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Transfusion and Bleeding in Coronary Artery Bypass Grafting: An On-Pump Versus Off-Pump Comparison

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Abstract: Blood transfusion rates in coronary artery bypass grafting (CABG) surgery using cardiopulmonary bypass (CPB) are typically higher compared with off-pump CABG (OPCAB). However, few studies have specifically examined intraoperative hemodilution as a contributing factor. The aim of this retrospective review was to compare the effect of using CPB or OPCAB on red blood cell (RBC) transfusion and postoperative bleeding. The lowest intraoperative hematocrit (Hct) was used as marker of intraoperative hemodilution. We reviewed the perioperative data of all isolated CABG patients at a metropolitan hospital from January 2003 to June 2005. Stepwise regression analyses were performed to determine whether CPB was an independent predictor of RBC transfusion, reoperation for bleeding, or postoperative chest drainage. Of a total of 1043 patients, there were 433 CPB and 610 off-pump cases. CPB use was not significantly related to increased RBC transfusions (odds ratio [OR], 0.98; 95% confidence interval [CI], 0.63–1.52; $p = .921$) and was associated with a lower incidence of reoperations for bleeding (OR, 0.4; 95% CI, 0.2–0.8; $p = .009$). There was less chest drainage over the first 12 hours in patients undergoing CPB ($p < .0001$); however, total postoperative chest drainage was not significantly related to operative procedure ($p = .122$). The lowest documented intraoperative Hct was a significant factor in RBC transfusions (OR, 0.89; $p < .0001$), an increased reoperation rate for bleeding (OR, 0.9; $p = .001$) and more postoperative chest drainage ($\log_{10}$-transformed: at 12 hours, $b = -0.009$, $p < .0001$; total, $b = -0.006$, $p < .0001$). CPB is not an independent risk factor in the incidence of RBC transfusions and is not associated with increased postoperative bleeding for isolated CABG. However, intraoperative hemodilution is an independent risk factor, with a lower intraoperative Hct associated with more RBC transfusions, increased reoperations for bleeding, and increased postoperative chest drainage. Addressing intraoperative hemodilution is important in minimizing CPB-associated morbidities.
Keywords: coronary artery bypass grafting, cardiopulmonary bypass, off pump coronary artery bypass, blood transfusion, hemodilution. *JECT. 2007;39:24–30*

Traditionally, most cardiac surgery has been performed using cardiopulmonary bypass (CPB). CPB allows the heart to be arrested, thereby providing a motionless and bloodless field to enable optimal and complete coronary artery bypass grafting (CABG). There is a resurgence in performing CABG on the beating heart without CPB (off-pump CABG [OPCAB]) (1). Although there are inconclusive differences between patients undergoing OPCAB and patients undergoing CPB in terms of postoperative morbidity, adequacy of revascularization, and quality of grafts, studies typically show that patients undergoing CPB are transfused more blood (2–4).

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There is a morbidity associated with homologous blood products, such as transfusion reactions, wound infections, sepsis, and increased hospital mortality and post-discharge survival (5–9). Because of these issues, there are pressures to minimize blood transfusions.

It is unclear whether the increased transfusion rate observed with CPB may be related to increased intraoperative hemodilution or more postoperative bleeding. Few studies have specifically examined the contribution of intraoperative hemodilution in influencing the transfusion rates in CABG surgery (10).

The aim of this retrospective review was to compare the effect of using CPB or OPCAB on red blood cell (RBC) transfusion and postoperative bleeding. The lowest intraoperative hematocrit (Hct) was used as marker of intraoperative hemodilution. This was undertaken by examining the data of all patients undergoing isolated CABG at a metropolitan hospital from January 2003 to June 2005.

MATERIALS AND METHODS

Patients

All patients who underwent isolated CABG using a median sternotomy approach at a metropolitan hospital in Sydney, Australia, between January 2003 and June 2005 were acquired from a prospective administrative database. The decision to perform the operation on-pump or off-pump was made by the operating surgeon.

Patients who were intended to be operated off-pump but were converted to on-pump after initiation of coronary grafting were excluded. Also excluded were patients having lateral thoracotomy incisional approaches.

The study was approved by the hospital's research Ethics Committee.

Dependent Variables

The primary endpoints of interest were packed red blood cell transfusions, reoperation rate for bleeding or cardiac tamponade, and 12 h and total postoperative chest tube drainage. Only intraoperative and postoperative homologous packed RBC transfusions were recorded.

Independent Variables

Pre-operative parameters analyzed included age, sex, body surface area (BSA), left main coronary artery stenosis >50%, antiplatelet medications within 7 days before operation, pre-operative heparin therapy, recent history of myocardial infarction (within 6 months), ejection fraction <30%, previous cardiac surgery, chronic renal failure, cerebrovascular disease, antifibrinolytic drugs, and last preoperative Hct. Intraoperative data consisted of number of distal anastomoses performed, use of internal mammary arteries (IMA), and lowest intraoperative Hct documented.

Pre-operative Hct was determined from full blood counts taken before transfer to the operation theater. Lowest intraoperative Hct was analyzed on a bench top blood gas analyzer. Because not all patients undergoing OPCAB had blood gases measured intraoperatively, the first arterial blood gas taken immediately on transfer to the intensive care unit (ICU) was used.

Anesthesia and Anticoagulation Management

Both patients undergoing OPCAB and patients undergoing CPB received the same anesthetic regimen. Before CPB, a bolus dose of 300–400 IU/kg of heparin was given to achieve a kaolin activated clotting time (ACT) of at least 480 seconds. Additional heparin was infused on CPB if required. After termination of CPB, 3–4 mg/kg protamine was given to fully reverse the anticoagulant effect of heparin. In the OPCAB group, 150 IU/kg of heparin was administered before division of the internal mammary artery to maintain an ACT of 250–350 seconds. On completion of anastomoses in patients undergoing OPCAB, 0.75 mg/kg protamine was given to partially reverse the heparin. Antifibrinolytics in the form of aprotinin or epsilon aminocaproic acid were injected at the surgeon's discretion.

Operative and Perfusion Procedure

OPCAB surgery was performed through a sternotomy incision. Stabilization of the target coronary artery was achieved by using either a compression device or suction apparatus. Operative blood was aspirated into a blood salvaging system to be concentrated, washed, and transfused if enough was collected. A perfusionist remained on standby for emergency institution of CPB if required.

CPB surgery was performed through a full sternotomy incision using a membrane oxygenator and a roller pump. The circuit was primed with 2200 mL of Hartman solution or 1700 mL Hartman and 500 mL 4% albumin solution with 10,000 units of heparin. The addition of 10 g of mannitol was added to the CPB prime of patients with a preoperative creatinine of >0.15 mmol/L. Institution of CPB was achieved by cannulating the ascending aorta and right atrium. After cross-clamping, antegrade or retrograde blood cardioplegia was infused for myocardial protection of the arrested heart. Minimum systemic temperatures ranged from 28°C to 34°C. Perfusionist preference determined whether all or part of the cardiotomy blood was returned to the CPB circuit or collected in a cell-saving device for subsequent processing. After weaning from CPB, the residual blood in the extracorporeal circuit was salvaged and either processed through a cell-saving device or simply bagged before patient reinfusion. At least two chest drains were inserted in the pericardium and pleura if internal mammary arteries were harvested. These drains were connected to a low suction system (–20 cm H_2O) after closure of the chest. Total chest drainage was recorded as the volume of blood in the collection receptacle from closure of the chest until removal of the chest drains.

Postoperative Care

Treatment of both patients undergoing OPCAB and patients undergoing CPB followed a standardized care from operation to discharge without regard to the procedure performed. An autologous transfusion system was used to reinfuse chest drainage in both groups.

Transfusion protocol

For both patients undergoing CPB and patients undergoing OPCAB, the decision to transfuse homologous packed RBCs was based on the patient's clinical status and/or a Hct <20%. Postoperatively, blood transfusions were based on the patient's clinical status and/or hemoglobin <8.0 g/dL.

Reoperation Protocol

Reexploration of the chest was usually performed if bleeding exceeded 200 mL/0.5 h, >300 mL/h, or >200 mL/h for 2 hours despite correction of any coagulopathies. Reoperations were also indicated if there were clinical signs of cardiac tamponade such as tachycardia, increasing central venous pressures, or decreasing urine output, usually associated with a sudden reduction in chest tube drainage.

Data Collection and Statistical Analysis

Patients' demographics, risk factors, clinical status, intraoperative and postoperative data were prospectively written on a datasheet to be entered into a customized Microsoft Access cardiac surgery database by a data manager. Hct data were retrospectively taken from the operating theater blood gas machine and hospital hematologic laboratory archives.

Statistical analyses were performed using StatView (StatView; Abacus Concepts, Berkeley, CA) with two-tailed tests performed and a $p < .05$ considered significant. Data are summarized as the mean ± SD unless otherwise indicated.

The two groups (CPB vs. OPCAB) were compared using the χ^2 statistic or Fisher exact test for categorical data and unpaired *t* tests. Because postoperative chest tube drainage was positively skewed, the volumes were $\log_{10}$-transformed to satisfy the requirements of parametric tests.

To determine whether CPB was an independent predictor of RBC transfusion, reoperation for bleeding, or postoperative chest drainage, the following analyses were performed. Multiple logistic regression was used to identify univariate predictors of either RBC transfusion or reoperation for bleeding. A univariate $p < .25$ qualified the variable for inclusion in the maximum multivariate model. A backward stepwise elimination process was used to remove covariates from the maximum multivariate model whose multivariate *p* value was >.10. The term CPB was forced to remain in the model. A similar process using multiple linear regression was used to identify predictors of postoperative chest tube drainage. Operation type was a binary variable, with 1 indicating CPB and 0 indicating OPCAB.

In multivariate analysis, the effect of multiple variables on an outcome can be studied simultaneously. For example, if univariate analyses show that both variable A and variable B are related to outcome C, multivariate analysis may show which relationship is most direct. If both variables remain significant in the multivariate model, both are said to be independently associated with the outcome of interest. If variable A remains significant but variable B becomes non-significant in the multivariate analysis, the overall conclusion would be that variable A has the most direct relationship with outcome C. Because variable B becomes non-significant in the multivariate model, it is less likely to have a strong direct causal relationship with outcome C.

RESULTS

Of a total of 1043 patients, there were 433 CPB and 610 OPCAB cases. Both the patients undergoing CPB and patients undergoing OPCAB were similar in terms of preoperative anticoagulants, recent myocardial infarctions, redo operations, unstable angina, and incidence of diabetes. The patients undergoing CPB were more likely to be men, were slightly younger, had a significantly higher incidence of left main disease, had a poorer ejection fraction, and were given antifibrinolytics. Patients undergoing OPCAB were more likely to have a smaller BSA, be on antiplatelet medications, and have a history of chronic renal failure and cerebrovascular disease. Pre-operative Hct was similar for both groups. The number of distal anastomoses performed was significantly higher in the CPB group (3.2 ± 0.9 vs. 2.6 ± 1.0, $p < .01$), whereas patients undergoing OPCAB had more internal mammary arteries harvested. The lowest recorded intraoperative Hct was significantly lower in patients on CPB (23.8 ± 4.6% vs. 31.2 ± 5.6%, $p < .01$; Table 1).

Table 2 depicts the postoperative data. Both the patients undergoing OPCAB and patients undergoing CPB had similar postoperative chest drainage and reoperation rates for bleeding. However, the rate of RBC transfusion was significantly higher for patients undergoing CPB (36.0% vs. 23.8%, $p < .01$).

Table 1. Patient demographics and intraoperative data—CPB vs. OPCAB.

Variable	CPB	OPCAB	*p*
Sex (female)	21.7%	27.5%	.0324
Age (years)	65.4 ± 10.4	66.7 ± 10.7	.0456
BSA (m^2)	1.93 ± 0.21	1.90 ± 0.22	.0293
Antiplatelets	24.5%	35.7%	.0001
Anticoagulants	39.0%	34.3%	.1145
Left main disease ≥ 50%	22.4%	15.9%	.0079
Recent MI < 90 days	33.5%	29.0%	.1235
Ejection fraction < 30%	12.2%	4.9%	<.0001
Redo operations	6.2%	4.1%	.1181
Unstable angina	60.0%	54.1%	.0562
Chronic renal failure	2.8%	5.6%	.0257
Cerebrovascular disease	9.9%	15.4%	.0098
Diabetes	30.0%	26.2%	.0178
Antifibrinolytics	21.2%	0.5%	<.0001
Preoperative Hct	40.7 ± 4.7	40.1 ± 4.9	.0590
Distal anastomoses	3.2 ± 0.9	2.6 ± 1.0	<.0001
IMA	89.4%	94.1%	.0052
Lowest intraoperative Hct	23.8 ± 4.6	31.2 ± 5.6	<.0001

Table 2. Postoperative data—CPB vs. OPCAB.

	CPB	OPCAB	*p*
Transfusion RBC	36.0%	23.8%	<.0001
Reoperation for bleeding	4.6%	4.8%	.919
12-h postoperative chest drainage (mL)	728 ± 353 (650)	770 ± 390 (700)	.076
Total chest drainage (mL)	1133 ± 523 (1025)	1146 ± 577 (1025)	.919

Medians given in parentheses.

Table 3. RBC transfusion—logistic regression final adjusted model.

	OR	95% CI	*p*
CPB	0.98	0.63–1.52	.921
Lowest intraoperative Hct	0.89	0.85–0.93	<.0001
BSA (m^2)	0.24	0.11–0.53	.0004
Age (years)	1.03	1.01–1.04	.001
Preoperative Hct	0.95	0.91–0.99	.011
Ejection fraction < 30%	2.05	1.22–3.47	.007
Chronic renal failure	2.28	1.12–4.66	.023

OR, odds ratio; CI, confidence interval.

After controlling for all variables found to be significant predictors of RBC transfusion, CPB use was not found to be significantly related to increased RBC transfusions [odds ratio (OR), 0.98; 95% confidence interval (CI), 0.63–1.52; $p = .92$]. ORs, CIs, and *p* values are shown in Table 3. Therefore, after accounting for the individual effects of the identified independent predictors of RBC transfusion in the final multivariate model, being on-pump was not associated with a higher chance of being transfused RBCs.

After controlling for all variables found to be significant predictors of reoperation for bleeding, CPB use was found to be a significant factor in reducing the incidence of bleeding-indicated reoperations (OR, 0.4; 95% CI, 0.2–0.8; $p < .01$; Table 4). If all other identified independent predictors of bleeding reoperations are held constant in the final multivariate model, being off-pump was associated with a higher chance of being reopened for bleeding.

Controlling for all possible confounders, there was significantly less chest drainage over the first 12 hours in patients undergoing CPB ($p < .01$); however, total postoperative chest drainage was not significantly different between the two groups ($p = .12$; Tables 5 and 6). Therefore, after the individual effects of the identified independent predictors of chest drainage are accounted for, being on-pump was not associated with greater chance of increased bleeding.

The lowest documented intraoperative Hct was found to be a significant factor in all models. A lower intraoperative Hct was associated with a higher RBC transfusion rate (OR, 0.89; $p < .01$), an increased reoperation rate for bleeding (OR, 0.9; $p < .01$), and more postoperative chest drainage ($\log_{10}$-transformed: at 12 hours, $b = -0.009$, $p < .01$; total, $b = -0.006$, $p < .01$).

Table 4. Reoperation for bleeding—logistic regression final adjusted model.

	OR	95% CI	*p*
Lowest intraoperative Hct	0.9	0.9–1.0	.001
Ejection fraction < 30%	3.1	1.4–6.6	.004
CPB	0.4	0.2–0.8	.009
Distal anastomoses	1.3	1.0–1.7	.077

OR, odds ratio; CI, confidence interval.

Table 5. Log_{10} 12-h chest drainage—linear regression final adjusted model.

	b	SE b	*p*
CPB	–0.074	0.019	<.0001
Lowest intraoperative Hct	–0.009	0.002	<.0001
Sex (male)	0.084	0.016	<.0001
Antifibrinolytics	–0.114	0.024	<.0001
Ejection fraction < 30%	0.080	0.023	.0006
Preoperative Hct	0.005	0.002	.0018
IMA	0.079	0.024	.001
Age (years)	0.002	0.001	.0104
Redo operation	–0.071	0.030	.0181
Previous MI	–0.0003	0.0001	.0332
Anticoagulants	–0.027	0.013	.0372

b, regression coefficient; SE b, standard error of b.

Table 6. Log_{10} total chest drainage—linear regression final adjusted model.

	b	SE b	*p*
CPB	–0.025	0.016	.1216
Sex (male)	0.096	0.016	<.0001
Lowest intraoperative Hct	–0.006	0.001	<.0001
Antifibrinolytics	–0.086	0.022	.0001
Ejection fraction < 30%	0.081	0.022	.0002
IMA	0.083	0.023	.0003
Redo operation	–0.084	0.028	.0029
Age (years)	0.002	0.001	.0044
BSA (m^2)	–0.062	0.031	.0501
Anticoagulants	–0.027	0.012	.0282
Previous MI	–0.0002	0.0001	.0481
Diabetic	–0.024	0.013	.0687

b, regression coefficient; SE b, standard error of b.

DISCUSSION

This retrospective review failed to show that CPB is an independent risk factor for the subsequent need for RBC transfusions in isolated CABG. Furthermore, CPB is not associated with a higher incidence of reoperations for bleeding or increased postoperative chest drainage. However, intraoperative hemodilution is an independent risk factor whereby, the higher the intraoperative Hct, the lower the RBC transfusion rate, the fewer reoperations for bleeding, and the less postoperative chest drainage.

The inclusion of the lowest intraoperative Hct as a marker of hemodilution provides a more complete understanding of the mechanism of the need for blood transfusions after cardiac surgery. Our results suggest that intraoperative hemodilution and not differences in postoperative blood losses or reoperations for bleeding accounts for any apparent differences in transfusion rates attributable to on-pump and off-pump patients.

Previous studies have shown that CPB was associated with increased blood transfusions but did not investigate the contribution of intraoperative hemodilution (11–13). Other studies have speculated that their observed increased blood transfusion rate for on-pump compared to off-pump patients was caused by increased postoperative bleeding (14,15). However, our patients undergoing CPB did not bleed more than patients undergoing OPCAB. Further studies have shown similar findings of no difference in postoperative bleeding between off-pump and on-pump patients and were able to associate predictors of intraoperative anemia (i.e., low postoperative Hct, positive fluid balance, or postoperative albuminemia) with increased blood transfusions (13,16). The study of Dial et al. (10) is the only research we identified that specifically showed that a lower intraoperative Hct in 545 on-pump and 68 off-pump patients undergoing CABG was associated with more blood transfusions.

In patients undergoing CABG, intraoperative hemodilution being associated with perioperative blood transfusions has been indirectly implicated using variables associated with low RBC volume derived from female sex, smaller BSA, increasing age, and a lower pre-operative Hct (11,17,18). Furthermore, renal failure, lower cardiac ejection fraction, and emergent operations have been recognized as independent risk factors for homologous blood transfusions (19) A lower BSA, increasing age, lower preoperative Hct, impaired ejection fraction, and renal failure were also identified in our study as independent predictors for RBC transfusions; independently of the effect of the other identified predictors in the final multivariate model.

The lowest intraoperative Hct was identified in this study as an independent risk factor in postoperative blood loss; the higher the intraoperative Hct (a marker of less hemodilution), the less bleeding. Hemodilution dilutes all blood components including platelets and plasma proteins coagulation factors, thereby potentially exacerbating postoperative coagulopathies.

Although there was no difference in total postoperative chest drainage for both the off-pump and on-pump patients, OPCAB was associated with more blood loss at 12 hours. Increased circulating heparin in the off-pump group may be the explanation. Partial reversal of heparin is our protocol for OPCAB to address the potential procoagulant state seen in the immediate postoperative period with concerns of graft thrombosis. Nuttal et al. (20) observed a similar phenomenon. In their study of 200 patients undergoing CABG, the 100 off-pump patients bled more at 4 hours, with no differences between on and off-pump patients seen at 12 and 24 hours. A similar partial reversal of heparin protocol in the off-pump group was used. Like our study, their on-pump cases had significantly more blood transfusions, and this was predominantly given intraoperatively, hinting to a CPB-induced hemodilution.

The logistic regression adjusted model identified the lowest intraoperative Hct as a significant independent predictor for bleeding-related reoperations. Despite less intraoperative hemodilution being associated with reduced chest reopenings, CPB was an independent risk factor in reducing bleeding induced reoperations.

Randomized studies have shown no difference in reopening for bleeding in off-pump vs. on-pump cases (13,15,21). However, marked differences in reoperation rates between various study sites suggest that surgeon technique and not patient characteristics may play a greater role (10). Dilutional coagulopathies may also be implicated though increased circulating heparin in the early postoperative period in off-pump patients cannot be discounted.

By identifying intraoperative hemodilution as an important trigger for transfusion in on-pump CABG, the perfusionist should use strategies to minimize CPB-associated intraoperative hemodilution by focusing on the patient's RBC mass, blood volume, and the prime volume of the CPB circuit. Minimizing the CPB circuitry and concomitant prime volume has reduced transfusions, particularly in patients presenting with reduced blood volumes (22–25). Another technique to reduce CPB hemodilution is to use the patient's blood to displace the crystalloid prime in the CPB circuit just before starting bypass—a procedure called retrograde autologous priming (RAP). Randomized studies using RAP have reported significantly reduced transfusions (26,27). Although both RAP and control patients generally end with similar total prime volumes on leaving the operating theater, the minimum Hct seen when first going on CPB is attenuated, thereby avoiding obligatory transfusions triggered by Hct values decreasing below institutional decreed minimum safety thresholds. These minimum safety thresholds also need to be addressed, because they may be a source of unnecessary transfusions. Simply lowering a hemoglobin transfusion threshold by 1 g/dL has been shown to significantly reduce postoperative RBC transfusions by 20% in low-risk patients undergoing CABG without adversely affecting patient outcome (28).

The safe lowest Hct tolerated is unknown and highly patient dependent; it is important to customize transfusion threshold to the patient, with sicker, higher-risk patients needing a higher Hct. Another approach used successfully to reduce transfusions was to avoid arbitrary transfusion triggers and use the mixed venous saturations on CPB instead (29). Other techniques to minimize intraoperative hemodilution include measures to maximize the patient's RBC mass by vigilant RBC salvaging using a cell-saver device. Furthermore, hemoconcentrators and diuretics can reduce the patient's circulating plasma volume, thereby concentrating the RBCs.

Despite the use of statistics to dissociate the hemodilution aspect of CPB from all other bleeding and transfusion implications of CPB, a true separation cannot be made because this study's findings are limited by its non-randomized retrospective nature. Also, unaccounted or unavoidable selection biases may have occurred, including the tendency for patients undergoing OPCAB to have fewer intraoperative blood gas samples, thereby possibly obscuring a real lower Hct. Furthermore, it is possible in some cases that the lowest intraoperative Hct was measured after intraoperative RBC transfusions, thereby obfuscating the analyses. Prospective randomized studies would further elucidate the role of CPB in blood transfusions with particular attention made to factors implicated in hemodilution including intraoperative fluid balances, cell-saving volumes, the timing of transfusions, blood product types, and details of hematologic parameters.

The resurgence of OPCAB as an alternative to traditional CPB needs to be challenged. CPB remains the gold standard in cardiac surgery technique, affording the surgeon an ideal still and dry operative field. Its purported associated morbidity can be partly redressed by perfusionists aggressively minimizing CPB-induced hemodilution. This study suggests that if patients on CPB were hemodiluted to the same degree as off-pump patients, blood transfusion rates would become more comparable.

In summary, this study shows that CPB is not an independent risk factor in the incidence of more RBC transfusions and is not associated with increased postoperative bleeding for isolated CABG. However, intraoperative hemodilution is an independent risk factor, with a higher intraoperative Hct associated with fewer RBC transfusions, reduced reoperations for bleeding, and less postoperative chest drainage. Addressing intraoperative hemodilution is a very important issue in minimizing CPB-associated morbidities.

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