-Value
All patients (%)	27/119 (23)	30/202 (15)	11/117 (9)	0.018
No transfusion (%)	5/51 (10)	14/127 (11)	11/114 (10)	0.93
Transfusion (%)	22/68 (32)	16/75 (21)	0/3 (0)	0.23
p-Value	0.0037	0.047	1.00	

Relationship among nadir HCT, transfusion status, and 1-year mortality. *Abbreviations*: HCT = hematocrit.

TABLE 7 Multivariable predictors of one year mortality

	p-value	Odds ratio	95% CI
Transfusion	0.0045	2.42	1.32–4.46
Female patients	0.031	1.95	1.06–3.57
Age	0.0001	1.07	1.03–1.11
Baseline creatinine	<0.0001	2.08	1.52–2.84
COPD	0.027	2.17	1.09–4.31
Urgent/emergent PCI	0.013	1.87	1.14–3.07
OL–other bleed	0.01	2.88	1.29–6.46

C-statistic = 0.81. *Abbreviations*: CI = confidence interval; COPD = chronic obstructive pulmonary disease; OL = out of lab; PCI = percutaneous coronary intervention.

demonstrated that RBC transfusion was also associated with increased mortality in the coronary artery bypass graft surgery patient.[21] Given the concern that anemia will induce cardiac ischemia and the conflicting data about the value of blood transfusion in other settings, it is not surprising that a widely accepted "transfusion threshold" does not exist after PCI. Our data suggest that 1-year mortality is not increased with nadir HCT levels as low as 24%.

We chose to study a subgroup of patients with a documented decline of hematocrit >10%. This was done to limit the impact of chronic anemia and to isolate patients with acute blood loss anemia. The nadir hematocrit of 28 ± 7 in the control group, and 24 ± 3 in the transfused patients is below the threshold established by Carson for increased postoperative mortality. The entire subgroup population was older, with a majority being female and having a smaller body size. Hypertension and renal insufficiency were common and the majority of these patients presented for urgent or emergency interventions. A high incidence risk of vascular complications, such as retroperitoneal bleed, occurred in this population. All these factors have been previously shown to increase mortality after PCI. Thus, the 3% in-hospital and 10% 1-year mortality for the control population is not surprising.

The striking and alarming increase in mortality in transfused patients merits discussion. The need for transfusions might be nothing more than a surrogate for severity of illness. We developed a propensity score to determine which variables increased risk of transfusion. This score was not independently associated with increased mortality. Therefore, it appears that transfusions themselves, and not the propensity for need of transfusion, is the factor influencing mortality. Transfusion of RBCs was independently associated with a 2.42 times increase in risk of death at 1 year. Since transfused patients developed a lower nadir HCT and suffered more vascular complications, it is not possible to remove these factors entirely with greater levels of blood loss. Unfortunately, blood transfusion may actually compound the problem since only patients who received blood appeared to have increased mortality at low HCT levels. In addition, blood transfusion appears to be particularly detrimental in patients undergoing more high-risk PCI procedures (emergent vs. elective).

We also observed a higher mortality for patients receiving old RBCs. Examination of the Kaplan–Meier curves suggests that most of the deaths occurred within 30 days of PCI in the transfused patients. This observation suggests that acute tissue ischemia may be the inciting event. Marik has demonstrated that splanchnic ischemia occurs after transfusion of old RBCs in septic patients.[22] As RBCs age, cytokine release is increased,[23] the RBCs become less deformable,[24,25] and 2, 3-diphoshoglycerate (DPG) levels decrease. All these factors may contribute to diminished oxygen delivery. A RBC of normal size is approximately 8 microns in size. These cells must often traverse capillaries as small as 2–3 microns. Therefore, aged RBCs could plug capillary beds, including the myocardial microcirculation.

Our findings should be construed as a cautionary note for the use of RBC transfusions after PCI. Clearly, a more restrictive policy will decrease transfusions, lessening the pressure on the nation's blood supply. Importantly, numerous individual patient characteristics, such as acute MI, valvular disease, LVH, and completeness of revascularization, will influence the decision for transfusion. To automatically assume that RBC transfusions will improve clinical status cannot be supported by our findings. Our findings concerning age of the RBC are further cause for concern and need to be confirmed. Since 27% of our transfusions were performed with blood more than 30 days old, availability of fresh blood may need to be incorporated into risk analysis for planned PCI.

Elderly patients, women of small body size, and those with baseline anemia or renal insufficiency merit particular concern. These patients often suffer vascular or systemic bleeding complications. Alternatives to heparin, such as bivalirudin, may be especially important in these patients. The ACUITY trial demonstrated a significantly decreased risk of major bleeding with bivalirudin use, from 5.7 to 3.0%.[26] In addition, Gurm *et al*.[27] demonstrated that bivalirudin decreases the need for transfusion from 4.0 to 1.7%. Use of IABP is usually accompanied by systemic anticoagulation. Whether systemic anticoagulation is needed to prevent thrombotic complications from the balloon pump is unknown. This practice is known to be associated with excessive bleeding risk.[28]

Clearly, prospective randomized trials of RBC transfusion after PCI are urgently needed. The age of RBCs should be considered in the design of these trials. RBC substitutes, such as bovine hemoglobin,[29] may be an alternative to RBC transfusion in PCI patients.

In 1991, the FDA suggested that a 2-week limit on storage of RBCs be considered. This proposal was not implemented because bacterial contamination was not documented in blood stored longer than 2 weeks.[30]

Study Limitations

This study is a prospective, observational, single-center experience. Outcomes from a high-volume, high-operator volume center may not represent widespread practice. Whether acute blood loss causes adverse events or is a consequence of them is difficult to sort out. In addition, since transfusion decisions were not by protocol, clinical judgment about patient severity of illness could not be quantified. Therefore, this report cannot be taken as conclusive proof that transfusions are harmful in the setting of acute blood loss. We do believe that our data on RBC storage age are a cause for concern. We do believe that this report can be useful in planning future prospective randomized trials.

Conclusions

Acute blood loss anemia at levels >4% HCT drop are associated with adverse clinical events after PCI. In-hospital and 1-year mortality is alarmingly elevated when HCT loss exceeds 10%. In these patients, one in four PCI patients who receive transfusions after severe blood loss will die within 1 year. Older patients, women of small body size, and those with COPD or renal insufficiency have increased risk of death in this setting. Future trials are required to establish clear parameters for the use of RBC transfusion and to determine the maximum time of RBC storage for PCI patients.

References

1. Meade D: *President, Guidant Vascular Intervention*, Mountain View, CA, Personal Communication
2. Kinnaird TD, Stabile E, Mintz GS, Lee CW, Canos DA, et al.: Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. *Am J Cardiol* 2003;92(8):930–935
3. Moscucci M, Ricciardi M, Eagle KA, Kline E, Bates ER, et al.: Frequency, predictors, and appropriateness of blood transfusion after percutaneous coronary interventions. *Am J Cardiol* 1998;81(6):702–707
4. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, et al.: Thrombolysis in Myocardial Infarction (TIMI) Trial–phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988;11(1):1–11
5. The GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329(10):673–682
6. Moscucci M, Fox KA, Cannon CP, Klein W, López-Sendón J, et al.: Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003;24(20):1815–1823
7. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, et al.: A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. *J Am Coll Cardiol* 2006;47(4):809–816
8. Sullivan MT, Wallace EL: Blood collection and transfusion in the United States in 1999. *Transfusion* 2005;45(2):141–148
9. Sullivan MT, McCullough J, Schreiber GB, Wallace EL: Blood collection and transfusion in the United States in 1997. *Transfusion* 2002;42(10):1253–1260
10. Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, et al.: Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996;348(9034):1055–1060
11. Sadeghi HM, Grines CL, Chandra HR, Dixon SR, Boura JA, et al.: Percutaneous coronary interventions in octogenarians. Glycoprotein IIb/IIIa receptor inhibitors' safety profile. *J Am Coll Cardiol* 2003;42(3):428–432
12. Weiskopf RB, Viele MK, Feiner J, Kelley S, Lieberman J, et al.: Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA* 1998;279(3):217–221
13. Hagl S, Heimisch W, Meisner H, Erben R, Baum M, et al.: The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. *Basic Res Cardiol* 1977;72(4):344–364
14. Yoshikawa H, Powell WJ, Bland JH, Lowenstein E: Effect of acute anemia on experimental myocardial ischemia. *Am J Cardiol* 1973;32(5):670–678
15. McKechnie RS, Smith D, Montoye C, Kline-Rogers E, O'Donnell MJ, et al., Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2): Prognostic implication of anemia on in-hospital outcomes after percutaneous coronary intervention. *Circulation* 2004;110(3):271–277
16. Reinecke H, Trey T, Wellmann J, Heidrich J, Fobker M, et al.: Hemoglobin-related mortality in patients undergoing percutaneous coronary interventions. *Eur Heart J* 2003;24(23):2142–2150
17. Nikolsky E, Mehran R, Aymong ED, Mintz GS, Lansky AJ, et al.: Impact of anemia on outcomes of patients undergoing percutaneous coronary interventions. *Am J Cardiol* 2004;94(8):1023–1027
18. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM: Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001;345(17):1230–1236
19. Hébert PC, Yetisir E, Martin C, Blajchman MA, Wells G, et al., Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group: Is a low transfusion threshold safe in critically ill patients with cardiovascular disease? *Crit Care Med* 2001;29(2):227–234
20. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, et al.: Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 2004;292(13):1555–1562
21. Koch CG, Li L, Duncan AI, Mihaljevic T, Loop FD, et al.: Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. *Ann Thorac Surg* 2006;81(5):1650–1657
22. Marik PE, Sibbald WJ: Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993;269(23):3024–3029

23. Kristiansson M, Soop M, Saraste L, Sundqvist KG: Cytokines in stored red blood cells concentrates: promoters of systemic inflammation and stimulators of acute transfusion reactions? *Acta Anaesthesiol Scand* 1996;40(4):496–501
24. Nakao M, Nakao T, Yamazoe S: Adenosine triphosphate and maintenance of shape of human red cells. *Nature* 1960;187:945–946
25. Card RT, Mohandas N, Mollison PL: Relationship of post-transfusion viability to deformability of stored red cells. *Br J Haematol* 1983;53(2):237–240
26. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, et al., ACUITY Investigators: Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355(21):2203–2216
27. Gurm HS, Rajagopal V, Fathi R, Vivekanathan D, Yadav JS, et al.: Effectiveness and safety of bivalirudin during percutaneous coronary intervention in a single medical center. *Am J Cardiol* 2005;95(6):716–721
28. Rabah M, Mason D, Muller DW, Hundley R, Kugelmass AD, et al.: Heparin after percutaneous intervention (HAPI): a prospective multicenter randomized trial of three heparin regimens after successful coronary intervention. *J Am Coll Cardiol* 1999;34(2):461–467
29. York GB, Eggers JS, Smith DL, Jenkins DH, McNeil JD, et al.: Low-volume resuscitation with a polymerized bovine hemoglobin-based oxygen-carrying solution (HBOC-201) provides adequate tissue oxygenation for survival in a porcine model of controlled hemorrhage. *J Trauma* 2003;55(5):873–885
30. Goldman M, Blajchman MA: Bacterial contamination. In *Transfusion Reactions*. (Ed. Popovsky MA), pp 125–165. Bethesda, MD: American Association of Blood Banks Press, 1996