Post-operative Outcomes of CABG Patients Given Blood Transfusion Based on Society of Thoracic Surgeons Guidelines on Blood Transfusion

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Background --- The worldwide practice in cardiac surgery regarding blood transfusion is towards a more conservative approach. The aim of the present study is to compare the postoperative outcome in terms of mortality and duration of mechanical ventilation among patients undergoing first-time CABG using the STS Guidelines' threshold in transfusion and the current practice at PHC.

Methods --- All adult patients aged 18-65 years undergoing elective cardiac surgery including aortocoronary bypass, heart valve replacement and correction of congenital cardiac anomaly at the Philippine Heart Center starting September 2008 until August 2009 were included in the study. Patients were randomized to Group 1, Restricted group and Group 2, Liberal group. Decisions regarding intraoperative and post-operative blood transfusion for the Liberal group were made by the attending surgeon and anesthesiologist. For the Restricted Group, decisions on blood transfusion were based on the STS Guidelines that is packed red cells will only be transfused for hemoglobin values less than 7 gm/dl. Postoperative outcome in terms of duration of mechanical ventilation and mortality were evaluated.

Results --- A total of 71 patients were enrolled in the study. Thirty-four were randomly assigned to the restricted transfusion group and 37 to the liberal transfusion group. The average age of patients included in the restricted group was 44 years while patients of the liberal group had an average age of 47 years. Pre-operative factors were homogenous for both groups. Preoperative hemoglobin and hematocrit values were significantly higher for the restricted group. The amount of packed red cells transfused was significantly higher in the liberal group, 2.35 ± .53 units, compared to the restricted group, 0.18 ± 0.75 units. (p-value = 0.00.) Comparison of mediastinal drainage revealed lesser amount in the restricted group, 132.21 ± 63.10 ml, than the liberal group, 195.27 ± 81.10 ml (p-value= 0.01). Duration of mechanical ventilation was shorter among the restricted group with only 14.7% requiring >48 hours of MV compared to 43.24% for the liberal group (p value=0.18). Mediastinal chest tubes were removed earlier in the restricted group with only 11.76% having CT >48 hours compared to 45.94% patients in the liberal group, (p value=0.00). Other outcome variables such as post-op dialysis, inotropic support >48hrs, sepsis, arrhythmia and hospital stay was not different for both groups. No mortality was recorded for both groups.

Conclusion --- Adherence to the STS Guideline recommendation of 7gm/dL cut-off for PRBC transfusion may benefit the patient in terms of lesser mediastinal drainage, shorter duration of mechanical ventilation and earlier removal of chest tubes. No mortality was noted for both groups. ***Phil Heart Center J 2012; 16(2):47-54***

Key Words: Blood Transfusion ■ Society of Thoracic Surgeon's Guidelines ■ Cardiopulmonary Bypass

Coronary artery bypass surgery is one of the major operations frequently requiring blood transfusion. This is due to the deleterious side effects of heart-lung machine on blood. Although most of these transfusions are performed for appropriate reasons, studies have documented substantial rates of unnecessary transfusions. Currently, the worldwide practice in cardiac surgery regarding blood transfusion is towards a more conservative approach, taking into mind the untoward effects of blood transfusion. Less than 20% of patients in developed

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countries who undergo cardiac surgery received postoperative blood transfusion. The current practice in Philippine Heart Center (PHC) is postoperative transfusion of at least two (2) units of blood components, particularly packed red blood cells (PRBC), fresh frozen plasma, (FFP), platelet concentrate, and cryoprecipitate.

Blood transfusion is associated with increased perioperative and long-term mortality including stroke, delirium, renal dysfunction, bacteremia, surgical site infection, prolonged ventilation and the increased use of healthcare resources, with prolonged intensive care unit and hospital stays.

Transfusion rates in coronary artery bypass grafting (CABG) continue to vary substantially, although guidelines for allogeneic transfusion have been developed. Many methods have been studied to minimize allogeneic blood transfusion among cardiac surgery patients. The Society of Thoracic Surgeons has recently released last May 2007 Practice Guidelines to minimize perioperative blood transfusion and blood conservation strategies for cardiac surgery.

Administration of packed red blood cells (PRBCs) has been associated with morbidity and mortality for both medical and surgical patients. Transfusions are associated with transmission of infectious agents,[1] postoperative infectious complications,[2] sternal wound infections,[3] postoperative pneumonia,[4] renal dysfunction,[5] impaired postoperative pulmonary function,[6] multiple organ failure,[7] increased intensive care unit[8] and hospital length of stay,[2] and increased short-[2] and long-term mortality.[9]

Rao et al[10] recently reported on the association of blood transfusion and mortality in the setting of anemia during hospitalization for acute coronary syndromes. Patients who received at least one blood transfusion during their hospitalization had a risk-adjusted increase in the hazard for 30-day death. In a prospective multicenter observational investigation, Vincent et al[11] examined the prevalence of anemia and PRBC usage in 1,136 critically ill patients. Transfused patients had higher mortality rates at every admitting hemoglobin level when compared with nontransfused patients. Similarly, in a multicenter observational cohort of intensive care unit patients, Corwin et al[9] reported an association between PRBC units transfused and worse clinical outcome.

The beneficial effects of blood transfusions have been described and widely accepted. Multiple factors, including shortages, costs, infectious risks, immunologic risks, and the risk/benefit ratio to the patient, have made the medical community reassess the guidelines for transfusion. Cardiac surgery presents a unique subset of patients, because intervention at multiple stages in the care of these patients is possible to decrease the need for transfusion.

Stroke, myocardial infarction, low cardiac output, cardiac arrest, renal failure, prolonged ventilation, pulmonary edema, reoperation due to bleeding, sepsis, and multi-organ failure were all significantly increased as lowest hematocrit value decreased below 22%.[11] Cardiopulmonary bypass promotes endothelial activation and neutrophil sequestration, and patients under going cardiac surgery have been identified in epidemiologic studies as being at increased risk of developing transfusion- associated lung injury.[17]

The American Society of Anesthesiology, through the formulated 2006 Practice Guidelines on Perioperative Blood transfusion, strongly agree that intraoperatively, red blood cells should usually be administered when the hemoglobin level is less than 6 g/dl and strongly agree that red blood cells are usually unnecessary when the level is more than 10 g/dl. The determination of whether intermediate hemoglobin concentrations (i.e., 6–10 g/dl) justify or require red blood cell transfusion should be based on any ongoing indication of organ ischemia, potential or actual ongoing bleeding (rate and magnitude), the patient's intravascular volume status, and the patient's risk factors for complications of inadequate oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption.[11]

Blood transfusion in the setting of acute coronary syndromes is associated with higher mortality.[10] Hence, adherence to proper indications for blood component therapy is essential because of the potential adverse effects and costs of transfusion.

The indications for blood product transfusion in cardiac surgery include treatment of coagulopathies and correction of anemias with the ultimate goal of limiting bleeding and improving oxygen-carrying capacity.

The Society of Thoracic Surgeons and Cardiovascular Anesthesiologists Society formulated Guidelines on Blood Transfusion last May 2007. According to the guidelines, among post-operative cardiac patients with hemoglobin levels below 6 g/dL, red blood cell transfusion is reasonable, as this can be life-saving. Transfusion is reasonable in most postoperative patients whose hemoglobin is less than 7 g/dl, but no high-level evidence supports this recommendation. (Class IIA, level of evidence C).[14]

Red blood cells are usually unnecessary when the hemoglobin concentration is more than 10 g/dL. These conclusions may be altered in the presence of anticipated blood loss. The determination of whether intermediate hemoglobin concentrations (i.e., 6-10 g/dl) justify or require RBC transfusion should be based on any ongoing indication of organ ischemia, potential or actual ongoing bleeding (rate and magnitude), the patient's intravascular volume status, and the patient's risk factors for complications of inadequate oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption.[11]

The aim of the present study is to compare the postoperative outcome in terms of mortality and pulmonary complications among patients undergoing first-time CABG using the STS Guidelines' threshold in transfusion and the current practice at PHC.

Methodology

This is a randomized comparative experimental study. We enrolled all adult patients undergoing elective cardiac surgery including aorto-coronary bypass, heart valve replacement and correction of congenital cardiac anomaly at the Philippine Heart Center starting September 2008 until August 2009. Excluded from the study were patients with (1) age <18 years and >65 years (2) preoperative anemia with hemoglobin less than 10g/dl (3) concomitant surgical procedures (e.g. any surgery other than cardiac surgery) (4) a history of any bleeding diathesis or coagulopathy (5) patients with thrombocytopenia (less than 50,000mm^2) (6) emergency cardiac surgery (7) refusal of blood products (Jehovah's witness) (8) post- operative hemoglobin more than 10g/dl.

After the protocol had been given an IRB approval, all patients who underwent elective cardiac surgery in PHC were candidates for inclusion. All patients who had met the inclusion criteria and signed the informed consent were randomized to Group 1, the Restricted Group and Group 2, the Liberal Group. Randomization was computer-generated. The following demographic data were obtained from the patient: age, sex, presence of diabetes mellitus (requiring treatment with insulin or oral antidiabetic drugs), presence of chronic renal failure (plasma creatinine >2 mg/dl), history of antiplatelet and anticoagulation therapy, preoperative laboratory exams (hemoglobin, hematocrit, platelet count, PTPA, INR, APTT).

All operations were performed under cardiopulmonary bypass with moderate hypothermia (28°to 32°C). Systemic heparinization (3mg/kg) were achieved and the activated clotting time were maintained greater than 480 seconds. The following intraoperative data were collected: duration of cardiopulmonary bypass circulation, duration of ischemic time, presence or absence of Modified Ultrafiltration (MUF), hematocrit pre- and post-bypass and number of units of blood products intraoperatively.

After weaning from cardiopulmonary bypass, the heparin was reversed with protamine sulfate in dosages sufficient to return the activated clotting time to baseline. Satisfactory hemostasis was achieved with electrocoagulation. Mediastinal and pleural drainage tubes were placed prior to sternal closure and connected to a hard-shell cardiotomy reservoir. Before chest closure, mediastinal and pleural drains were positioned, and a low-grade suction instituted.

Decisions regarding intra-operative and post-operative blood transfusion for the control group were made by the attending surgeon and anesthesiologist. For the treatment group, decisions

on blood transfusion were based on the STS Guidelines as follows:

1. For patients on CPB with risk of critical end-organ ischemia/injury, hemoglobin levels above 7g/dl is recommended

2. In the setting of hemoglobin values exceeding 6g/dl while on CPB, transfusion of red cells were based on the patient's risk for complications of inadequate oxygenation.

3. Postoperatively, packed RBC transfusions were given if the patient's hemoglobin was less than 7 g/dl or if the patient was hemodynamically unstable (systolic blood pressure <90mmHg) due to volume loss or with mediastinal bleeding >100cc/hour.

Fresh frozen plasma (FFP) were given for correction of microvascular bleeding in the presence of elevated (> 1.5 times normal) PT or PTT, for correction of microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume and when PT and PTT cannot be obtained in a timely fashion. Cryoprecipitate transfusions were recommended in bleeding patients with hypofibrinogenemia. Platelet transfusion was recommended after cardiopulmonary bypass in patients with normal coagulation values and platelet counts below 100 x 10^9/l when major unexplained bleeding occurs. [14]

All patients received routine postoperative care as per the patient management protocols of the surgical ICU. After extubation, patients were transferred to the ward for convalescence until ready for discharge. Postoperative data only included hospital stay for the same admission. Postoperative data included (1) hemoglobin and hematocrit (after arrival at RR, 12 hrs post-op); (2) number of units of blood transfused (PRBC, FFP, platelet concentrate, cryoprecipitate); (3) amount of chest tube drainage; (4) length of mechanical ventilation; (5) lung dysfunction (poor gas exchange that requires more than 48 hours of mechanical ventilation); and (6) mortality. *Postoperative mortality* was defined as an in-hospital death. *Prolonged postoperative ventilatory support* was defined as mechanical ventilatory support for > 48 hours postoperatively.

Data Analysis. To determine homogeneity of the characteristics of the patients in the 2 groups, t-test and chi-square tests were used. Comparison of the outcome were done using t-test and chi-square if there are no probable confounders, otherwise analysis of covariance or logistic regression were used to adjust for confounders. A p value ≤ 0.05 were considered significant.

Sample size. Sample size computed was 116 per group or a total of 232 at $\alpha = 0.05$, $\beta = 0.20$ and assumed difference in the rate of prolonged ventilatory support of 9.3%. The assumption was based on the paper of Koch, Liang and Li[16] with a 0.44% prolonged ventilatory rate in the restrictive group and 9.1% in the liberal group.

Results

A total of 71 patients were enrolled in the study. Thirty-four (34) were randomly assigned to the restricted transfusion group and 37 to the liberal transfusion group.

The average age of patients in the restricted group was 44 years while in the liberal group, the average age is 47 years. No significant difference was noted with the age group of both groups (*Table 1*).

Majority of the patients in both groups were male, with hypertension present in about 40% among patients. DM was present in six patients for Group 1 and four patients in Group 2. Both groups had two patients with renal failure. Right-sided failure was more common in the liberal group with seven patients, with only one patient had this in the restricted group. More patients in the liberal group had preoperative anticoagulation, while the use of antiplatelets were equal in both groups. (*Table 1*).

Comparison of baseline characteristics shows that there is no significant difference between the two groups in terms of gender, presence of hypertension, diabetes mellitus, dyslipidemia, renal failure, smoking habits and use of anticoagulation or antiplatelets. The restrictive group had higher hemoglobin, hematocrit values, and APTT values compared to the liberal group. The preoperative laboratory exams show that there is a significant statistical

Table 1. Baseline characteristics of patients undergoing elective cardiac surgery according to the blood transfusion group (PHC, 2010)

Variable	Restricted Group N=34 n (%)	Liberal Group N=37 n (%)	p-value
Age, mean ± SD	44.4 ± 15.42	47.49 ± 14.16	0.389
Gender, Male	20 (59)	22 (60)	1.00
Hypertension	14 (41)	16 (43)	1.00
Diabetes Mellitus	6 (18)	4 (11)	0.62
COPD	0	2 (5)	0.49
Smoker	10 (29)	7 (19)	0.45
Dyslipidemia	11 (32)	4 (11)	0.54
Renal Failure	2 (6)	2 (5)	1.00
Right Sided Failure	1 (3)	7 (19)	0.57
Anticoagulation Use	2 (6)	7 (19)	0.15
Antiplatelet Use	7 (21)	7 (19)	1.00
Hemoglobin, mean ± SD	135.50 ± 16.31	114.78 ± 16.35	***0.00 (S)***
Hematocrit, mean ± SD	0.41 ± .055	0.34 ± 0.52	***0.00 (S)***
Platelet Count, mean ± SD	343.32 ± 86.45	314.27 ± 136.55	0.28
PTPA, mean ± SD	81.59 ± 11.52	72.16 ± 21.64	***0.02 (S)***
INR, mean ± SD	1.209 ± 0.14	1.314 ± 0.35	0.11
Creatinine, mean ± SD	0.123 ± 0.02	0.114 ± 0.03	0.30
APTT, mean ± SD	42.53 ± 4.84	75.32 ± 4.15	***0.00 (S)***

COPD - Chronic Obstructive Pulmonary Disease *PTPA - Promthrombin Time Percent Activity*
INR - International Normalized Ratio *APTT - Activated Partial Thromboplastin TIme*

difference between the hemoglobin, hematocrit, PTPA and APTT values of the two groups. (*Table 1)*.

The liberal group had longer bypass times, (32 minutes longer than restrictve group) and the ischemic time in this group was longer by 18 minutes. The hematocrit post-bypass and use of platelet concentrate were the same for both groups. Transfusion of pRBC as well as the use of MUF intraoperatively was significantly higher in the liberal group (*Table 2*).

Comparing blood component transfusion postoperatively, PRBC transfusions were significantly less in the restrictive group by more than 2 units of PRBC. Although liberal group had more FFP transfusions, it was not statistically significant. Platelet concentrate transfusions for both groups were almost the same (*Table 3)*.

Comparing the laboratory exams immediate post-op and 12 hrs post-op, the values of examination taken immediately after operation showed no significant difference between the groups. However, 12 hrs post-op, these examinations had a statistical difference between the two groups, except for the APTT value. The hemoglobin, hematocrit, platelet and PTPA were significantly higher in Group 2 probably because of the liberal transfusions in this group (*Table 4*).

The mediastinal drainage of the restricted group was significantly less than the liberal group by 63ml (*Table 5*). There is statistically significant difference between the two groups in terms of duration of mechanical ventilation and retention of chest tubes more than 48 hours. Only 14% of the restricted group had mechanical ventilation more than 48 hours compared to 43% in the liberal group. Likewise, only four patients in Group 1 had their chest tubes retained for more

Table 2. Comparison of Intra-operative Data of patients undergoing elective cardiac surgery according to the blood transfusion group (PHC, 2010)

	Restricted Group N=34	Restricted Group N=37	p-value
Bypass Time, min	153.85 ± 44.03	185.32 ± 80.64	0.06
Ischemic Time, min	116.21 ± 35.93	134.19 ± 74.93	0.19
Hematocrit post-bypass	0.27 ± 0.03	0.27 ± 0.02	0.98
ACT, sec	145.18 ± 6.11	150.59 ± 7.95	***0.00 (S)***
PRBC, units	0.21 ± 0.53	0.95 ± 0.91	***0.00 (S)***
Platelet Concentrate, units	3.50 ± 0.96	3.57 ± 1.5	0.82
FFP, units	2.82 ± 1.71	3.46 ± 2.69	0.23
MUF			
(+)	10 (29)	27 (73)	***0.01 (S)***
(-)	24 (71)	10 (27)	

ACT - Activated Clotting Time *MUF - Modified Ultrafiltration* FFP Fresh Frozen Plasma PRBC Packed Red Blood Cell

Table 3. Comparison of Transfusion Postperatively of patients undergoing elective cardiac surgery according to the blood transfusion group (PHC, 2010)

Number of units Transfused	Restricted Group N=34	Liberal Group N=37	p-value
PRBC	0.18 ± 0.75	2.35 ± .53	0.00 (S)
FFP	2.82 ± 1.71	3.46 ± 2.69	0.236
Platelet concentrate	3.51 ± 0.96	3.59 ± 1.23	0.821

FFP Fresh Frozen Plasma PRBC Packed Red Blood Cell

than 48 hours compared to Group 2 which had 17 patients who still had their chest tubes after 48 hours. Other variables such as dialysis post-op, retention of inotropes >48 hrs, sepsis, arrhythmia and hospital stay did not show any statistical difference. No mortality was noted in both groups (*Table 6*).

Discussion

Practice guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints.

The American Society of Anesthesiologists together with Society of Thoracic Surgeons strongly agree that red blood cells should usually be administered when the hemoglobin level is less than 6 g/dL, and strongly agree that red blood cells transfusion is reasonable in most post-operative patients whose hemoglobin is less than 7 g/dL. They likewise agreed that transfusion is unlikely to improve oxygen transport when the hemoglobin concentration is greater than 10 g/dL and is not recommended.

The Philippine Heart Center is the leading institution in the Philippines catering to patients with cardiac diseases. Hence, our standard of care should be at par with worldclass standards by following practice guidelines set by international committees. The indications for blood product transfusion in cardiac surgery include treatment of coagulopathies and correction of anemias with the ultimate goal of limiting bleeding and improving oxygen-carrying capacity.

This study illustrates the advantages of adhering to these practice guidelines. However, this study shows significantly higher preoperative hemoglobin and hematocrit values of the restricted group than the liberal group, possibly affecting the postoperative transfusion requirements. Intraoperative data shows the liberal group had longer bypass and ischemic times. This could also affect the

Table 4. Comparison of Post-Operative Data of patients undergoing elective cardiac surgery according to the blood transfusion group (PHC, 2010)

	Restricted Group N=34	Liberal Group N=37	p- value
Immediate			
Hemoglobin	87.62 ± 7.68	87.08 ± 6.45	0.75
Hematocrit	0.26 ± .02	0.25 ± .02	0.08
Platelet	205.59 ± 33.49	207.24 ± 46.09	0.86
PTPA	73.24 ± 10.01	69.59 ± 19.24	0.31
INR	1.23 ± .09	1.31 ± .25	0.09
APTT	37.07 ± 4.45	43.5 ± 5.12	0.78
12hr post-op			
Hemoglobin	83.88 ± 6.38	98.22 ± 6.91	***0.00 (S***)
Hematocrit	0.24 ± .02	0.28 ± .02	***0.00 (S)***
Platelet	158.74 ± 17.71	173.59 ± 34.33	***0.02 (S)***
PTPA	68.56 ± 9.76	77.62 ± 9.51	***0.00 (S)***
INR	1.20 ± .05	1.16 ± .09	***0.02 (S)***
APTT	40.1 ± 4.38	43.5 ± 4.59	0.49

PTPA - Promthrombin Time Percent Activity INR - International Normalized Ratio
APTT - Activated Partial Thromboplastin TIme

Table 5. Comparison of Outcome Variables of patients undergoing elective cardiac surgery according to the blood transfusion group (PHC, 2010)

Variables	Restricted Group N=34 (%)	Liberal Group N=37 (%)	P value
Mediastinal drainage ml	132.21 ±63.10	195.27± 81.10	***0.01 (S)***
MV Duration >48hrs			
(+)	5 (15)	16 (43)	***0.18 (S)***
(-)	29 (85)	21 (57)	
Dialysis			
(+)	4 (12)	6 (16)	0.84
(-)	30 (88)	31 (84)	
Inoptropes >48hrs			
(+)	15 (44)	21 (57)	0.41
(-)	19 (56)	16 (43)	
Sepsis			
(+)	4 (12)	7 (19)	0.61
(-)	30 (88.)	30 (81)	
Arrhythmia			
(+)	5 (15)	11 (30)	0.22
(-)	29 (85)	26 (70)	
CTT >48hrs			
(+)	4 (12)	17 (46)	***0.00 (S)***
(-)	30 (88)	20 (54)	
Hospital stay	7.79 ± 1.98	7.65 ± 2.15	0.77

transfusion requirements requiring more blood for the liberal group particularly during hemostasis. These preoperative and intraoperative factors possibly result in significantly higher PRBC transfusions for the liberal group.

Hematologic data 12 hours postoperatively also reflect a significant difference for the two groups, taking note that these parameters could have been taken after blood components were transfused. These proves that liberal group had more transfusions postoperatively.

Looking at the outcome variables, postoperative cardiac patients who were restricted from receiving PRBC tranfusions exceeding 7gm/dl resulted in lesser mediastinal drainage, shorter duration of mechanical ventilation and faster removal of mediastinal chest tubes. This is a significant advantage for the cardiac patients undergoing operations.

This study, however, did not meet the required number of subjects. Hence, the conclusion obtained here may still be inadequate to recommend such guideline in our setting. The preliminary result proves that there is indeed an advantage in restricting blood transfusions particularly packed red cells. Completion of this study in the future may lead to recommendations that may serve as guidelines for the Philippine Heart Center.

Conclusion

Adherence to the STS Guideline recommendation of 7gm/dl cut-off for PRBC transfusion may benefit the patient in terms of lesser mediastinal drainage, shorter duration of mechanical ventilation and earlier removal of chest tubes. No mortality was noted for both groups.

Recommendation

This study did not reach the adequate number of subjects for each group. Hence, we recommend that the study be continued. The results gathered here reflect the advantage of the proposal and further investigation may benefit our future cardiac patients.

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