Effect of the fresh whole blood transfusion on perioperative bleeding in adult patients undergoing emergency coronary artery bypass grafting surgery: a randomized study

Rabie Soliman[a,b], Walid Abukhudair[c]

[a]Department of Anesthesia, Cairo University, Cairo, Egypt, Departments of [b]Cardiac Anesthesia, [c]Cardiac Surgery, King Fahd Armored Forces Hospital, Jeddah, Saudi Arabia

Correspondence to Rabie Soliman, MD, Department of Anesthesia, Cairo University, Cairo, 11516, Egypt. Tel: +20 111 508 6363; fax: +202 2364 1687; e-mail: rabiesoliman@hotmail.com

Received: 8 April 2020
Revised: 12 June 2020
Accepted: 29 July 2020
Published: 15 February 2021

The Egyptian Journal of Cardiothoracic Anesthesia 2020, 14:84–91

Objective
The present study aimed to assess the hemostatic effects of fresh whole blood (FWB) transfusion on bleeding and blood product transfusion in patients on clopidogrel undergoing emergency coronary artery bypass grafting surgery (CABG).
Design
A randomized study was conducted.
Setting
The study was conducted at a cardiac center.
Patients and methods
The study included 124 patients undergoing CABG surgery. The patients were divided into two groups: FWB group patients received two to six units of FWB after weaning off cardiopulmonary bypass and in the cardiac surgery ICU. Control group patients received blood products (packed red blood cells, platelets, fresh frozen plasma, or cryoprecipitate) after weaning off cardiopulmonary bypass and after surgery in cardiac surgery ICU. Total number of the transfused FWB, platelets, packed red blood cell, fresh frozen plasma, and cryoprecipitate (intraoperative and postoperative transfusion), bleeding time, and platelet aggregation function were measured. Moreover, the thorax closure time and amount of blood losses, re-exploration, pulmonary edema, and postoperative mechanical ventilation were monitored.
Results
FWB significantly decreased the blood loss and blood product transfusion compared with the control group (P=0.001 and 0.001, respectively). The bleeding time and platelet aggregation function were better in the FWB group compared with the control group (P=0.020 and 0.034, respectively). Moreover, the thorax closure time, cardiac tamponade, re-exploration, pulmonary edema, and postoperative mechanical ventilation decreased significantly in the FWB group compared with the control group ($P<0.05$).
Conclusion
FWB decreased the blood loss, blood product transfusion, cardiac tamponade, and re-exploration in patients on preoperative clopidogrel undergoing emergency CABG.

Keywords:
bleeding time, blood loss, blood product transfusion, Clopidegrel, fresh whole blood, platelet aggregation, re-exploration, thorax closure time

Egypt J Cardiothorac Anesth 14:84–91

1687-9090

Introduction

The antiplatelet combination of clopidogrel and aspirin is the most common medication used in patients with acute coronary syndrome and to reduce the in-stent thrombosis after the percutaneous coronary intervention [1,2].

Clopidogrel reduces the risk of incidence of myocardial ischemia and infarction, strokes, and mortality. Clopidogrel inhibits adenosine 5′-diphosphate-induced platelet aggregation, whereas aspirin inhibits cyclooxygenase and reduces thromboxane A2 [3–5].

The clopidogrel inhibits platelet aggregation irreversibly [6], and AHA/ACC guidelines recommend that clopidogrel must be discontinued for at least 5 days and preferably for 7 days before coronary artery bypass grafting (CABG) [7]; however, in the case of urgent CABG, it impossible to wait for 5 days, being sufficient for generation of new young platelets that would be adequate to maintain firm

hemostasis, and therefore, it might expose the patient to severe and sometimes refractory perioperative bleeding, cardiac tamponade, complications of massive blood products transfusion, surgical re-exploration, prolonged length of hospital stay, and mortality that impair the outcome after cardiac surgery [8–11].

Fresh whole blood (FWB) transfusion is defined as the transfusion of the whole blood through 48 h from donation [12]. FWB transfusion results in a combination of fresh red blood cells, increased function and number of platelets, along with increased coagulation factor levels, contributing to improved hemostasis and lower donor exposure rates [13,14].

We hypothesize that the FWB transfusion is associated with a decrease in perioperative bleeding than the platelet transfusion during cardiac surgery. The present study aimed to assess the hemostatic effects of FWB transfusion on perioperative bleeding and blood product transfusion in adult patients on preoperative clopidogrel undergoing emergency CABG surgery.

Patients and methods

Outcomes

The primary outcomes were blood loss and requirements for blood product transfusion. The secondary outcome was the safety of FWB and blood product transfusion which was assessed by the occurrence of complications.

Sample size calculation

Power analysis was performed using the χ^2-test for independent samples on the frequency of patients experiencing perioperative bleeding and requiring blood transfusion, because it was the main outcome variable in the present study. A pilot study was done before starting this study to assess the frequency of patients with decreased perioperative bleeding and blood transfusion in patients undergoing urgent cardiac surgery. The results of the pilot study (eight cases in each group) showed that the incidence of severe perioperative bleeding was 37.5% in the fresh blood group, and 62.5% in the control group. Taking power 0.8, α error 0.05, and β 0.2, a minimum sample size of 62 patients was calculated for each group.

Patients

The study was carried out as a prospective randomized during the period from December 2016 to November 2019. After local Ethics Committee approval, all patients scheduled for urgent CABG plus or minus valve surgery and on preoperative clopidogrel (discontinuation of administration <24 h) and platelet aggregation inhibition >40% (mean of clopidogrel platelet aggregation inhibition therapy 64 ±25%) [15], and ventricular function (ejection fraction >40%) were screened for eligibility enrollment. The exclusion criteria included patients who had aneurysmal aortic surgery, thrombolytic therapy less than 24 h preoperatively, or severe liver disease. The study included 124 cases, and the patients were assessed using the New York Heart Association, American Society of Anesthesiologists Physical Status Score, and Euroscore. Included patients were those who still had refractory bleeding either intraoperatively (there were excessive generalized oozing and unable to close the chest) or postoperatively (if the chest loss >3 ml/kg/h). This was defined by persisting bleeding despite accurate surgical hemostasis and reversal of heparin by protamine guided by activated clotting time (ACT). The surgical bleeding source was excluded by surgical re-exploration. For these patients, FWB or blood products were administered when the blood loss amount evoked a significant compromise in systemic hemodynamics (severe bleeding that decreases hemoglobin <9 g/dl and associated with a decrease in MAP <70 mmHg). The patients were randomly allocated to one of the two groups (62 patients in each group). FWB group patients received two to six units of FWB (donated <24 h before surgery) after weaning off cardiopulmonary bypass (CPB) in addition to other blood products if needed (platelets, fresh frozen plasma, or cryoprecipitate) and postoperatively in the cardiac surgery ICU (CSICU) to maintain the hemoglobin greater than 9 g/dl. Control group patients did not receive FWB and received only other blood products (packed red blood cells, platelets, fresh frozen plasma, or cryoprecipitate) after weaning off CPB and postoperatively in the CSICU.

Anesthetic technique

Anesthetic technique: for all patients and under local anesthesia, the radial arterial cannula and central venous line were inserted before induction to enable continuous hemodynamic monitoring. Induction was done by intravenous fentanyl (3–5 μg/kg), etomidate (0.3 mg/kg), rocuronium (0.8 mg/kg). The anesthesia was maintained with oxygen/air (50%), sevoflurane (1–3%), fentanyl infusion (1–3 μg/kg/h), and cisatracurium (1–2 μg/kg/min). The patients received tranexamic acid as 20 mg/kg as a bolus dose over 10 min,

then infusion 5 mg/kg/h after induction and continuously throughout the operation until skin closure. All patients received 4 mg/kg of heparin before bypass, aiming to provide an ACT greater than 480 s. After bypass, heparin was reversed with protamine which was titrated to achieve an ACT less than 140 s. CPB used centrifugal pumps with 1–1.5 l prime of ringer lactate, in addition to antibiotics, solu-medrol, and mannitol. Both antegrade blood cardioplegia and retrograde blood cardioplegia were used. Cooling was passive to around 34°C or active to 22°C. FWB, platelets, packed red blood cells, fresh frozen plasma, and cryoprecipitate were administered according to the study protocol (to control the bleeding and to maintain hemoglobin >9 g/dl). The transfusion was done either intraoperatively (if there was excessive generalized oozing with the inability to close the chest) and/or postoperatively if the chest drains' loss was more than 3 ml/kg/h. At the end of surgical intervention, the patients were prepared for weaning off CBP. If there was difficulty to wean off CPB, pharmacological support (dopamine, epinephrine, norepinephrine, or nitroglycerine) or mechanical support (IABP) was started. At the end of surgery, the patients were transferred to cardiac surgery ICU with full monitoring.

Patients monitoring

For all patients, the following laboratory investigations were closely monitored: bleeding time (BT), platelet aggregation inhibition, prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), ACT platelets, fibrinogen, D-dimer, hemoglobin, total number of the transfused FWB, platelets, packed red blood cell, fresh frozen plasma, and cryoprecipitate (intraoperative and postoperative transfusion). Moreover, the thorax closure time and amount of blood losses through the postoperative 24 h were monitored. Chest radiography was done on admission to CSICU, and as indicated to rule out widened mediastinum.

Statistical analysis

Data were statistically described in terms of mean± ±SD, or frequencies (number of cases) and percentages when appropriate. A comparison of numerical variables between the study groups was done using the Student *t*-test for independent samples. For comparing categorical data, a χ^2 test was performed. The exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, Illinois, USA) version 15 for Microsoft Windows.

Results

Table 1 shows no significant differences in the demographic data, co-morbidities, preoperative medications, New York Heart Association class, American Society of Anesthesiologists Physical Status Score physical status score, and the Euroscore ($P>0.05$).

Table 2 shows the coagulation profiles of patients. The preoperative BT and platelet aggregation inhibition were significantly higher than the normal level in patients of the two groups, but the difference between the two groups was insignificant ($P=0.830$ and 0.310, respectively). There was no significant difference in the preoperative PT, INR, aPTT, ACT, platelets number, fibrinogen, and D-dimer between the two groups ($P>0.05$). The postoperative BT significantly decreased in patients of the two groups compared with the preoperative values, but the decrease was significantly lower in the FWB group compared with the control group ($P=0.020$). The postoperative platelet aggregation inhibition significantly decreased in patients of the two groups compared with the preoperative values, but the decrease was significantly lower in the FWB group than the control group ($P=0.034$). There was no significant difference in the postoperative PT, INR, aPTT, ACT, platelets number, and fibrinogen between the two groups ($P>0.05$). Postoperatively, the D-dimer increased mildly in patients of both groups, but the difference between the two groups was insignificant ($P=0.403$).

Table 3 shows the blood losses and blood products transfusion. The mean blood loss during the first 24 postoperative hours was lower in the FWB group than the control group ($P=0.001$). The number of transfused platelets was significantly lower in the FWB group compared with the control group ($P=0.001$). Patients of FWB group received fresh frozen plasma less than the control group patients ($P=0.001$). Moreover, the number of transfused cryoprecipitate units was significantly lower in the FWB group compared with the control group ($P=0.001$). There was no significant difference in the postoperative hemoglobin level between the two groups ($P=0.150$).

Table 4 shows the surgical data of patients. There was no significant difference in the types and number of surgical procedures (CABG or mitral valve repair) between the two groups ($P>0.05$). There was no significant difference in the postoperative mean

Table 1 Preoperative data of patients (data are presented as mean±SD, number, %)

Variable	FWB group (*n*=62)	Control group (*n*=62)	*P* value
Age (years)	56.70±10.20	53.22±11.50	0.077
Weight (kg)	86.40±13.78	88.15±14.50	0.492
Sex			
Male : female	46 : 16	40 : 22	0.330
Diabetes mellitus	62 (100)	62 (100)	1.000
Hypertension	52 (83.87)	45 (72.58)	0.191
Ischemic heart diseases	62 (100)	62 (100)	1.000
Atrial fibrillation	36 (58.06)	42 (67.74)	0.352
Mitral valve regurgitation	19 (30.64)	13 (20.96)	0.304
Pulmonary hypertension	12 (19.35)	7 (11.29)	0.318
Ejection fraction	47.40±5.30	48.15±5.80	0.453
Angiotensin-converting-enzyme inhibitors	39 (62.90)	43 (69.35)	0.569
β-Blockers	48 (77.41)	56 (90.32)	0.087
Calcium channels-blockers	25 (40.32)	32 (51.61)	0.279
Aspirin	62 (100)	62 (100)	1.000
Clopidogrel	62 (100)	62 (100)	1.000
Statins	57 (91.93)	52 (83.87)	0.270
Chronic renal impairment	9 (14.51)	13 (20.96)	0.369
Carotid stenosis			
<50%	18 (29.03)	24 (38.70)	0.342
Unilateral	11 (17.74)	16 (25.80)	0.384
Bilateral	5 (8.06)	8 (12.90)	0.557
Smoking			
Current smokers	35 (56.45)	28 (45.16)	0.281
Ex-smokers	13 (20.96)	19 (30.64)	0.304
NYHA			
III : IV	25 : 37	29 : 33	0.586
ASA			
III : IV	18 : 44	23 : 39	0.445
Euroscore (%)	16.63±5.30	15.87±5.13	0.418
Blood sugar (mmol/l)	7.25±1.17	7.44±1.30	0.394
Body surface area (m^2)	1.74±0.15	1.78±0.17	0.167
Hemoglobin (g/dl)	13.70±1.17	14.02±1.46	0.180

ASA, American Society of Anesthesiologists Physical Status Score; FWB group, fresh whole blood group; NYHA, New York Heart Association.

heparin dose and ACT, protamine dose, CPB duration, aortic cross-clamping time, and temperature between the two groups ($P>0.05$). The mean thorax closure time was significantly lower in the FWB group compared with the control group ($P=0.001$).

Table 5 shows the postoperative outcomes of patients. The dose of pharmacological support after weaning off CPB was lower in FWB group than in the control group ($P<0.05$). The incidence of postoperative cardiac tamponade was two patients in FWB group and seven patients in the control group ($P=0.166$). Surgical re-exploration (because of postoperative bleeding or cardiac tamponade) was needed in four patients in FWB group and 13 patients in the control group ($P=0.034$), and in all cases, the bleeding was owing to generalized oozing. The number of patients who experienced pulmonary edema and required postoperative mechanical ventilation was significantly lower in FWB group than the control group ($P=0.028$). The incidence of allergic reactions was significantly lower in the FWB group than the control group ($P=0.047$). The incidence of renal failure was insignificant between the two groups ($P=0.241$). The ICU and hospital length of stay were shorter in the FWB group compared with the control group ($P=0.002$ and 0.016, respectively). There was no incidence in the anaphylactic reaction, disseminated intravascular coagulopathy, postoperative graft occlusion and acute myocardial infarction, thromboembolism, neurological complications, or mortality in the two groups.

Discussion

The present study showed that the FWB is effective to decrease the perioperative blood loss and blood product transfusion in patients on preoperative clopidogrel undergoing emergency CABG surgery. The BT and platelet aggregation inhibition significantly decreased in patients of the two groups, but the decrease was

Table 2 Coagulation profiles of patients (data are presented as mean±SD, number, %)

Variables	FWB group (*n*=62)	Control group (*n*=62)	*P* value
Preoperative coagulation profiles			
BT (min)	17.24±7.55	16.96±6.93	0.830
Platelet aggregation inhibition (%)	57.36±8.46	55.90±7.48	0.310
PT (s)	10.08±1.09	10.15±1.10	0.722
INR	1.04±0.13	1.07±0.17	0.271
aPTT (s)	40.96±6.30	41.20±7.15	0.843
ACT (s)	131.35±11.65	129.80±12.70	0.480
Platelets ($\times10^3/\mu l$)	265.83±67.30	272.40±70.50	0.596
Fibrinogen (g/l)	3.31±0.47	3.44±0.43	0.110
D-dimer (μg/ml)	0.24±0.16	0.21±0.15	0.283
Postoperative coagulation profiles			
BT (min)	9.42±1.78†	10.25±2.15†	0.020*
Platelet aggregation inhibition (%)	33.03±4.93†	35.11±5.85†	0.034*
PT (s)	11.15±1.24	10.92±1.16	0.288
INR	1.24±0.19	1.21± 0.23	0.430
aPTT (s)	42.47±6.15	41.35±5.26	0.278
ACT (s)	133.2±5.58	132.50±5.25	0.433
Platelets ($\times10^3/\mu l$)	245.48±47.80	249.00±51.40	0.693
Fibrinogen (g/l)	3.22±0.42	3.31±0.48	0.268
D-dimer (μg/ml)	1.18±0.45	1.12±0.34	0.403

ACT, activated clotting time; aPTT, activated thromboplastin time; BT, Bleeding time; FWB group, Fresh whole blood group; INR, international normalized ratio; PT, prothrombin time. *$P<0.05$ significant comparison between the two groups. †$P<0.05$ significant within the same group compared with the preoperative value.

Table 3 Blood losses and blood products transfusion (Data are presented as mean±SD)

Variables	FWB group (*n*=62)	Control group (*n*=62)	*P* value
Blood loss (ml/24 h)	815.55 ±126.40	1183.90 ±150.10	0.001*
Fresh whole blood	4.60±1.56	–	0.001*
Packed red blood cells (unit)	–	9.58±2.80	0.001*
Platelets (unit)	3.75±2.15	13.40±4.70	0.001*
Fresh frozen plasma (unit)	3.15±2.86	14.80±3.40	0.001*
Cryoprecipitate (unit)	3.20±1.50	9.70±3.35	0.001*
Hemoglobin (g/dl)	11.55±1.30	11.23±1.16	0.150

Group FWB, fresh whole blood group. *$P<0.05$ significant comparison between the two groups.

significantly more in the FWB group compared with the control group, and this means that FWB improved the platelet function than the transfused platelets, in spite there being no difference in the postoperative number of platelets. Mohr *et al.* [16] found that fresh blood improved the platelet function as shown by the improvement of the platelet aggregation and BT with the fresh blood than the transfused platelet after cardiac surgery. Moreover, they found that the hemostatic effect of one-unit FWB after CPB is at least equal, if not superior, to the effect of 10 units of platelets. Another study showed improved hemostasis in cardiac surgery after FWB administration compared with the transfused platelets, as the FWB contains large and potent platelets than the transfused platelet concentrate [17]. The large platelets in the FWB resist inhibition, aggregate better, and induce a superior hemostatic effect than the transfused platelets [18–20].

The fresh blood has preserved clotting factors and full platelet activity [16,21], and many studies showed the use of FWB improves hemostasis, reduces exposures to cytokines and inflammatory mediators with the stored packed red blood cells, and also reduces the overall blood product exposures [22–25].

One study showed that the mixture of one unit of RBC has a hematocrit of 55%, one unit of platelet concentrate has platelets level 5.5×10^{10}, and one unit of FFP has 80% coagulation factors activity. In contrast, one unit of FWB has a hematocrit of 33–43%, 130 000–350 000 platelets per microliter, and 86% activity of coagulation factors [21,26]. Moreover, unlike the use of the stored blood products, FWB is anticipated to have full platelet activity [16,21,27–30]. Lavee *et al.* [28] showed a similar effect of whole blood on the preservation of platelet function by showing that platelet aggregation as assessed by electron microscopy after CPB in adult patients was restored by one unit of whole blood to a level equivalent to 8–10 platelet units.

Whole fresh blood is the product of choice if massive bleeding is expected, as it provides volume

Table 4 Surgical data of patients (data are presented as mean±SD, number, %)

Variables	FWB group (*n*=62)	Control group (*n*=62)	*P* value
Emergency surgery	62 (100)	62 (100)	1.000
Coronary artery bypass grafting	62 (100)	62 (100)	1.000
Number of coronary grafts			
2	8 (12.90)	5 (8.06)	0.559
3	26 (41.93)	30 (48.38)	0.863
4	18 (29.03)	21 (33.87)	0.698
5	10 (16.12)	6 (9.67)	0.421
Mitral valve repair	12 (19.35)	7 (11.29)	0.318
CPB time (min)	118.30±25.45	125.16±27.80	0.154
Cross-clamping time (min)	92.40±20.35	95.10±23.00	0.230
Temperature (°C)	29.48±3.15	28.86±4.03	0.341
Total heparin dose (mg)	318.60±66.83	311.55±62.79	0.546
Post heparin ACT (s)	584.74±115.60	610.15±123.30	0.238
Total protamine dose (mg)	345.25±63.50	337.90±60.85	0.511
Postprotamine ACT (s)	134.07±12.46	135.20±15.90	0.959
Thorax closure time (min)	72.50±15.35	84.00±17.70	0.001*

ACT, activated clotting time; CPB, cardiopulmonary bypass; FWB group, fresh whole blood group. *$P<0.05$ significant comparison between the two groups.

Table 5 Intraoperative data and outcome of patients (data are presented as mean±SD, number, %)

Variables	FWB group (*n*=62)	Control group (*n*=62)	*P* value
Dopamine(μg/kg/min)	6.50±2.80	8.18±3.40	0.003*
Norepinephrine (μg/kg/min)	0.06±0.03	0.08±0.04	0.002*
Nitroglycerine (μg/kg/min)	1.37±0.29	1.50±0.39	0.037*
Postoperative cardiac tamponade	2 (6.45)	7 (11.29)	0.166
Surgical re-exploration	4 (3.22)	13 (20.96)	0.034*
Postoperative graft occlusion and acute MI	–	–	
Pulmonary edema	5 (8.06)	15 (24.19)	0.028*
Postoperative mechanical ventilation	5 (8.06)	15 (24.19)	0.028*
Allergic reaction	3 (4.83)	11 (17.74)	0.047*
Renal failure	5 (8.06)	9 (14.51)	0.241
Neurological complication (stroke)	–	–	
ICU length of stay (days)	5.10±1.30	6.03±1.45	0.002*
Hospital length of stay (days)	10.75±2.65	12.10±3.50	0.016*
Anaphylactic reaction	–	–	
Disseminated intravascular coagulopathy	–	–	
Thromboembolism	–	–	
Mortality	–	–	

Acute MI, acute myocardial infarction; FWB group, fresh whole blood group; MI, myocardial infarction. *$P<0.05$ significant comparison between the two groups.

replacement, higher oxygen-carrying capacity, and coagulation factor replacement [31]. Jobes *et al.* [12] found that the FWB is associated with an improvement of hemostasis and decreased blood product transfusion as a result of preserved platelet function in the FWB in cardiac operations in children younger than 2 years old. Moreover, the FWB reduced the donor exposures compared with other blood products of multiple donors, and similar results were shown by other studies [13,14]. Another study showed that the reversal of the antiplatelet effect required 12 units of platelets that were 48 h after extraction, compared with four units of fresh platelets [32].

In the present study, the transfusion of FWB decreased the transfusion of other blood products such as platelets, fresh frozen plasma, and cryoprecipitate in patients on preoperative clopidogrel undergoing emergency CABG. Therefore, FWB group is associated with a lower dose of pharmacological support, decreased incidence of postoperative cardiac tamponade, allergic reaction, pulmonary edema, postoperative mechanical ventilation, and renal failure. Moreover, the ICU and hospital length of stay were shorter with FWB than the control group. Some studies showed that FWB in pediatric cardiac surgery significantly improved the clinical outcomes, reduced the postoperative chest tube volume loss

during the first 24 h, and significantly decreased the required inotropic support, ventilation time, and hospital length of stay [25,33,34].

Contrary to the results of the present study, McLean *et al*. [35] showed that there was no significant increase in bleeding in the patients receiving clopidogrel undergoing urgent CABG, and Karabulut *et al*. [36] suggest that preoperative use of clopidogrel does not increase perioperative bleeding, surgical exploration, or blood product transfusion after CABG.

There is limitation to the present study as thromboelastography was not used to assess the efficiency of blood coagulation, as it was not available.

Conclusion

FWB decreased the blood loss, blood product transfusion, cardiac tamponade, and re-exploration in patients on preoperative clopidogrel undergoing emergency CABG.

Acknowledgements

The authors appreciate the help and support of the staff nurses in the operative rooms and postoperative CSICU.

The authors thank all staff nurses in the operative rooms, post anesthesia care unit, and intensive care unit for their efforts and performance during the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Reed GW, Kumar A, Guo J, Aranki S, Shekar P, Agnihotri A, *et al.* Point-of-care platelet function testing predicts bleeding in patients exposed to clopidogrel undergoing coronary artery bypass grafting: Verify Pre-Op TIMI 45–a pilot study. Clin Cardiol 2015; 38:92–98.

2 Petricevic M, Biocina B, Milicic D, Rotim C, Boban M. Platelet function testing and prediction of bleeding in patients exposed to clopidogrel undergoing coronary artery surgery. Clin Cardiol 2015; 38:443–444.

3 Arora RR, Rai F. Antiplatelet intervention in acute coronary syndrome. Am J Ther 2009; 16:29–40.

4 Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Clopidogrel in unstable angina to prevent recurrent events trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345:494–502.

5 Genoni M, Tavakoli R, Hofer C, Bertel O, Turina M. Clopidogrel before urgent coronary artery bypass graft. J Thorac Cardiovasc Surg 2003; 126:288–289.

6 Coukell AJ, Markham A. Clopidogrel. Drugs 1997; 54:745–750.

7 Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, *et al.* for the2004 Writing Committee Members. 2007 Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, developed in collaboration with the Canadian Cardiovascular Society, endorsed by the American Academy of Family Physicians: 2007 writing group to review new evidence and update the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction, writing on behalf of the 2004 writing committee. Circulation 2008; 117:296–329.

8 Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, *et al.* Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 2011; 32:2933–2944.

9 Ferraris VA, Ferraris SP, Moliterno DJ, Camp P, Walenga JM, Messmore HL, *et al.* The Society of Thoracic Surgeons practice guideline series: aspirin and other antiplatelet agents during operative coronary revascularization (executive summary). Ann Thorac Surg 2005; 79:1454–1461.

10 Hongo RH, Ley J, Dick SE, Yee RR. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. J Am Coll Cardiol 2002; 40:231–237.

11 Kulik A, Chan V, Ruel M. Antiplatelet therapy and coronary artery bypass graft surgery: perioperative safety and efficacy. Expert Opin Drug Saf 2009; 8:169–182.

12 Jobes DR, Sesok-Pizzini D, Friedman D. Reduced transfusion requirement with use of fresh whole blood in pediatric cardiac surgical procedures. Ann Thorac Surg 2015; 99:1706–1711.

13 Ignjatovic V, Than J, Summerhayes R, Newall F, Horton S, Cochrane A, *et al.* The quantitative and qualitative responses of platelets in pediatric patients undergoing cardiopulmonary bypass surgery. Pediatr Cardiol 2012; 33:55–59.

14 Ranucci M, Carlucci C, Isgro G, Baryshnikova E. A prospective pilot study of platelet function and its relationship with postoperative bleeding in pediatric cardiac surgery. Minerva Anestesiol 2012; 78:556–563.

15 Malinin A, Pokov A, Spergling M, Defranco A, Schwartz K, Schwartz D, *et al.* Monitoring platelet inhibition after clopidogrel with the VerifyNow-P2Y12 (R) rapid analyzer: the VERIfy Thrombosis risk ASsessment (VERITAS) study. Thromb Res 2007; 119:277–284.

16 Mohr R, Martinowitz U, Lavee J, Amroch D, Ramot B, Goor DA. The hemostatic effect of transfusing fresh whole blood versus platelet concentrates after cardiac operations. J Thorac Cardiovasc Surg 1988; 96:530–534.

17 Mohr R, Goor DA, Yellin A, Moshkovitz Y, Shinfeld A, Martinowitz U. Fresh blood units contain large potent platelets that improve hemostasis after open heart operations. Ann Thorac Surg 1992; 53:650–654.

18 Haver VM, Geor ARL. Functional fractionation of platelets. J Lab Clin Med 1981; 97187–97204

19 Jakubowski JA, Alder B, Thompson CP, Valeri CR. Influence of platelet volume on the ability of prostacycline to inhibit platelet aggregation and the release reaction. J Lab Clin Med 1985; 105:271–276

20 Sperling S, Vinholt PJ, Sprogøe U, Yazer MH, Frederiksen H, Nielsen C. The effects of storage on platelet function in different blood products. Hematology 2019; 24:89–96.

21 Hardy JF, Moerloose P, Samama M. Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. Can J Anesth 2004; 51: 293–310.

22 Manno CS, Hedberg KW, Kim HC, Bunin GR, Nicolson S, Jobes D. Comparison of the hemostatic effects of fresh whole blood, stored whole blood, and components after open heart surgery in children. Blood 1991; 77:930–936.

23 Mou SS, Giroir BP, Molitor-Kirsch EA, Leonard SR, Nikaidoh H, Nizzi F, *et al.* Fresh whole blood versus reconstituted blood for pump priming in heart surgery in infants. N Engl J Med 2004; 351:1635–1644.

24 Friesen RH, Perryman KM, Weigers KR, Mitchell MB, Friesen RM. A trial of fresh autologous whole blood to treat dilutional coagulopathy following cardiopulmonary bypass in infants. Pediatr Anesth 2006; 16:429–435

25 Valleley MS, Buckley KW, Hayes KM, Fortuna RR, Geiss DM, Holt DW. Are there benefits to a fresh whole blood vs. packed red blood cell cardiopulmonary bypass prime on outcomes in neonatal and pediatric cardiac surgery?. J Extra Corpor Technol 2007; 39:168–176.

26 Hess JR. Resuscitation of trauma-induced coagulopathy. Hematol Am Soc Hematol Educ Program 2013; 2013:664–667.

27 Martinowitz U, Goor DA, Ramot B, Mohr R. Is transfusion of fresh plasma after cardiac operations indicated? J Thorac Cardiovasc Surg 1990; 100:92–98.

28 Lavee J, Martinowitz U, Mohr R, Goor DA, Golan M, Langsam J, *et al.* The effect of transfusion of fresh whole blood versus platelet concentrates after cardiac operations. A scanning electron microscope study of platelet aggregation on extracellular matrix. J Thorac Cardiovasc Surg 1989; 97:204–212.

29 Erber WN. Massive blood transfusion in the elective surgical setting. Transfus Apher Sci 2002; 27:83–92.

30 Spinella PC, Pidcoke HF, Strandenes G, Hervig T, Fisher A, Jenkins D, *et al.* Whole blood for hemostatic resuscitation of major bleeding. Transfusion 2016; 5:190–202.

31 Davis RW, Patkin M. Ultrafresh blood for massive transfusion. Med J Aust 1979; 1:172–174.

32 Handin RI, Valeri CR. Hemostatic effectiveness of platelets stored at 22 degrees C. N Engl J Med 1971; 285:538–543.

33 Gruenwald CE, McCrindle BW, Crawford-Lean L, Holtby H, Parshuram C, Massicotte P. Reconstituted fresh whole blood improves clinical outcomes compared with stored component blood therapy for neonates undergoing cardiopulmonary bypass for cardiac surgery: a randomized controlled trial. J Thorac Cardiovasc Surg 2008; 136:1442–1449

34 Williams GD, Bratton SL, Ramamoorthy C. Factors associated with blood loss and blood product transfusions: a multivariate analysis in children after openheart surgery. Anesth Analg 1999; 89:57–64.

35 McLean DS, Sabatine MS, Guo W, McCabe CH, Cannon CP. Benefits and risks of clopidogrel pretreatment before coronary artery bypass grafting in patients with ST-elevation myocardial infarction treated with fibrinolytics in CLARITY-TIMI 28. Thromb Thrombolysis 2007; 28:1025–32.

36 Karabulut H, Toraman F, Evrenkaya S, Goksel O, Tarcan S, Alhan C. Clopidogrel does not increase bleeding and allogenic blood transfusion in coronary artery surgery. Eur J Cardiothorac Surg 2004; 25:419–423.