Use of blood products and risk of stroke after coronary artery bypass surgery

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Background. The impact of blood transfusion on the development of post-operative stroke after coronary artery bypass grafting (CABG) is not well established. We, therefore, investigated this issue.

Materials and methods. Complete data on peri-operative blood transfusion were available for 2,226 patients who underwent CABG in three Finnish hospitals.

Results. Stroke occurred post-operatively in 53 patients (2.4%). Logistic regression showed that pre-operative creatinine (OR 1.003, 95% CI 1.000-1.006), extracardiac arteriopathy (OR 2.344, 95% CI 1.133-4.847), pre-operative atrial fibrillation (OR 2.409, 95% CI 1.149-5.052), and the number of packed red blood cell units transfused (OR 1.121, 95% CI 1.065-1.180) were significantly associated with post-operative stroke. When the various blood product transfusions instead of transfused units were included in the multivariable analysis, solvent/detergent treated plasma (Octaplas®) transfusion (OR 2.149, 95% CI 1.141-4.047), but not red blood cell transfusion, was significantly associated with postoperative stroke. Use of blood products ranging from no transfusion (stroke rate 1.6%) to combined transfusion of red blood cells, platelets and Octaplas® was associated with a significant increase in post-operative stroke incidence (6.6%, adjusted analysis: OR 1.727, 95% 1.350-2.209). Patients who received >2 units of red blood cells, >4 units of Octaplas® units and >8 units of platelets had the highest stroke rate of 21%. CART analysis showed that increasing amount of transfused Octaplas®, platelets and history of extracardiac arteriopathy were significantly associated with post-operative stroke.

Conclusions. Transfusion of blood products after CABG has a strong, dose-dependent association with the risk of stroke. The use of Octaplas® and platelet transfusions seem to have an even larger impact on the development of stroke than red blood cell transfusions.

Keywords: Coronary artery bypass surgery, stroke, blood transfusion, red blood cells.

Introduction

A recent meta-analysis of the impact of re-exploration for excessive bleeding after cardiac surgery in adults showed a significantly increased risk of post-operative stroke which was consistent among the studies included[1]. We hypothesised that this negative prognostic effect of re-exploration for bleeding may be mediated by the use of blood products during the early post-operative period. There is some evidence that intra-operative anaemia is a determinant of post-operative stroke[2,3], although whether this is due to anaemia-induced brain ischaemia or a possible prothrombotic status induced by blood transfusion is unclear. We investigated this issue in a consecutive series of patients who underwent coronary artery bypass grafting (CABG) in three Finnish hospitals.

Material and methods

This study is part of a wider protocol in progress to assess thrombotic and bleeding complications of cardiac procedures in western Finland[4-6]. The present study is based on a consecutive series of patients who underwent CABG between January 2008 and December 2010 at the Oulu University Hospital,

Turku University Hospital and Vaasa Central Hospital, Finland. During the study period, 2,234 consecutive patients underwent CABG in these hospitals. Complete data on the peri-operative use of blood products such as red blood cells, platelets and solvent/detergent treated plasma (Octaplas®, Octapharma AG, Lachen, Switzerland) were available for 2,226 patients who are the subjects of the present analysis. The patients' characteristics are summarised in Table I.

Baseline and operative data were obtained from local institutional clinical registries in which information is prospectively collected in computerised databases. Furthermore, the full medical records of the eligible patients were reviewed in order to determine the peri-operative antithrombotic strategies and the incidence of major operative complications.

Table I - Baseline characteristics and operative data for 2,226 patients who underwent coronary artery bypass surgery. Results of univariable and multivariable analyses for prediction of post-operative stroke are reported.

	N. of patients	Univariable analysis p-value	Multivariable analysis OR, 95% CI
Age (years)*	67.1±9.2	0.047	
Females	476 (21.4)	0.31	
Haemoglobin (g/L)	137±16	0.98	
Creatinine (μmol/L)*	90±52	<0.0001	1.003, 1.000-1.006
INR	1.1±0.7	0.88	
Dialysis	17 (0.8)	0.060	
Pulmonary disease	213 (9.6)	0.48	
Diabetes	594 (26.6)	0.88	
Hypertension	1,557 (69.9)	0.65	
Atrial fibrillation*	187 (8.4)	0.011	2.409, 1.149-5.052
Transient ischaemic attack	67 (3.0)	0.67	
Stroke	92 (4.1)	1.00	
Neurological dysfunction	38 (1.7)	0.060	
Extracardiac arteriopathy*	201 (9.0)	0.011	2.342, 1.133-4.844
Previous PCI	288 (12.9)	0.15	
Previous cardiac surgery	52 (2.3)	0.63	
Pre-operative clopidogrel*	613 (27.5)	0.030	
Pre-operative aspirin	2,109 (94.7)	0.73	
Pre-operative warfarin	169 (7.6)	0.10	
Recent myocardial infarction	831 (37.3)	0.13	
Left ventricular ejection fraction*		0.037	
>50%	1,651 (74.2)	0.037	
30-50%	449 (20.2)		
<30	100 (4.5)		
Systemic pulmonary pressure >60 mmHg	35 (1.6)	0.20	
Unstable angina*	329 (14.8)	0.010	
Critical pre-operative status	130 (5.8)	0.55	
Emergency surgery	201 (9.0)	0.28	
Epi-aortic ultrasound	850 (38.2)	0.64	
Diseased ascending aorta	111 (5.0)	0.73	
Off-pump coronary surgery	804 (36.1)	0.80	
Intra-operative use of tranexamic acid	1,641 (73.7)	0.98	
N. of distal anastomoses	3.5±1.1	0.53	
Logistic EuroSCORE (%)	5.6±8.4	0.003	

Legend: Continuous variables are reported as mean and standard deviation or counts (%); INR: International Normalised Ratio; PCI: percutaneous coronary intervention; *: variable included in the logistic regression model.

Operative risk was assessed by the EuroSCORE risk scoring method[7].

Peri-operative antithrombotic treatment

Aspirin 100 mg p.o. was discontinued pre-operatively in most of the patients undergoing elective surgery and administered until the day of surgery in patients with acute coronary syndrome.

Heparin (2.5-4.0 mg/kg) was administered intravenously after sternotomy to maintain an activated clotting time of more than 400 seconds and it was neutralised at the end of the procedure by protamine sulphate (1.5-3.0 mg/kg). Further protamine was given in the case of bleeding during closure of the chest or within the first hour after surgery according to the activated coagulation time. Aprotinin was not used in any of these patients. Tranexamic acid was administered intra-operatively at the discretion of the anaesthetist. Octaplas® as well as platelets were transfused according to the amount of bleeding, International Normalised Ratio (INR) levels and platelet counts. Enoxaparin (40-80 mg once daily) was started in all patients on the evening of the day of surgery. Warfarin was started in the case of persistent atrial fibrillation. Clopidogrel was used post-operatively in these patients only in the case of allergy to aspirin or recent percutaneus coronary intervention.

Surgical techniques

Intermittent antegrade and retrograde cold blood cardioplegia was used during conventional CABG. Proximal anastomoses were sutured to the ascending aorta during cross clamping, when the latter was considered safe. Epi-aortic ultrasound was performed according to the surgeon's preference. The ascending aorta was left untouched in the case of grade III diseased aorta[8]. An Octopus® stabiliser, intracoronary shunts and, in some instances, a Starfish® stabiliser (Medtronic, Minneapolis, MN, USA) were used in patients who underwent off-pump coronary surgery.

Outcome end-points

The primary outcome end-point of this study was stroke. Secondary outcome end-points were in-hospital death, new onset renal failure requiring dialysis, re-exploration for excessive bleeding, use of blood products and duration of stay in the intensive care unit.

Stroke was defined as a new neurological deficit following surgery lasting >24 hours accompanied by new structural changes detected by computed tomography or magnetic resonance imaging. In the case of absence of structural changes at imaging, the diagnosis of stroke was made clinically by a neurologist. Renal failure was defined as a post-operative renal failure requiring temporary or prolonged dialysis. Low cardiac output syndrome was defined as a post-operative cardiac index <2.0 L/min/m^2. A composite outcome end-point included in-hospital death, low cardiac output syndrome, *de novo* dialysis, stroke, re-exploration for excessive bleeding, or intensive care unit stay ≥5 days. The outcome events were collected from the period of the index hospitalisation.

Ethical considerations

The study protocol was approved by the Institutional Review Boards of Turku and Oulu University Hospitals. This study was not financially supported.

Statistical analysis

Data were analysed with the use of PASW version 18 statistical software (IBM SPSS Inc., Chicago, IL, USA). Continuous variables are reported as the mean ± standard deviation. Pearson's chi-square test, Fisher's exact test and Mann-Whitney's test were used for univariate analysis. Correlations between continuous variables were assessed by Spearman's test. Logistic regression with the help of backward selection was used for multivariate analysis. Only variables with a $p<0.050$ at univariate analysis were included in the logistic regression model.

We estimated the prognostic impact of blood transfusion by defining *a priori* classes of increasing amount of transfused blood products according to the type of blood product (red blood cells units: 0, 1-2 units, or >2 units; platelet units: 0, 1-8 units, or >8 units; Octaplas® units: 0, 1-4 units, or >4 units). The sum of these classes was used to estimate the overall amount of blood products and to identify those patients who received large amount of blood products, i.e. red blood cells >2 units, Octaplas® >4 units and platelets >8 units. This was done assuming that only patients who received >2 units of red blood cells, >4 units of Octaplas® and/or >8 units of platelets were

those at higher risk of transfusion-related adverse events. These cut-off values were later on confirmed by classification and regression tree analysis (CART).

CART analysis was performed to identify independent risk factors for post-operative stroke. Validation of the classification tree procedure was assessed by cross-validation through 25 folds. The minimum number of patients for the parent node was set at 30 and the minimum for the child node was 1. The maximum classification tree depth was 5. Gini's method was used to measure impurity, which is the extent to which a node does not represent a homogenous subset of cases. A minimum change in improvement was set at 0.0001. Receiver operating characteristic (ROC) curve analysis was used to estimate the area under the curve of probabilities values estimated by the CART analysis model outcome.

We observed that patients who received all three types of blood products had a significantly higher risk of stroke compared to those who did not receive any blood transfusion. These two groups differed markedly with respect to pre-operative co-variables; such differences between the study groups, i.e. patients who did not receive any blood product and those who received red blood cells, Octaplas® and platelet transfusion, were accounted for by developing a propensity score for the treatment method. Propensity score analysis was used to control for all known patients' factors that might be related to the decision to administer blood products, and thus potentially to the outcome of interest. The propensity score was calculated by logistic regression with backward selection by including clinical variables with a certain difference between the study groups as indicated by $p<0.050$ in univariable analysis. ROC curve analysis was used to estimate the area under the curve of the model, predicting the probability of being included in the study groups The calculated propensity score was employed only for one-to-one matching, because our purpose was to identify two study groups with similar characteristics in order to fulfil the criteria of comparability. One-to-one propensity score matching between study groups was done according to a difference in the logit of propensity score of less than 0.04 between each pair of patients in the study groups. Such a caliper width was equal to 0.2 of the standard deviation of the logit of the herein calculated propensity score[9]. Standardised differences were estimated to compare the means of continuous and binary variables between the study groups. Standardised differences less than 0.1 were taken to indicate a negligible difference in the mean or prevalence of covariates between the study groups[9]. The propensity score was used to adjust transfusion of all three types of blood products in predicting post-operative stroke. A p value <0.050 was considered statistically significant.

Results

Stroke occurred in 53 patients (2.4%). These strokes were regarded of ischaemic origin. Table II summarises other in-hospital post-operative adverse events observed in this series of patients.

Prognostic impact of types of transfused blood products

Since there was a strong correlation between the amount of transfused red blood cell units and transfused platelet units (rho: 0.467, $p<0.0001$) as well as transfused Octaplas® units (rho: 0.423, $p<0.0001$), all these three risk factors were analysed further. The area under the ROC curve for predicting post-operative stroke was 0.653 (95% CI 0.570-0.736) for red blood cell units, 0.627 (95% CI 0.543-0.712) for Octaplas® units and 0.618 (95% CI 0.532-0.703) for platelet units.

Figure 1 summarises the unadjusted rate of post-operative stroke according to increasing amount of red blood cell units (0, 1-2 units, or >2 units), platelets units (0, 1-8 units, or >8 units) and Octaplas® units (0, 1-4 units, or >4 units) transfused ($p<0.0001$ adjusted for pre-operative haemoglobin and post-operative blood loss). When the use of all blood products was summed, a dose-dependent increase of post-operative stroke was observed (when adjusted for pre-operative haemoglobin and post-operative blood loss: OR 1.474, 95% CI 1.262-1.720, $p<0.0001$, Figure 2). Similarly, the increase in the use of blood product types ranging from no transfusion to combined transfusion of red blood cells, platelets and Octaplas® was associated with a significantly increased rate of post-operative stroke (when adjusted for pre-operative haemoglobin and post-operative blood loss: OR 1.727, 95% CI 1.350-2.209, $p<0.0001$, Figure 3).

Table II - Adverse events during the immediate post-operative period after coronary artery bypass surgery. Results of univariable and multivariable analyses for prediction of post-operative stroke are reported.

	N.	Univariable analysis p-value	Multivariable analysis OR, 95% CI
In-hospital mortality	50 (2.2)	-	
Stroke	53 (2.4)	-	
Low cardiac output syndrome	324 (14.6)	0.001	
Post-operative blood loss (mL)	858±590	0.16	
Resternotomy for bleeding	138 (6.2)	0.57	
"Surgical bleeding"	83 (3.7)	0.72	
RBC transfusion	1,134 (50.9)	0.005	
RBC units transfused*	2.0±3.1	<0.0001	1.121, 1.065-1.180
Octaplas® transfusion	486 (21.8)	<0.0001	
Octaplas® units transfused*	0.8±2.0	<0.0001	
Platelet transfusion	458 (20.6)	<0.0001	
Platelet units transfused*	1.8±4.9	<0.0001	
De novo dialysis	41 (1.8)	<0.0001	
Atrial fibrillation*	799 (35.9)	0.043	
ICU stay (days)	2.2±3.1	-	
ICU stay ≥5 days	222 (10.0)	-	
Composite outcome end-point	548 (24.6)	-	

Legend: Continuous variables are reported as mean ± standard deviation or counts (%); RBC: red blood cell; ICU: intensive care unit; Composite end-point: in-hospital death, low cardiac output syndrome, *de novo* dialysis, stroke, repeat sternotomy for excessive bleeding, or intensive care unit stay ≥5days; *: variable included in the logistic regression model.

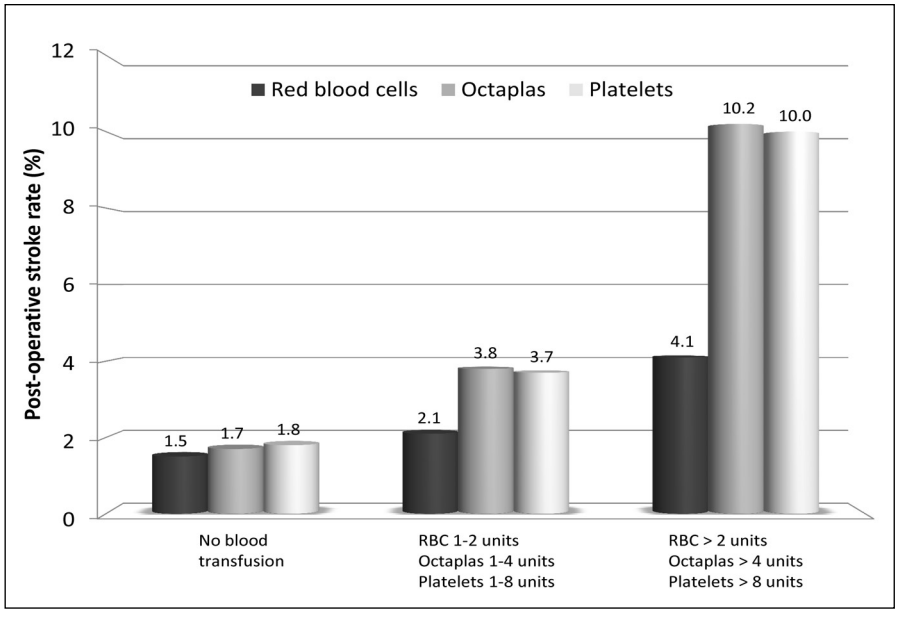

Figure 1 - Post-operative stroke rates according to increasing amount of red blood cell (RBC) units (0=none, 1=1-2 units, 2=>2 units; p=0.002), platelets units (0=none, 1=1-8 units, 2=>8 units; p<0.0001) and Octaplas® units (0=none, 1=1-4 units, 2=>4 units; p<0.0001) transfused.

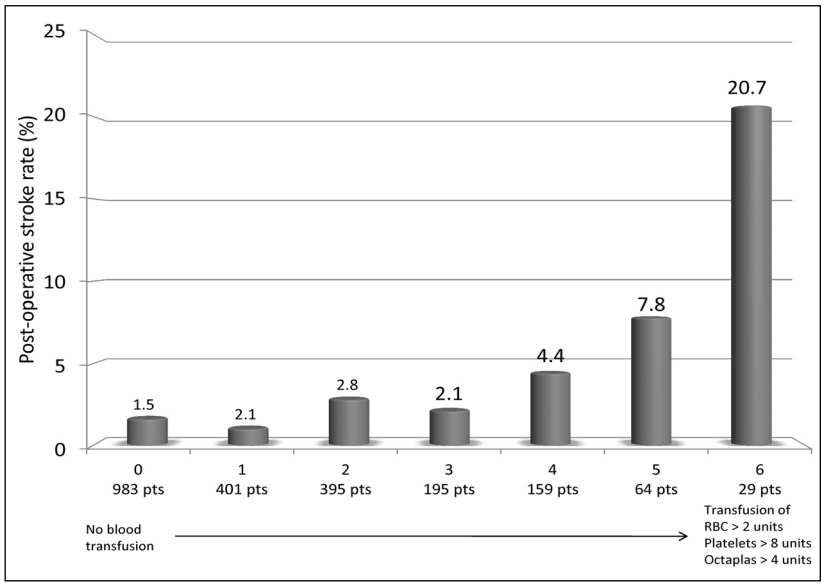

Figure 2 - Post-operative stroke rates according to the sum of increasing amount of red blood cell (RBC) units (0=none, 1=1-2 units, 2=>2 units), platelets units (0=none, 1=1-8 units, 2=>8 units) and Octaplas® units (0=none, 1=1-4 units, 2=>4 units) transfused (p<0.0001).

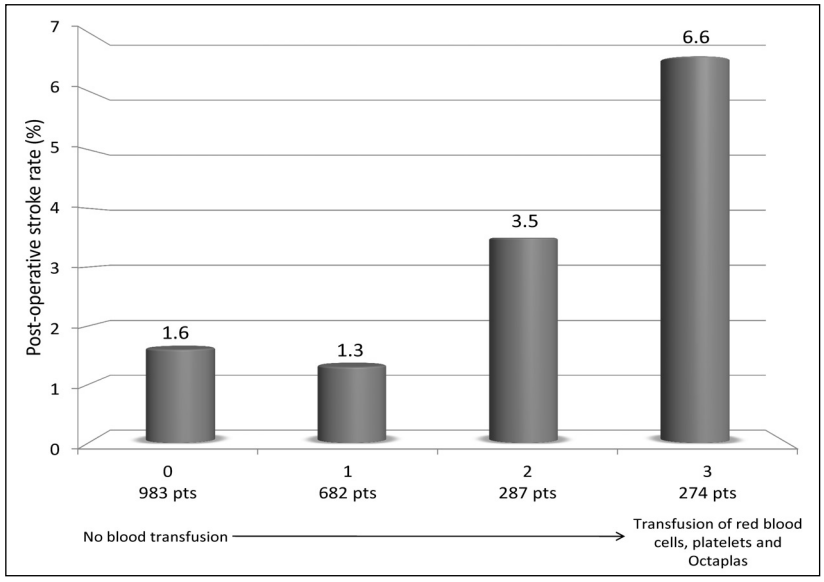

Figure 3 - Post-operative stroke rates according to the sum of any type of transfusion (ranging from 0=no blood transfusion to 3=transfusion of red blood cells, platelets and Octaplas®) (p<0.0001).

Logistic regression

Logistic regression including the risk factors indicated in Tables I and II showed that pre-operative creatinine (p=0.040, OR 1.003, 95% CI 1.000-1.006), extracardiac arteriopathy (p=0.022, OR 2.344, 95% CI 1.133-4.847), pre-operative atrial fibrillation (p=0.020, OR 2.409, 95% CI 1.149-5.052), and the amount of red blood cell units transfused (p<0.0001, OR 1.121, 95% CI 1.065-1.180) (Hosmer-Lemeshow's test: p=0.433) were significantly associated with post-operative stroke. When type of blood product instead of their specific amount was included in the multivariable analysis, Octaplas® transfusion (p=0.018, OR 2.149, 95% CI

1.141-4.047), but not red blood cell transfusion, was significantly associated with post-operative stroke along with pre-operative creatinine, pre-operative atrial fibrillation and extracardiac arteriopathy. Stroke rate was not significantly different between the three hospitals (p-values ranging from 0.186 to 0.820) when the hospitals were in the regression models.

Classification and regression tree analysis

Renal failure, pre-operative atrial fibrillation and extracardiac arteriopathy were included in the CART model along with classes of increasing amount of transfused red blood cells, Octaplas® and platelets. This model showed that increasing amount of transfused Octaplas®, platelets and history of extracardiac arteriopathy were significantly associated with post-operative stroke (area under the ROC curve for this predictive model: 0.631, 95% CI 0.546-0.716) (Figure 4).

Propensity score analysis

The propensity score was calculated to estimate the risk of receiving transfusion of all types of blood products (red blood cells, Octaplas® and platelets). Logistic regression showed that patient's age, pre-operative haemoglobin, pre-operative exposure to clopidogrel, chronic use of warfarin, previous cardiac surgery, recent myocardial infarction, emergency operation, critical operative status, no diabetes and no intra-operative use of tranexamic acid were significantly associated with peri-operative use of all types of blood products (Hosmer-Lemeshow's test p=0.731). The area under the ROC curve for this predictive model was 0.820 (95% CI 0.791-0.848).

When use of all three types of blood products was adjusted for the propensity score, the former was significantly associated with post-operative stroke (OR 4.832, 95% CI 2.370-9.851).

One-to-one propensity score matching allowed us to get 210 pairs of patients who did not receive any blood transfusion and patients who received transfusion of red blood cells, Octaplas® and platelets (Table III). It is noteworthy that despite the optimal area under the ROC curve of the propensity score as well as adequate goodness of fit for this logistic regression model, there were still a few differences between the study groups as denoted by standardised differences (Table III). Patients who did not receive blood products had a post-operative stroke rate of 1.0%, whereas it was 6.7% in patients who received all three types of blood products (p=0.004, Table IV). Logistic regression showed that, when adjusted for different institutions (p-values ranging from 0.277 to 0.537), transfusion of all three blood products was associated with a rather high post-operative stroke risk (OR 9.497, 95% CI 1.949-46.265). Overall, transfusion of all three types of blood products was associated with a remarkably higher risk of all major adverse postoperative end-points (Table IV) except in-hospital mortality, for which the difference did not reach statistical significance (2.4% vs. 5.7%, p=0.08).

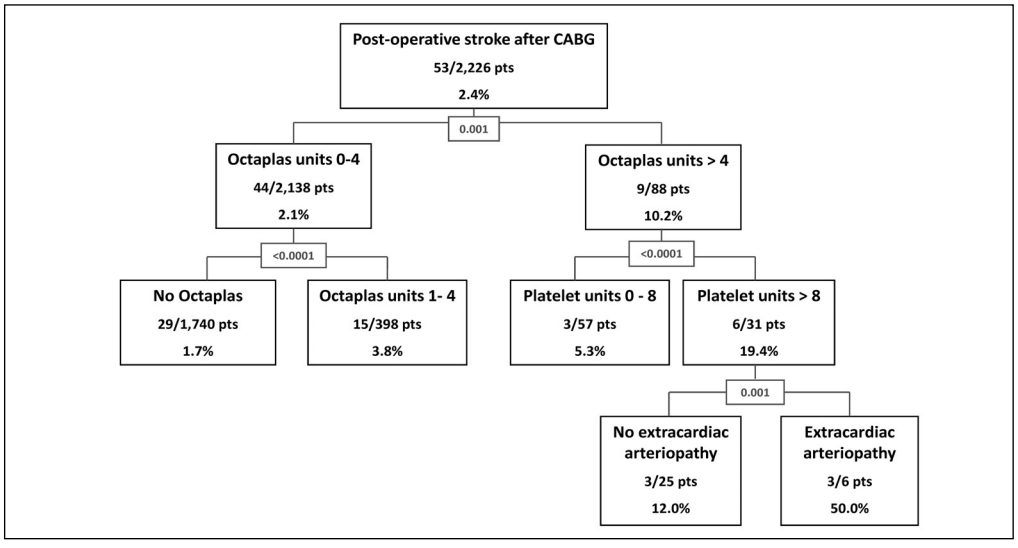

Figure 4 - Classification and regression tree analysis of post-operative stroke after CABG. Percentages refer to post-operative stroke rates. Numerical values at splitting nodes are improvement values.

Table III - Baseline characteristics and operative data on 210 propensity score matched pairs who underwent coronary artery bypass surgery who did not receive any blood transfusion and those who received all three types of blood products peri-operatively.

	Nº blood transfusion 210 patients	Transfusion of RBC, Octaplas and platelets 210 patients	Standardised difference	p-value
Age (years)	68.7±8.8	68.3±8.9	0.05	0.733
Females	42 (20.0)	43 (20.5)	0.01	0.903
Haemoglobin (gr/L)	135±14	136±15	0.07	0.543
Creatinine (µmol/L)	89±61	96±77	0.1	0.455
INR	1.2±0.3	1.2±0.3	0.32	0.010
Dialysis	0 (0)	0 (0)	-	-
Pulmonary disease	20 (9.5)	23 (11.0)	0.05	0.629
Diabetes	36 (17.1)	38 (18.1)	0.03	0.798
Hypertension	139 (66.2)	126 (60.0)	0.13	0.189
Atrial fibrillation	22 (10.5)	22 (10.5)	0	1.000
Transient ischaemic attack	5 (2.4)	13 (6.2)	0.19	0.089
Stroke	17 (8.1)	6 (2.9)	0.23	0.018
Neurological dysfunction	4 (1.9)	4 (1.9)	0	1.000
Extracardiac arteriopathy	23 (11.0)	27 (12.9)	0.06	0.547
Previous PCI	35 (16.7)	21 (10.0)	0.20	0.044
Previous cardiac surgery	9 (4.3)	8 (3.8)	0.03	0.804
Pre-operative clopidogrel	84 (40.0)	89 (42.4)	0.05	0.620
Pre-operative aspirin	197 (93.8)	201 (95.7)	0.09	0.381
Pre-operative warfarin	20 (9.5)	18 (8.6)	0.03	0.734
Recent myocardial infarction	90 (42.9)	97 (46.2)	0.07	0.492
Left ventricular ejection fraction				0.017
>50%	163 (77.6)	144 (71.6)	0.14	
30-50%	45 (21.4)	45 (22.4)	0.02	
<30%	2 (1.0)	12 (6.0)	0.27	
Systemic pulmonary pressure >60 mmHg	1 (0.5)	4 (1.9)	0.13	0.372
Unstable angina	30 (14.3)	46 (21.9)	0.20	0.043
Critical pre-operative status	12 (5.7)	17 (8.1)	0.09	0.336
Emergency surgery	19 (9.0)	22 (10.5)	0.05	0.622
Epi-aortic ultrasound	92 (44.9)	74 (35.2)	0.20	0.045
Diseased ascending aorta	15 (8.9)	10 (5.5)	0.13	0.224
Off-pump coronary surgery	95 (45.2)	68 (32.4)	0.26	0.007
Intra-operative use of tranexamic acid	139 (66.2)	143 (68.1)	0.04	0.678
N. of distal anastomoses	3.3±1.1	3.9±1.1	0.51	<0.0001
Logistic EuroSCORE (%)	5.7±7.3	7.0±9.8	0.15	0.090

Legend: Continuous variables are reported as mean and standard deviation or counts (%); INR: International Normalised Ratio; PCI: percutaneous coronary intervention; RBC: red blood cells.

Post-operative outcome according to the EuroSCORE

Since certain differences persisted between study groups in the propensity score matching analysis, we assessed the immediate post-operative outcome in patients with increasing operative risk as estimated by additive EuroSCORE classes (additive EuroSCORE 0-5, 6-9 and >9 points). This sensitivity analysis confirmed the major impact of transfusion of all three types of blood products on the development of stroke as well as other major adverse events (Table V).

Table IV - Adverse events during the immediate post-operative period after coronary artery bypass surgery in 210 propensity score matched pairs of patients who did not receive any blood transfusion and those who received all three types of blood products. Results of univariable and multivariable analyses for prediction of post-operative stroke are reported.

	No blood transfusion 210 patients	Transfusion of RBC, Octaplas and platelets 210 patients	p-value
In-hospital mortality	5 (2.4)	12 (5.7)	0.08
Stroke	2 (1.0)	14 (6.7)	0.004
Low cardiac output syndrome	14 (6.7)	46 (21.9)	<0.0001
Post-operative blood loss (mL)	683±347	1385±910	<0.0001
Re-sternotomy for bleeding	3 (1.4)	57 (27.1)	<0.0001
"Surgical bleeding"	2 (1.0)	41 (19.5)	<0.0001
De novo dialysis	1 (0.5)	12 (5.7)	0.003
Atrial fibrillation	64 (30.6)	92 (43.8)	0.005
ICU stay (days)	1.1±3.0	3.2±4.1	<0.0001
ICU stay ≥5 days	4 (1.9)	36 (17.1)	<0.0001
Composite outcome end-point	20 (9.5)	108 (51.4)	<0.0001

Legend: Continuous variable are reported as mean ± standard deviation or counts (%); RBC: red blood cells; ICU: intensive care unit; Composite end-point: in-hospital death, low cardiac output syndrome, *de novo* dialysis, stroke, re-sternotomy for excessive bleeding, or intensive care unit stay ≥5 days.

Table V - Adverse events during the immediate post-operative period after coronary artery bypass surgery in patients who did not receive any blood transfusion and those who received all three types of blood products. Results are according to increasing additive EuroSCORE classes.

	Additive EuroSCORE 0-5		Additive EuroSCORE 6-9		Additive EuroSCORE >9	
	No blood transfusion 804 patients	Transfusion of RBC, Octaplas and platelets 117 patients	No blood transfusion 142 patients	Transfusion of RBC, Octaplas and platelets 91 patients	No blood transfusion 22 patients	Transfusion of RBC, Octaplas and platelets 54 patients
In-hospital mortality	1 (0.1)	2 (1.7)*	1 (0.7)	6 (6.6)*	4 (18.2)	13 (24.1)
Stroke	13 (1.6)	6 (5.1)*	3 (2.1)	7 (7.7)*	0 (0)	4 (7.4)
Low cardiac output syndrome	32 (4.0)	18 (15.4)*	10 (7.0)	23 (25.3)*	8 (36.4)	24 (44.4)
Post-opertative blood loss (mL)	723±395	1,546±970*	650±366	1,138±820*	663±267	975±682*
Re-sternotomy for bleeding	7 (0.9)	37 (31.6)*	0 (0)	17 (18.7)*	1 (4.5)	7 (13.0)
"Surgical bleeding"	4 (0.5)	27 (23.1)*	0 (0)	11 (12.1)*	0 (0)	5 (9.3)
De novo dialysis	3 (0.4)	2 (1.7)	1 (0.7)	7 (7.7)*	2 (9.1)	8 (14.8)
Atrial fibrillation	221 (27.5)	43 (36.8)*	48 (33.8)	47 (51.6)*	11 (50.0)	31 (57.4)
ICU stay (days)	1.4±2.1	2.5±3.9*	1.4±1.2	3.4±3.6*	2.0±3.0	5.3±4.9
ICU stay ≥5 days	18 (2.2)	11 (9.4)*	4 (2.8)	20 (22.0)*	2 (9.1)	23 (42.6)*
Composite outcome end-point	58 (7.2)	53 (45.3)*	14 (9.9)	47 (51.6)*	10 (45.5)	44 (81.5*

Legend: Continuous variable are reported as mean ± standard deviation or counts (%); RBC: red blood cells; ICU: intensive care unit; Composite end-point: in-hospital death, low cardiac output syndrome, *de novo* dialysis, stroke, re-sternotomy for excessive bleeding, or intensive care unit stay ≥5 days; *: p<0.050.

Logistic regression including additive EuroSCORE classes, amount of post-operative bleeding, different institutions and transfusion of all three blood products, showed that the last variable was the only independent predictor of post-operative stroke (p<0.0001, OR 4.212, 95% CI 2.053-8.643).

Discussion

Stroke is one of the most severe complications occurring after cardiac surgery. It has a significant impact on patient's immediate and late outcome and quality of life[10,11]. The aetiopathogenesis of stroke is complex, multifactorial and related to a large number

of peri-operative factors and patient comorbidities[12]. Intra-operative embolism is considered the most important mechanism of post-operative stroke, but the role of various contributing factors is difficult to ascertain or investigate. Use of off-pump surgery and a no-touch aorta technique in the case of diseased ascending aorta[8,13], improving cardiopulmonary bypass techniques and materials[12,14], as well as reducing cardiopulmonary bypass time[15], avoidance of peri-operative arrhythmias[16], hypoperfusion[17] and haemodilutional anaemia[3] are measures which may significantly reduce the risk of post-operative stroke.

Excessive bleeding requiring re-exploration has recently been shown to be associated with a high risk of post-operative stroke[1], an observation which confirms that acute surgical anaemia is a major determinant of neurological events[2,3]. Indeed, a study by Kulier and colleagues[18] also provided evidence of an increased risk of post-operative stroke after CABG among patients with pre-operative anaemia, but this finding was not confirmed by the present or other previous studies[2,19,20] probably because pre-operative anaemia is now actively corrected before or at the start of surgery. However, severe peri-operative haemodilutional anaemia may certainly induce significant cerebral ischaemia. Experimental data indicate that under moderate or profound hypothermic conditions, severe cerebral ischaemia develops when the haematocrit sinks below 10-15%[21,22]. In accordance, clinical data indicate that the risk of post-operative neurological events increases in cardiac surgery in adults with haematocrit levels <20-22%[3,23], thereby confirming the importance of avoiding excessive bleeding during cardiac surgery. However, these findings do not take into consideration the amount of post-operative bleeding and immediate post-operative anaemia, which can be even more profound than intra-operatively.

On the other hand, the use of blood products to correct anaemia and restore coagulation may also contribute to the development of neurological events[2,24]. Recently, Barhainwala and colleagues[2] provided strong evidence about the independent prognostic impact of both post-operative haemoglobin levels and the need for intra-operative red blood cell transfusion on the risk of post-operative stroke. In the present study, logistic regression showed the amount of transfused packed red blood cells was an independent predictor of stroke, but the detailed analysis of type of transfused blood products demonstrated that need for Octaplas® transfusion was an independent predictor of stroke, whereas that of red blood cells was not. This finding was confirmed also by CART analysis, which showed the significant impact of transfusion of Octaplas® >4 units and platelets >8 units (stroke rate, 19.4%). Our findings are in agreement with the results of the study by Whitson and colleagues[2], which indicated that the risk of stroke as well as of mortality and other important adverse events is increased by the need for excessive blood product transfusion rather than minimal need of transfusion. Similarly, Figures 2 and 3 show that, in the present series, transfusion of all three types of blood products was dose-dependently associated with stroke risk. Importantly, this risk was evident when Octaplas® >4 units and platelets >8 units were transfused but to a much less extent when red blood cell >2 units were transfused (Figure 1). In the absence of data on peri-operative haemoglobin and haematocrit nadir, we may speculate that the need for transfusion of all three types of blood products certainly indicates significant bleeding, even if the amount of post-operative blood loss was not associated with post-operative stroke.

The evidence of an increased risk of stroke after cardiac surgery in patients who received recombinant activated factor VII[25] suggests that the beneficial haemostatic effects of coagulation-promoting drugs could be counterbalanced by severe atherothrombotic events. Although this may be purely speculative, large amounts of transfused blood products may also induce a prothrombotic status. There are no specific data about the clinical impact of Octaplas® transfusion in patients undergoing cardiac surgery, but De Maistre and colleagues[26] observed an increased risk of venous thromboembolism after transfusion of fresh-frozen plasma in patients who underwent abdominal aortic surgery. The reported lower level of protein S in Octaplas® compared with in fresh-frozen plasma is of concern[27]. Administration of solvent/detergent-treated plasma has been shown to be associated with decreased protein S activity[28,29], which may be detrimental in patients with congenital or acquired protein S deficiency. We, therefore, suspect that a prothrombotic status may be further

enhanced by solvent/detergent-treated plasma in patients undergoing major surgery.

There are limited data indicating that platelet transfusion may be associated with an increased risk of thromboembolism[30]. A propensity score matched analysis by McGrath and colleagues[31] did not demonstrate an increased morbidity risk with the use of platelet transfusion in cardiac surgery in adults. However, the authors did not take into account the amount of platelet units transfused and, therefore, no data on patients who received large numbers of platelet units were reported. However, it is known that platelet storage is associated with microparticles[32] and the possible association of such microparticles with thrombotic risk is a very active area of investigation.

Our findings could have been affected by a number of factors. First, this is a retrospective analysis of data from three hospitals with different peri-operative approaches. Second, we do not have data about intra- and post-operative levels of haemoglobin and haematocrit, which would have been useful to confirm the independent impact of blood products on post-operative neurological events. Third, we do not have data on the possible use of procoagulant drugs other than tranexamic acid. However, potent procoagulants such as recombinant factor VII are only rarely used in our Institutions, mainly in the treatment of severe bleeding occurring after valve and aortic surgery. Fourth, the impact of patient's comorbidities as well as operative technique are not easily assessable because of the complexity of the aetiopathogenesis of stroke and the interaction of variables resulting in excessive bleeding and at the same time in a prothrombotic state. However, Table IV shows that the rate of post-operative stroke and other major adverse events after transfusion of all three types of blood products is so high that patients' comorbidities and peri-operative anaemia cannot be the only determinants of these complications. This is further confirmed by the sensitivity analysis of different additive EuroSCORE classes (Table V).

In conclusion, the present results indicate that transfusion of large amounts of blood products after CABG is associated with a very high risk of post-operative stroke. It is of particular interest that use of Octaplas® and platelet transfusions seems to have an even larger impact on the development of stroke than transfusion of red blood cells.

The Authors declare no conflicts of interest.

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