Platelet transfusions and patient outcomes after cardiac surgery

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PART II

Platelet transfusions in cardiac surgery patients

CHAPTER 5

5

Does a platelet transfusion independently affect bleeding and adverse outcomes in cardiac surgery?

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Background

Conflicting results have been reported concerning the effect of platelet transfusion on several outcomes. The aim of this study was to assess the independent effect of a single early intraoperative platelet transfusion on bleeding and adverse outcomes in cardiac surgery patients.

Methods

For this observational study 23,860 cardiac surgery patients were analysed. Patients who received one early (shortly after cardiopulmonary bypass while still in the operating room) platelet transfusion, and no other transfusions, were defined as the intervention group. By matching the intervention group 1:3 to patients who received no early transfusion with most comparable propensity scores, the reference group was identified.

Results

The intervention group comprised 169 patients and the reference group 507. No difference between the groups was observed concerning reinterventions, thromboembolic complications, infections, organ failure, and mortality. However, patients in the intervention group experienced less blood loss and required vasoactive medication 139 of 169 (82%) versus 370 of 507 (74%; odds ratio, 1.65; 95% CI, 1.05 to 2.58), prolonged mechanical ventilation 92 of 169 (54%) versus 226 of 507 (45%; odds ratio, 1.47; 94% CI, 1.03 to 2.11), prolonged intensive care 95 of 169 (56%) versus 240 of 507 (46%; odds ratio, 1.49; 95% CI, 1.04 to 2.12), erythrocytes 75 of 169 (44%) versus 145 of 507 (34%; odds ratio, 1.55; 95% CI, 1.08 to 2.23), plasma 29 of 169 (17%) versus 23 of 507 (7.3%; odds ratio, 2.63; 95% CI, 1.50–4.63), and platelets 72 of 169 (43%) versus 25 of 507 (4.3%; odds ratio, 16.4; 95% CI, 9.3–28.9) more often compared to the reference group.

Conclusions

In this retrospective analysis, cardiac surgery patients receiving platelet transfusion in the operating room experienced less blood loss and more often required vasoactive medication; prolonged ventilation; prolonged intensive care and blood products postoperatively. However, early platelet transfusion was not associated with reinterventions, thromboembolic complications, infections, organ failure, or mortality.

Abstract

Introduction

Patients undergoing cardiac surgery are at increased risk for excessive bleeding. Excessive bleeding may lead to surgical re-exploration. Both excessive blood loss and re-exploration are associated with increased postoperative mortality and morbidity.[1-3] Thus efficient prevention and treatment of the cause of bleeding is an important issue in cardiac surgery. As expected, part of the postoperative bleedings is due to surgically induced injury, but a significant proportion of the observed bleedings can be explained by acquired hemostatic defects.[4,5] Impaired platelet function, mainly due to cardiopulmonary bypass (CPB) and anti-platelet drug therapy, is considered one of the most important hemostatic factors leading to postoperative bleeding.[4-8] Platelet transfusions are thus commonly administered to treat bleeding.[9]

The platelet-transfusion rates vary greatly in cardiac surgery, both nationally and internationally [10], in spite of existing guidelines.[11] This wide variety in platelet transfusion use among cardiac surgery centres, illustrates the lack of consensus on the indication for a platelet transfusion in certain clinical situations. Presumed platelet dysfunction in patients using platelet inhibiting drugs is not always confirmed by a measurement before platelets are transfused. Furthermore, just as in other clinical areas[12,13], there is a lack of clinical evidence establishing the effectiveness of administering platelets in cardiac surgery.[14]

In addition, conflicting results have been reported concerning the effect of platelet transfusions on serious adverse events, like stroke, infections, vasoplegia and death in cardiac surgery.[15-22] The recently published results of a multicenter randomized controlled trial (Platelet Transfusion in Cerebral Haemorrhage (PATCH) trial) comparing standard care to standard care with platelet transfusion in patients using antiplatelet therapy before intracerebral hemorrhage, showed that platelet transfusions seemed inferior to the standard care.[23]

Our hypothesis was that a single early platelet transfusion, in the absence of concomitant erythrocyte or plasma transfusion, is associated with less bleeding complications and is associated with more adverse events, in patients undergoing cardiac surgery.

Patients and methods

Data collection

The analyses were performed using data from the Amphia Cardiac Surgery Registry consisting of 23,860 patients who underwent cardiac surgery at the Amphia Hospital

between 1997 and 2013. Details of this database have been described previously.[24] In this ongoing cohort study, detailed baseline and perioperative data of all consecutive patients undergoing cardiac surgery in the Amphia Hospital were collected. Data collection for the current analysis took place between January 1st 1997 and January 1th 2013 and was compliant with the definitions of the Dutch National Cardiac Surgery Registry, BHN, and the Dutch National Intensive Care Registry, NICE (instituted in 1996).[25] All patient-care decisions were taken by the attending physician in accordance with transfusion and coagulation hospital guideline based protocols. Members of our departmental review committee critically reviewed the analytical plan. The aim of the study, the inclusion and exclusion criteria, propensity score matching as the method to correct for confounding by indication, the postoperative endpoints, and logistic regression as the method to analyse the endpoints were determined before examination of the data. There was no *a priori* statistical power analysis calculation used to guide sample size. Sample size and analyses were based on the available data. The ratio and caliper of the propensity score matching were determined during examination of the data. An acknowledged Dutch medical ethical committee approved this study protocol and waived individual patient consent.

Patient sample

It was decided in advance to select only patients who received one early platelet transfusion, defined as one platelet transfusion after the end of cardiopulmonary bypass (CPB) while still in the operating room. Patients transfused with more than one unit of platelets were excluded presuming that these patients would not be comparable to patients who were not transfused with platelets. Also patients who received other blood products in the operating room were excluded aiming at studying the independent effect of an early platelet transfusion without the potential influence of erythrocyte or fresh frozen plasma (FFP) transfusions.

The platelet units transfused in this study consisted of five pooled buffy coats and contained approximately 300 * 10^9 platelets suspended in plasma with or without platelet additive solution. Since 2001 all platelet units were pre-storage leukocyte-reduced in The Netherlands, and before 2001, platelet units were leukocyte-reduced when indicated in the Amphia Hospital. The decision to transfuse platelets was made according to a cardiac surgery coagulation algorithm, with upscaling treatment modalities in which platelet transfusion is used as a last resort after considering other pharmacological strategies. Some degree of freedom was left to the discretion of the physicians, but platelet count lower than 50 * 10^9/l was an indication for platelet transfusion in any case. When platelet count was lower than 100 * 10^9/l and bleeding was present, this was also indication for

transfusion of platelets. No specific platelet function test was available, but in recent years rotational thromboelastometry was included in the algorithm.

Patients who received an early platelet transfusion may differ in various ways from patients who received no early transfusion, because there was a reason to administer the platelet unit (confounding by indication). To correct for this confounding we estimated a propensity score for these patients, representing the probability that the patient received platelets conditional on relevant covariates before the decision to transfuse platelets. The patients who received one early platelet transfusion and no other blood products, and were suitable for propensity score matching were defined as the intervention group. The intervention group was then matched to the reference group, consisting of patients who received no early transfusion and had the closest propensity scores. For the propensity score matching we used the "psmatch2" function in Stata Statistical Software (Release 14; StataCorp LP, College Station, TX, USA) as "greedy" in random order, nearest neighbour 1:3 matching with replacement. Only controls with a propensity score within 0.01 distance (caliper) of the propensity score of the case were selected.[26] We hereby aimed at selecting an intervention and reference group with comparable baseline characteristics. We excluded patients in whom an intraoperative circulatory arrest was part of the surgical procedure because of their exceptional hemodynamic and hemostatic state. Furthermore, Jehovah's Witnesses were excluded as they may be treated with different surgical and anesthesiologic strategies.

Postoperative outcomes

As a result of numerous previous articles reporting contradictory results about the effect of platelet transfusion in cardiac surgery patients, the aim of our study was to obtain an overall picture of all potential consequences for a clinician who is considering an early platelet transfusion for a cardiac surgery patient. So before initiation of the analysis of this study we defined the outcomes we were interested in (based on previous literature and clinical knowledge). Our objective was to study not only the intended effects of an early platelet transfusion (preventing / treating bleeding complications), but also the possible adverse events associated with a platelet transfusion. We aimed at analysing all relevant factors, so both the potential beneficial effects, and the potential undesired effects. We planned to study the following postoperative outcomes: amount of blood loss within 12 hours; early re-exploration for bleeding and/or tamponade; late intervention for tamponade; stroke; myocardial infarction (MI); infections; systemic inflammatory response syndrome; shock; acute kidney injury; multi organ failure; in-hospital mortality; composite endpoint (consisting of MI, stroke, acute kidney injury and in-hospital mortality). Definitions of postoperative MI, acute kidney failure, stroke were described previously.[21] Infection was categorized as pneumonia, mediastinitis, sepsis and others infections with the diagnoses requiring organisms isolated from culture(s) in combina-

tion with elevated temperature and leukocyte counts. Systemic inflammatory response syndrome was diagnosed if two or more of the following criteria were present: temperature > 38 or < 36 degree Celsius; tachypnea (> 20/minute) or hypocapnea (pCO_2 < 4,4 kPa / 32 mmHg); tachycardia (> 90 bpm) or need of mechanical ventilation and leukocyte count > 12 or < 4 * 10^9/l. Multi organ failure was defined as simultaneous or sequential dysfunction or failure of two or more organ systems. Shock was defined as a syndrome in which the effective capillary and tissue perfusion declined to a level detrimental to cellular metabolism. Also we compared duration of postoperative mechanical ventilation and intensive care unit (ICU) stay (both in hours); requirement of postoperative inotropic or vasoactive drugs and erythrocyte, FFP and platelet transfusions in the ICU. Amount of blood loss, duration of mechanical ventilation and ICU stay were analysed as being high or low, with the median as the cut-off point.

Statistical analysis

The continuous baseline variables were summarized by medians and interquartile ranges and the categorical variables were summarized by frequencies and percentages. The propensity score was generated with logistic regression and the variables, where the propensity score was based on, were chosen based on previous knowledge of the subject, as suggested in previous articles.[27-29] The following preoperative variables were included in the propensity score: age, gender, year of surgical procedure (per calendar year), previous cardiac surgery, history of MI, acetylicsalicylic acid or clopidogrel use, (continued up to surgery, stopped preoperatively, or never used), known vascular disease, chronic obstructive pulmonary disease, diabetes, atrial fibrillation, angina pectoris, active endocarditis, hemoglobin level, international normalized ratio, acute or chronic renal failure, left ventricular ejection fraction, immunosuppressant drug use, type of surgery, nonelective surgery, cardiopulmonary resuscitation within 24 h before surgery, respiratory insufficiency, off-pump surgery, CPB duration, and European System for Cardiac Operative Risk Evaluation (EuroScore). It was not in all years part of the standard care to determine fibrinogen level and platelet function before surgery and/or transfusion, so these measures were not available for analysis. Missing variables were imputed using single imputation strategies. For the propensity score matching, we used the "psmatch2" function in Stata Statistical Software (Release 14; StataCorp LP, USA), nearest neighbor 1:3 matching with replacement. Only controls with a propensity score within 0.01 distance (caliper) of the propensity score of the case were selected.29 To assess the balance in measured baseline characteristics after propensity score matching between treated and untreated patients, the standardized mean differences were determined. The matching procedure was optimized based on observed balance in baseline variables before examination of the outcome results. Comparisons of outcomes were made between the intervention and reference groups with regard to odds ratios with 95% CIs derived from multiple univariate logistic regression analyses. Given the fact

that 1:3 matching with replacement was applied, the clustered pattern of the data was taken into account in the estimation procedure by using a robust (sandwich) estimator in the logistic regressions, specifying the patient identifying number. Additionally, we performed two sensitivity analyses. First, we corrected the logistic models for baseline characteristics that remained unbalanced after the matching procedure. Second, we corrected the logistic regressions for a baseline characteristic with a standardized difference below 10% because of its high clinical relevance. No adjustments were made for testing multiple outcomes.

Results

Patient characteristics

The database comprised 23,860 patients in total, of whom 17,918 remained after application of the exclusion criteria (figure 1). Several of the relevant baseline characteristics of the 171 patients who received an early platelet transfusion were evidently different from the ones of the 17,747 patients who received no early transfusions (shown on the left side of table 1). By propensity score matching the patients were selected from the 17,747 patients who received no early transfusion and were most comparable with the patients who received an early platelet transfusion. Of the 171 patients who received one early platelet transfusion, 169 patients had propensity scores overlapping with the propensity scores of the patients who received no early transfusions (*i.e.* had the same "baseline risk" of receiving a platelet transfusion). So these 169 patients were suitable for propensity score matching and thereby formed the intervention group. The reference group, which was formed after 1:3 propensity score matching, consisted of 507 patients (who had not received any blood product in the operating room). Considering the fact that matching with replacement was

used control patients could be used multiple times: 444 controls were used once, 24 controls were used twice, and 5 were used three times, summing up to 473 unique controls out of 507 controls in total.

The majority of patients were men (81%), the median age was 67 years and about half the patients (49%) had a history of myocardial infarction. Most patients underwent isolated coronary artery bypass graft (CABG) (69%) and almost one quarter (23%) of all procedures was a nonelective procedure. As expected, the balance of multiple clinically important variables improved after propensity score matching. Among others the balance of gender, year of surgery, history of MI, clopidogrel use, type of surgery, EuroSCORE, nonelective surgery, CPR within 24 h before surgery and CPB time improved remarkably (shown on the right side of table 1). Standardized differences for

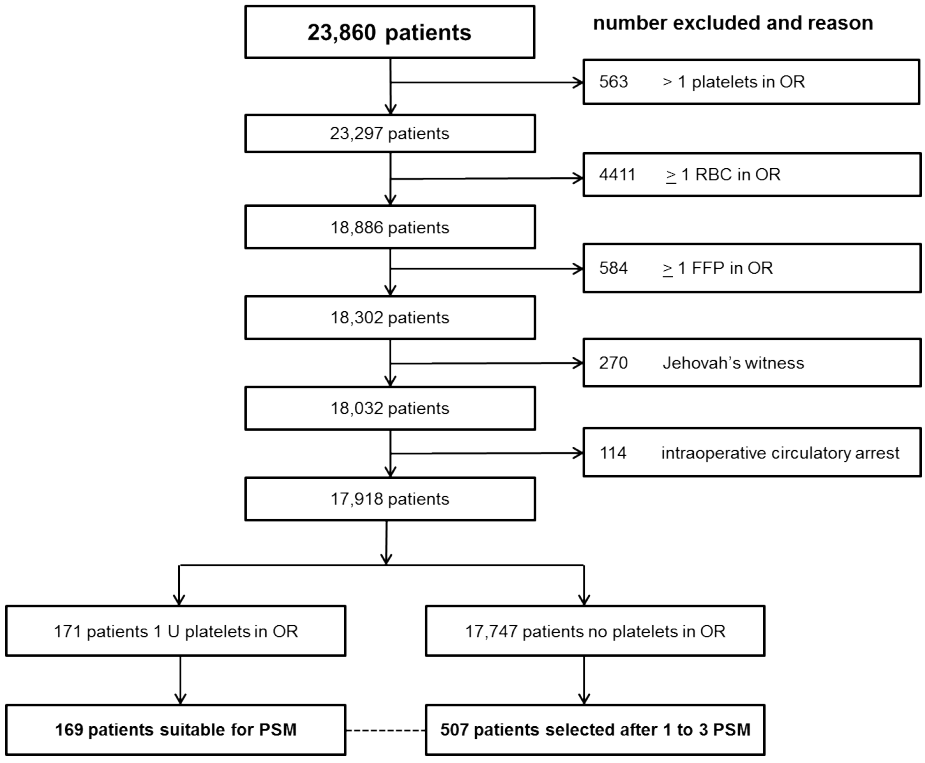

Figure 1 Flow chart of selection of the intervention and reference group

FFP fresh frozen plasma
OR operating room
PSM propensity score matching
RBC red blood cell

the baseline characteristics are reported for the unmatched and matched groups. Two of the measured covariates, "cellsaver blood returned or not" and "nadir intraoperative hemoglobin," had standardized differences that slightly exceeded 10%, indicative of imbalance in these covariates between matched-treated and untreated patients. The second sensitivity analysis was corrected not only for variables with standardized differences above 10%, but also for a variable with better balance, but with high clinical relevance, namely, the EuroSCORE.

Early platelet transfusion and outcomes

Patients in the intervention group less often experienced blood loss higher than 500 ml than patients in the reference group (odds ratio, 0.66; 95% CI, 0.46 to 0.94). However, the number of early re-explorations for bleeding and / or tamponade and number of late interventions for tamponade of patients in the intervention group did not significantly

Table 1 Patient characteristics before and after propensity score matching

	Before propensity score matching			After propensity score matching		
	1 early platelet transfusion n=171	no early transfusion n=17,747	SMD (%)	Intervention group n=169	Reference group n=507	SMD (%)
Preoperative variables						
Female sex*	33 (19.3)	4107 (23.1)	9.4	32 (18.9)	97 (19.1)	0.5
Age (year)*	67 (61-74)	66 (59-73)	0.5	67 (60-73)	67 (58-73)	4.3
Weight (kg)	81 (75-90)	80 (72-90)	10.2	81 (75-90)	80 (73-90)	9.9
Year of surgery*	2003 (1998-2008)	2004 (2001-2009)	26.5	2003 (1998-2008)	2003 (1999-2007)	2.5
Previous cardiac surgery*	21 (12.3)	1290 (7.3)	16.9	21 (12.4)	56 (13.2)	2.7
History of MI*	83 (48.5)	6441 (36.3)	24.9	81 (47.9)	253 (49.9)	4.0
Affected coronary arteries*	3 (1-3)	3 (1-3)	7.9	3 (1-3)	3 (1-3)	4.3
LV hypertrophy*	50 (29.2)	3623 (20.4)	20.5	50 (29.6)	166 (32.7)	7.3
LMCA occluded >50%	30 (17.5)	2661 (15.0)	6.9	29 (17.2)	95 (18.7)	4.3
Acetylsalicylic acid use*						
• Continued up to surgery	21 (12.3)	1133 (6.4)	20.3	20 (11.8)	60 (11.8)	0.0
• Stopped before surgery	81 (47.4)	9181 (51.7)	8.7	81 (47.9)	253 (49.9)	3.9
• Never	69 (40.4)	7433 (41.9)	3.1	68 (40.2)	194 (38.3)	4.0
Clopidogrel use*						
• Continued up to surgery	20 (11.7)	362 (2.0)	38.8	19 (11.2)	59 (11.6)	1.6
• Stopped before surgery	32 (18.7)	1974 (11.1)	21.4	31 (18.3)	101 (19.9)	4.4
• Never	119 (69.6)	15411 (86.8)	42.6	119 (70.4)	347 (68.4)	4.9
Hypertension	85 (49.7)	9443 (53.2)	7.0	84 (49.7)	251 (49.5)	0.4
Hypercholesteremia	105 (61.4)	11583 (65.3)	8.0	105 (62.1)	325 (64.1)	4.1
Smoking	29 (17.0)	3560 (20.1)	8.0	28 (16.6)	98 (19.3)	7.1
Vascular disease*	26 (15.2)	2558 (14.4)	2.2	25 (14.8)	76 (15.0)	0.6
COPD*	21 (12.3)	2485 (14.0)	5.1	20 (11.8)	53 (10.5)	4.1
Diabetes mellitus*						
Diabetes mellitus I	3 (1.8)	545 (3.1)	8.6	3 (1.8)	7 (1.4)	2.6
Diabetes mellitus II	23 (13.5)	2617 (14.7)	3.7	23 (13.6)	70 (13.8)	0.6
Atrial fibrillation*	20 (11.7)	2404 (13.5)	5.6	20 (11.8)	54 (10.7)	3.6
Endocarditis*	3 (1.8)	84 (0.5)	12.2	3 (1.8)	9 (1.8)	0.0
Hemoglobin (g/dL)*	14.0 (13.2-15.0)	14.2 (13.2-15.0)	9.0	14.0 (13.2-15.0)	14.2 (13.0-15.0)	0.7
APTT (s)	34 (28-40)	32 (28-38)	23.5	34 (28-40)	33 (28-40)	4.0
INR*						
• < 1.5	122 (71.3)	13620 (76.7)	12.3	122 (72.2)	356 (70.2)	4.5
• 1.5 – 2.5	38 (22.2)	3472 (19.6)	6.5	37 (21.9)	120 (23.7)	4.4
• > 2.5	11 (6.4)	655 (3.7)	12.5	10 (5.9)	31 (6.1)	0.9
Creatinine (µmol/L)	88 (76-101)	86 (75-99)	7.2	88 (76-101)	88 (77-103)	1.8
Chronic renal failure *	2 (1.2)	218 (1.2)	0.5	2 (1.2)	2 (0.4)	7.2
Acute renal failure*	4 (2.3)	130 (0.7)	13.1	4 (2.4)	12 (2.4)	0.0

Table 1 continued

	Before propensity score matching			After propensity score matching		
	1 early platelet transfusion n=171	**no early transfusion n=17,747**	**SMD (%)**	**Intervention group n=169**	**Reference group n=507**	**SMD (%)**
LV ejection fraction*						
• >50%	110 (64.3)	13386 (75.4)	24.3	108 (63.9)	344 (67.9)	8.6
• 25-50%	42 (24.6)	2813 (15.9)	21.7	42 (24.9)	107 (21.1)	9.4
• < 25%	19 (11.1)	1548 (8.7)	8.0	19 (11.2)	56 (11.1)	0.7
Immunosuppressive drugs*	8 (4.7)	604 (3.4)	6.5	7 (4.1)	25 (4.9)	4.0
Tricuspid valve pathology	6 (3.5)	476 (2.7)	4.8	6 (3.6)	16 (3.2)	2.3
Mitral valve pathology	33 (19.3)	2449 (13.8)	14.8	32 (18.9)	88 (17.4)	4.3
Aortic valve pathology	42 (24.6)	3885 (21.9)	6.3	42 (24.9)	115 (22.7)	5.1
Type of surgery*						
• Isolated CABG	115 (67.3)	12532 (70.6)	7.3	114 (67.5)	351 (69.2)	3.8
• Other than isolated CABG	56 (32.7)	5215 (29.4)	7.3	55 (32.5)	156 (30.8)	3.8
EuroSCORE I*	6 (3-9)	4 (2-7)	50.5	6 (3-9)	6 (3-9)	6.7
NYHA class IV*	35 (20.5)	2871 (16.2)	11.1	34 (20.1)	88 (17.4)	7.1
Non-elective surgery*	42 (24.6)	1089 (6.1)	52.8	41 (24.3)	114 (22.5)	5.1
CPR in 24 h before surgery*	6 (3.5)	128 (0.7)	19.4	6 (3.6)	16 (3.2)	2.7
Intra-operative variables						
Surgical procedure time (min)	251 (208-310)	233 (196-275)	30.0	251 (208-307)	255 (210-300)	4.4
Aortic occlusion time (min)	69 (47-95)	61 (44-80)	37.0	69 (48-95)	68 (53-90)	0.2
CPB use*	163 (95.3)	15653 (88.2)	26.1	161 (95.3)	488 (96.3)	3.6
CPB time (min)*	106 (78-149)	91 (69-116)	48.8	106 (78-148)	104 (83-136)	3.5
Cellsaver blood given, yes/no	64 (37.4)	6203 (35.0)	5.1	64 (37.9)	166 (32.7)	10.7
Nadir hemoglobin (g/dL)	8.6 (7.7-9.5)	8.7 (7.9-9.7)	11.1	8.6 (7.8-9.5)	8.7 (7.6-9.5)	10.5

* Marks variables that were used to calculate the propensity score.
Continuous variables are reported as median with interquartile range and categorical variables are reported as counts with percentages. Standardized differences are reported in % for assessing balance.
CABG coronary artery bypass graft
CPB cardiopulmonary bypass
CPR cardiopulmonary resuscitation
LMCA left main coronary artery
LV left ventricle
MI myocardial infarction
NYHA New York Heart Association
SMD standardized mean difference

differ from that of patients in the reference group (table 2). Patients in the intervention group did not endure more stroke, MI, infection, systemic inflammatory response syndrome, shock, acute kidney injury, multiorgan failure, death or composite endpoint than patients in the reference group (table 3). An early platelet transfusion was significantly associated with the need for postoperative vasoactive medication (odds ratio 1.65, 95% confidence interval (CI) 1.05 to 2.58); long (above median) mechanical ventilation (odds

Table 2 Postoperative bleeding related outcomes

	Intervention group n=169	Reference group n=507	odds ratio (95%CI)	p-value
Blood loss >500 mL first 12 h	79 (46.7)	290 (57.2)	0.66 (0.46;0.94)	0.021
Early re-exploration for bleeding and/or tamponade	4 (2.4)	23 (4.5)	0.51 (0.17;1.52)	0.227
Late intervention for tamponade	4 (2.4)	6 (1.2)	2.02 (0.52;7.89)	0.309

The absolute numbers and percentages of patients in the intervention and the reference group are given, the regression derived odds ratios with 95% confidence interval and exact p-values.

CI confidence interval

ratio 1.47, 95% CI 1.03 to 2.11) and long (above median) ICU stay (odds ratio 1.49, 95% CI 1.04 to 2.12). Also, patients in the intervention group required erythrocyte (44.4 versus 33.9%), FFP (17.2 versus 7.3%) and platelet transfusion in the ICU (42.6 versus 4.3%) more often as compared to patients in the reference group (table 3).

Discussion

Main findings

In this study, no statistically significant difference was observed with regard to reinterventions for bleeding, stroke, MI, infections, systemic inflammatory response syndrome, shock, acute kidney injury, multiorgan failure, death, or composite endpoint between patients who received a single early platelet concentrate and those who did not. However, patients in the intervention group experienced less blood loss and required postoperative vasoactive medication, long mechanical ventilation, long ICU stay, erythrocyte, FFP, and platelet transfusion in the ICU more often as compared to patients in the reference group.

Interpretation

The observed correlations between early platelet transfusion and less blood loss; longer postoperative mechanical ventilation; longer intensive care stay; and higher rate of administration of vasoactive drugs in the ICU might be explained by a causal effect of the platelet transfusion. For example, the fact that patients in the intervention group experienced less blood loss postoperatively could be due to the perioperative platelet transfusion. In the case of the vasoactive drugs, it may be possible that in the intervention group, more patients suffered from vasoplegia and therefore required vasoactive support more often compared to those in the reference group.. Vasoplegia as the indication, and thus possible causal explanation, of the higher risk of vasoactive

Table 3 Postoperative adverse outcomes

	Intervention group n=169	Reference group n=507	odds ratio (95%CI)	p-value
Stroke*	5 (3.0)	16 (3.2)	0.94 (0.32;2.71)	0.902
Myocardial infarction*	25 (14.8)	57 (11.2)	1.37 (0.82;2.28)	0.226
Patients with postoperative infection	35 (20.7)	88 (17.4)	1.24 (0.79;1.94)	0.340
• Mediastinitis	2 (1.2)	1 (0.2)	6.06 (0.54;67.4)	0.143
• Superficial wound infection	1 (0.6)	2 (0.4)	1.50 (0.14;16.7)	0.740
• Pneumonia	4 (2.4)	13 (2.6)	0.92 (0.30;2.87)	0.887
• Sepsis	11 (6.5)	23 (4.5)	1.47 (0.70;3.08)	0.313
• Other infections	27 (16.0)	62 (12.2)	1.36 (0.82;2.27)	0.230
SIRS	13 (7.7)	25 (4.9)	1.61 (0.79;3.25)	0.187
Shock	28 (16.6)	67 (13.2)	1.30 (0.79;2.14)	0.296
CVVH de novo*	9 (5.3)	19 (3.7)	1.44 (0.63;3.30)	0.383
Multi organ failure	7 (4.1)	16 (3.2)	1.33 (0.53;3.34)	0.549
In hospital mortality*	7 (4.1)	13 (2.6)	1.64 (0.64;4.19)	0.300
Composite endpoint	34 (20.1)	89 (17.6)	1.18 (0.76;1.85)	0.462
Ventilation >11h	92 (54.4)	227 (44.8)	1.47 (1.03;2.11)	0.034
ICU length of stay >26h	95 (56.2)	235 (46.4)	1.49 (1.04;2.12)	0.030
Vasoactive drugs	139 (82.2)	374 (73.8)	1.65 (1.05;2.58)	0.029
RBC transfusion in ICU	75 (44.4)	172 (33.9)	1.55 (1.08;2.23)	0.017
FFP transfusion in ICU	29 (17.2)	37 (7.3)	2.63 (1.50;4.63)	0.001
Platelet transfusion in ICU	72 (42.6)	22 (4.3)	16.4 (9.3;28.9)	<0.001

* Marks endpoints that make up the composite endpoint

The absolute numbers and percentages of patients in the intervention and the reference group are given, the regression derived odds ratios with 95% confidence interval and exact p-values.

CI confidence interval
CVVH continuous veno-venous hemofiltration
FFP fresh frozen plasma
ICU intensive care unit
RBC red blood cell
SIRS systemic inflammatory response syndrome

medication would be in agreement with previous findings of others. First of all it would be consistent with the finding that patients undergoing cardiac surgery with the use of CPB commonly encounter vasoplegia for which pharmacologic support, in the form of vasoactive drugs, is needed.[30,31] More importantly, it would be in agreement with the correlation, demonstrated by others, between platelet transfusion and an increased risk of vasoplegia after cardiac surgery.[16] In our data, the diagnoses shock, SIRS and sepsis, were equally distributed among the groups, and are therefore not a plausible explanation for the difference in vasoactive drug need. This presumed higher rate of vasoplegia

may further explain our finding that intraoperative platelet transfusions are associated with longer mechanical ventilation and intensive care stay.

However, although propensity score matching resulted in comparable baseline characteristics of both groups, it is also possible that the observed association is due to residual confounding, which is not visible in the measured baseline characteristics. Moreover, most of the observed associations are not strong so they might also be explained by random chance and then it would be incorrect to reject the null hypothesis (type I error). We did not adjust the *P* values in tables 2 and 3 for multiple testing, although we analysed multiple endpoints. If Bonferroni correction had been used, the associations between an early platelet transfusion and amount of blood loss; postoperative mechanical ventilation; intensive care stay; vasoactive drugs; and erythrocyte administration in the ICU would no longer be considered statistically significant. However, the associations between an early platelet transfusion and postoperative plasma and platelet transfusions in the ICU would remain statistically significant after Bonferroni correction. With considering the results of a Bonferroni correction, we reduce the chance on making type I errors, but risk missing subtle associations with potential clinical importance.

In our study, an early platelet transfusion did not seem to reduce the need for reinterventions for bleeding or tamponade, but was associated with a lower blood loss and a higher rate of erythrocyte, plasma, and platelet transfusions in the ICU. The fact that no statistically significant association was observed between an early platelet transfusion and early reexploration for bleeding and/or tamponade and late intervention for tamponade, might be explained by a lack of statistical power. A possible explanation for the higher rate of postoperative transfusions is that once one transfusion has been administered, the threshold for subsequent transfusions is lowered. Theoretically, a difference in preferences and convictions of treating physicians regarding transfusions, resulting in comparable patients receiving different treatment, could explain the higher transfusion rate in the ICU. However, in practice physicians who made the decision to transfuse platelets in the operating room were generally not responsible for the treatment in the ICU. Finally, in addition to all the above-mentioned considerations, it may also be the case that one postoperative endpoint influenced another postoperative endpoint, but this could not be verified in this database. For example, besides the early platelet transfusion, the plasma and platelet transfusions given in the ICU may also have contributed to the lower blood loss in the intervention group.

Comparison with previous studies

Several other studies have analysed the association between platelet transfusions and morbidity and mortality in cardiac surgery with varying findings. Our results are in contrast with the studies that report that transfusion of platelets increases the risk

of serious adverse outcomes.[17,20,21,32] There are various possible explanations for the discrepancy between the findings of these studies and our results. First, not in all studies appropriate and sufficient adjustment of potential confounding factors, like use of aprotinin or concomitant erythrocyte and plasma transfusions, was applied. Second, in contrast to these four studies, we aimed at analysing patients who only received one platelet unit and no other blood product shortly after end of CPB while still in the operating room. We focused on these patients because the indication for the platelet transfusion can be debatable and these patients are most comparable to patients who received no transfusion. Third, a considerable part of the platelet units examined in these studies was not leukocyte-reduced, and the vast majority of the units we studied were leukocyte-reduced.

Our results are consistent with several studies that showed no correlation between platelet transfusion and adverse outcomes like infection, low cardiac output syndrome, MI, stroke, renal failure, sepsis, and mortality.[15,18,33] One study ascertained an association between perioperative platelet transfusion and an increased risk of surgical reexploration for bleeding, which we did not observe. However the remaining results of this study, regarding postoperative mortality, composite endpoint, infectious, cardiac, renal, pulmonary and neurologic complications, were similar to ours.[19]

Strengths and limitations

To the best of our knowledge, this study is the first to analyze the effect of a single platelet transfusion in a broader cardiac surgery population, consisting both of patients who underwent coronary artery bypass graft and those undergoing (concomitant) valve procedures. Besides we report not only on adverse outcomes but also the intended effect of the transfusion, which is to prevent and/or stop

excessive bleeding. Hereby, we aimed at obtaining the overall picture of all potential consequences for a clinician who is considering a platelet transfusion for a cardiac surgery patient. A potential concern of our study is the 16-yr period that was studied because multiple developments occurred both in blood banking and in cardiac surgery and anesthesiology in this period. However, by including year of surgery in the propensity score, we strongly reduced the potential confounding impact of the developments. Furthermore, to the extent of our knowledge, we are the first to study patients who received just a single early platelet transfusion in the absence of concomitant transfusion of other blood products, which precludes potential influence of erythrocyte or FFP transfusions on the outcomes. Another strength of our study is that we adjusted for confounding by indication by propensity score matching. By using propensity score matching, we were able to identify the patients, out of the 17,747 selected patients, who received no early transfusion who were most comparable to the patients transfused

with a single early platelet concentrate. A limitation of our study is that despite accurate propensity score matching, residual confounding, by unknown confounders, cannot be completely ruled out. The large comprehensive cohort of 23,860 patients allowed the analysis of sufficient patients numbers after strict selection of the specific population of interest. Although for some endpoints, the 95% CI was relatively wide, which may be partially caused by a lack of power. Since the database was extensive and detailed, it was possible to include the factors that were considered relevant in the propensity score. Furthermore, since the data had been collected before and therefore independently of the current study, information and selection bias are minimum.

In this study, cardiac surgery patients receiving platelet transfusion in the operating room experienced less blood loss and required vasoactive medication, prolonged ventilation, prolonged intensive care and blood products more often postoperatively. However, our findings further show that an early platelet transfusion was not associated with other serious adverse outcomes like thromboembolic complications, infections, organ failure, in-hospital mortality, and reinterventions for bleeding.

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