RESEARCH ARTICLE

Mortality associated with standard prescription transfusions in cardiac surgery

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Abstract
Background: Before applying new blood management strategies, the extent of blood product transfusions and its correlation with perioperative mortality should be identified.
Methods: This study retrospectively analyzed the extent of perioperative transfusions of red blood cells (RBC), fresh frozen plasma (FFP), and platelets (PLT) in 565 consecutive cardiac surgery patients, who received transfusions based on standard prescriptions. Patients were stratified in four groups according to perioperative transfusion units (no transfusion, <5, 5-10, >10 units). Mortality was analyzed in relation to the type and extent of each blood product transfused and their combinations. Subsequently, the ability of transfusion volume to predict mortality was tested.
Results: Most patients received blood product transfusions perioperatively. The observed mortality (11.7 %) correlated significantly with the volume of transfusion. Patients transfused with >5 RBC or FFP units or >10 PLT units had increased mortality compared with those receiving fewer transfusions (23.9 % vs 4.5 %, 27.4 % vs 6 %, 24.5 % vs 8.5 %, p <0.05, respectively). Analysis revealed that cutoffs of >5 units of RBC or >15 units of RBC, FFP, and PLT additively (sensitivity: 74.2 % and 72.7 %, specificity: 68.7 % and 69.5 %, respectively) had an acceptable discrimination ability for perioperative mortality (Area under the ROC curve: 0.756, p <0.001, and 0.735, p <0.001, respectively).
Conclusions: This study confirmed a dose-dependent, transfusion-associated, increased mortality in cardiac surgery patients who received standard prescription transfusions. The results support the need for applying validated, patient-specific blood conservation strategies that correspond to the patient's actual perioperative transfusion needs.
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Keywords: Perioperative transfusion, cardiac surgery, mortality, blood components

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Introduction

Cardiac surgery patients use approximately 20 % of the hospital blood bank reserves in blood products worldwide[1]. Given the low availability of blood products and the increased morbidity and mortality associated with their administration, there is a need to reduce blood product consumption. Cardiac surgery and anesthesia services tend to endorse new protocols to guide blood products perioperatively, aiming to achieve effective bleeding control and minimize blood product use[2,3]. Additionally, the implementation of these late clinical practices has an economic impact that should be carefully balanced between the cost of acquiring monitoring technology and the savings that reduced blood product use can provide[4,5].

Exploring transfusion-related mortality in a cardiac center and detailing the transfusion-associated mortality before the implementation of new protocols may be a real challenge due to limited resources and the potential return on investment. Therefore, this study aimed to explore the volume of transfusion therapy, to investigate the mortality in our cardiac surgery patients and to identify correlations of the type of blood product, their combinations and the extent of transfusions with the associated mortality.

Materials and Methods

In the present study, we retrospectively examined blood product transfusions and in-hospital mortality of consecutive cardiac surgery patients, without differentiating between elective and emergency cases.

The standard prescription in our hospital required the administration of two units of fresh frozen plasma (FFP) after a coronary artery bypass grafting (CABG) operation and four units of FFP plus five units of platelets (PLT) for a valve or mixed cardiac operation, without any laboratory confirmation of coagulation disorder. Red blood cells (RBC) transfusions were applied when point of care measurements of hemoglobin concentrations were below 10 g/dL. Additional blood products could be transfused according to the clinical judgment of the attending physicians and laboratory confirmation that justified their administration. During the studied period, the blood bank could not provide cryoprecipitate preparations and the pharmacy could not dispense fibrinogen, vitamin K-dependent factor, or rFVIIa concentrates.

After obtaining Ethics Committee approval (18.10/10/2014, Item 13), we searched the hospital's revised Blood bank information system (only patients from its last upgrade that could provide all the necessary data were included, so the enrollment period included patients from 01/02/2010 up to 31/05/2014) and retrospectively assigned our patients to four perioperative transfusion classes (PTCs) based on the perioperative blood product administration. Handwritten diagrams of anesthesia and extracorporeal perfusion were also examined to retrieve demographic and somatometric data, patient's comorbidities and duration of extracorporeal circulation and cross-clamp times. A search in the Hematology laboratory information system provided data on full blood counts at the preoperative and the immediate postoperative phase, when the patients were admitted in the cardiac intensive care unit (CICU). Patients for whom we could not retrieve all the above data were excluded from the study.

Retrieved comorbidity data were hypertension (on chronic anti-hypertensive treatment), chronic obstructive pulmonary disease (COPD; as per EuroSCORE II[6]), pulmonary hypertension (moderate or severe, as per EuroSCORE II), prior cerebrovascular accident (with either permanent or resolved disability or transient ischemic attack), heart failure [HF; either chronic heart failure (CHF) on treatment or preoperative acute pulmonary edema, or use of inotropes], peripheral arteriopathy (as per EuroSCORE II), kidney dysfunction (creatinine clearance <85 ml/kg/min or on dialysis), diabetes mellitus (either on anti-diabetic medication or insulin treatment for at least one month), hyperlipidemia (blood cholesterol >200 mg/dL and/or triglycerides >150 mg/dL or on statin treatment). The term "other comorbidities" included: hyperlipidemia, thyroid disease, cancer, and any other comorbidity.

Perioperative blood product counts refer either to the intraoperative or the postoperative period but not the preoperative period. Platelet concentrates were only dispensed and reported in the form of single units. Because we were interested in investigating the effect of blood product transfusions on mortality and in contrast to the Universal Definition of Perioperative Bleeding (UDPB)[7], we did not omit RBC transfusions that were administered to treat anemia and not for active bleeding treatment. Thus, PTC-0 corresponds to no blood product transfusions; PTC-1 corresponds to the transfusion of less than five blood product units in total (either RBC or FFP or PLT additively); PTC-2 corresponds to five to 10 units, and PTC-3 corresponds to more than ten blood product units transfused perioperatively.

Statistical analysis

Statistical analysis was performed using the chi-square test to compare mortality rates. The normal distribution of data was tested (f test) and a Student's t-test with unequal variances was used in normally distributed variables' data, whereas a Mann-Whitney U-test was utilized if variances would be shown to differ significantly. Due to the lack of a power analysis sample size calculation, we applied a *post hoc* power analysis to evaluate the statistical strength of the results. Subsequently, receiver operator characteristics curve analysis (ROC) was used to identify cutoff points for blood product units that could reasonably predict mortality. Statistical significance was set to p <0.05. Statistical analyses were performed in IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, USA) version 23 and Microsoft Excel Data Analysis Tool (Microsoft Corp., Seattle, WA, USA) while *post hoc* analysis was performed with ClinCalc LLC, online statistic calculators (http://clincalc.com/Stats/Power.aspx).

Results

There were 565 cardiac surgery patients with complete data (141 patients were excluded due to incomplete data retrieval), who underwent cardiac surgery (Figure 1). Demographic data and co-morbidities are presented in Table 1. Studied patients underwent CABG either using extracorporeal circulation (on-pump) or with a beating heart (off-pump), heart valve replacement or repair, or mixed operations (also including ascending aortic aneurysm excision and grafting, Table 1). In all samples, hemoglobin, hematocrit, and platelet count values presented a normal distribution. The total number of units of RBC, FFP or PLT transfused were also normally distributed.

Hemoglobin and hematocrit counts

Only a few patients had severe anemia on the day of surgery [36 patients, 6.3 % with hemoglobin (Hb) values between 7 and 9.5 g/dL]. Postoperatively, 41 patients (7.2 %) were admitted to the Cardiac Intensive Care Unit (CICU) with Hb values of less than 8 g/dL. Another 99 patients (17.5 %) were admitted to the CICU with Hb between 8 and 10 g/dL (Table 2).

Platelet counts

Overall, 62 patients (10.9 %) entered the operating room with low platelet counts (<140 x 10^3/mm^3). At admission to the CICU, 117 patients (20.7 %) had a platelet count of <100 x 10^3/mm^3, and 19 of them (3.3 % of the total) had a platelet count of <55 × 10^3/mm^3 (Table 2).

Magnitude of transfusions

Almost all our patients (99.5 %) were transfused perioperatively with some blood products (Table 1). Based on the transfusions they received, patients were assigned to the following classes: PTC-0, n =3 (0.5 %); PTC-1, n =81 (14.3 %); PTC-2, n =132 (23.4 %); and PTC-3, n =349 patients (61.8 %).

Mortality

During hospitalization, 66 patients died (periopera-

Table 1: Demographics, somatometric and operations data, comorbidities and perioperative transfusions data of the 565 consecutive cardiac surgery patients with complete data who were enrolled in the study.

Parameter	*Mean ± SD, range*	*Co-morbidities*	*% (n)*
Males / Females (%)	77.7 / 12.3	**Arterial Hypertension**	53.3 (301)
Age (years)	69.2 ± 10.8, 28-92	**COPD**	7.3 (41)
Weight (kg)	76.7 ± 13, 45-117	**Pulmonary hypertension**	1.1 (6)
Height (meters)	1.66 ± 0.09, 1.39-1.91	**Cerebrovascular accident**	3.5 (20)
BMI (Kg/m²)	27.7 ± 4.3, 18.1-43.6	**HF**	1.8 (10)
BSA (m²)	1.83 ± 0.20, 1.21-2.50	**Arteriopathy**	7.8 (44)
Extracorporeal circulation (min)	143 ± 57, 45-399	**Hyperlipidemia**	44 (251)
Aortic Cross-clamp (min)	106 ± 193, 23-773	**Diabetes mellitus**	6.0 (34)
		Renal dysfunction	5.4 (31)
		Other comorbidities	11.7 (66)
Parameter	*% (n)*	*Perioperative transfusions*	*Blood product units Mean ± SD (median)*
CABG "on pump"	56.3 (318)	**RBC**	5.8 ± 4.5 (5.0)
CABG "off pump"	10.7 (128)	**FFP**	5.0 ± 4.7 (4.0)
Valve surgery, % (n)	22.7 (61)	**PLT**	8.0 ± 6.7 (5.0)
Mixed operations, % (n)	10.3 (58)		

n: number, SD: standard deviation, BMI: body mass index, BSA: body surface area, CABG: coronary artery bypass grafting, COPD: chronic obstructive pulmonary disease, HF: heart failure, RBC: red blood cells, FFP: fresh frozen plasma, PLT: platelets.

Table 2: Hemoglobin, hematocrit and platelet counts in the preoperative as well as the immediate postoperative period and at hospital discharge together with extracorporeal circulation and aortic cross-clamping time.

PTC class		Hb PRE	Hb CICU	Hb DISC	Hct PRE	Hct CICU	Hct DISC	Plt PRE	Plt CICU	Plt DISC	Time on ECC	Time of ACX
	Mean	13.9	11.2	13.0	42.1	33.9	40.5	222	161	301	1:50:00	1:29:20
	SD	0.9	1.6	3.0	3.2	3.3	6.2	45	96	83	0:21:47	0:22:30
0	Median	14.0	10.7	12.3	43.5	32.9	39.4	239	120	270	2:00:00	1:37:00
	Minimum	12.9	10.0	10.4	38.4	31.0	34.9	171	92	237	1:25:00	1:04:00
	Maximum	14.7	13.0	16.3	44.3	38.0	47.1	257	271	395	2:05:00	1:47:00
	Mean	13.3	10.3	10.9	40.0	31.0	33.4	210	141	228	2:18:46	1:37:04
	SD	1.9	1.5	1.5	5.3	4.4	4.2	55	45	103	0:51:51	0:43:09
1	Median	13.6	10.3	10.8	40.3	31.4	32.7	214	134	221	2:11:00	1:31:45
	Minimum	7.8	7.0	5.7	24.0	21.0	22.0	89	63	12	0:45:00	0:24:00
	Maximum	18.0	14.0	15.4	53.0	43.0	45.1	381	255	499	5:30:00	3:52:00
	Mean	13.3	10.3	11.1	39.9	30.7	33.4	233	141	215	2:20:17	2:08:43
	SD	1.9	1.6	1.6	5.3	4.5	4.7	71	51	98	0:59:42	6:26:21
2	Median	13.5	10.3	10.9	40.4	30.4	32.8	220	141	208	2:09:00	1:24:20
	Minimum	7.1	6.0	5.9	21.7	19.0	17.1	43	43	14	0:53:00	0:26:00
	Maximum	18.3	14.0	16.1	53.5	41.0	47.0	487	372	546	6:32:59	72:00:00
	Mean	13.0	10.2	10.9	39.1	30.5	33.2	234	145	234	2:26:37	1:39:54
	SD	1.8	1.6	1.6	4.8	4.7	4.7	78	54	123	0:57:48	0:46:26
3	Median	13.2	10.2	10.8	39.6	30.5	32.9	222	140	227	2:13:48	1:31:00
	Minimum	7.5	6.0	6.3	21.3	17.0	20.2	34	28	10	0:00:00	0:00:00
	Maximum	17.5	14.0	16.8	51.1	43.0	49.1	628	375	832	6:39:00	6:07:00
	Mean	13.2	10.3	11.0	39.5	30.6	33.3	231	144	229	2:23:43	1:46:25
	SD	1.9	1.6	1.6	5.0	4.6	4.7	74	52	115	0:57:20	3:14:10
Total	Median	13.3	10.3	10.8	39.8	30.6	32.9	219	139	221	2:11:32	1:28:56
	Minimum	7.1	6.0	5.7	21.3	17.0	17.1	34	28	10	0:00:00	0:00:00
	Maximum	18.3	14.0	16.8	53.5	43.0	49.1	628	375	832	6:39:00	72:00:00

PTC: perioperative transfusion class, Hb: hemoglobin, PRE: preoperative, CICU: cardiac intensive care unit, DISC: at discharge, Hct: hematocrit, Plt: platelet count, ECC: extra corporeal circulation, ACX: aortic cross clamping.

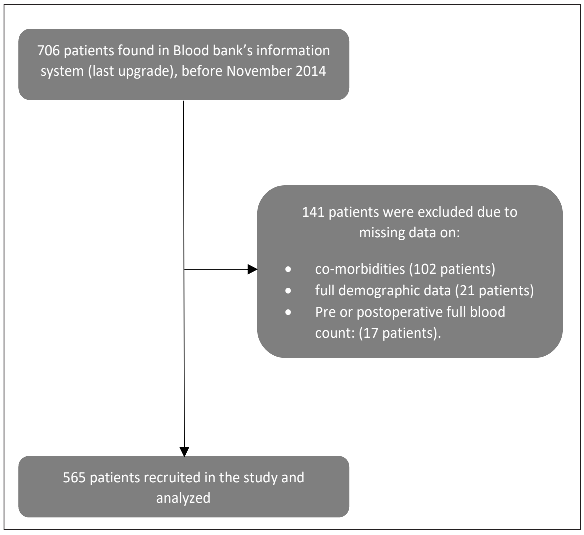

Figure 1: Recruitment of the 565 consecutive cardiac surgery patients with complete data who were enrolled in the study.

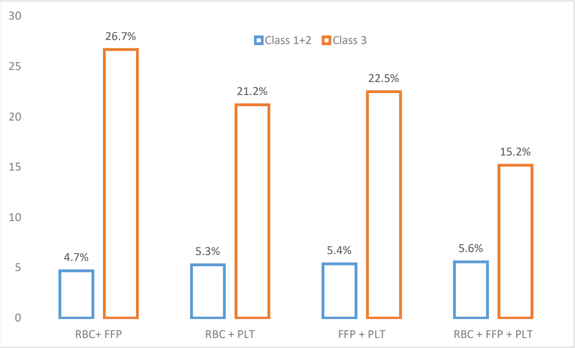

Figure 2: In hospital mortality rates according to the combination of blood products transfused. Mortality in patients who received ≤10 units (Class 1 + 2) vs >10 units (Class 3) of various combinations of blood products.

tive mortality: 11.7 %). Five patients died during surgery from intractable bleeding. Among the 61 patients who deceased in the CICU (CICU mortality: 10.8 %), eight patients died from intractable bleeding within the first six postoperative hours (1.4 % of total, 13.1 % of those who died); four because of irreversible arrhythmia (0.7 % of total, 6.5 % of those who died); five had a perioperative myocardial infarction and succumbed to acute heart failure (0.9 % of total, 8.2 % of those who died), and 44 died after the first 72 hours in the CICU because of multiple organ dysfunction syndrome (MODS) or respiratory failure (8.1 % of total, 72.1 % of those who died).

Mortality rate according to PTC class

Mortality rates were significantly different among PTC classes: PTC-1: 6.2 %, PTC-2: 5.3 %, and PTC-3: 15.2 % (p =0.002). Patients in PTC-0 had a mortality rate of 33 % because one of the three patients in this class died intraoperatively from a ruptured ascending aorta aneurysm before receiving any blood product transfusion. Thus, the PTC-0 class was excluded from further data analysis.

Patients transfused with >10 units of blood products (i.e., patients in PTC-3 vs PTC-1 + PTC-2) had an increased mortality rate compared with those transfused with ≤10 units (15.2 % vs 5.6 %, p =0.001; *post hoc* power, 95.3 %; Figure 2).

Further analysis revealed that any combination of two different blood products (RBC, FFP or PLT) was associated with an increase in patient's mortality when exceeding a certain number of units. Patients transfused with >10 units of RBC + FFP irrespective of PLT, had an increased mortality rate compared with those transfused with ≤10 units (26.7 % vs 4.7 %, p <0.0001; *post hoc* power, 100 %; Figure 2).

Patients transfused with >10 units of RBC + PLT irrespective of FFP, had an increased mortality rate compared with those transfused with ≤10 units (21.2 % vs 5.3 %, p <0.0001, *post hoc* power, 99.4 %; Figure 2).

Patients transfused with >10 units of FFP + PLT irrespective of RBC, had an increased mortality rate compared with those transfused with ≤10 units (22.5 % vs 5.4 %, p <0.0001, *post hoc* power, 100 %; Figure 2).

Mortality rate according to blood product type

Patients who received more than five units of RBC or FFP had a significantly increased mortality rate compared with those who received equal or less than five units (RBC, 23.9 % vs 4.5 %, p <0.001, *post hoc* power analysis, 100 %; FFP, 27.4 % vs 6 %, p <0.0001, *post hoc* power analysis, 100 %; Figure 3).

Patients who received ten or more units of PLT had a significantly increased mortality rate compared with those who received less than ten units (24.5 % vs 8.5 %, p <0.0001, *post hoc* power analysis, 98.3 %; Figure 3).

By plotting the ROC curve, our data pointed that a transfusion of five units of RBC received perioperatively (cutoff value: 5.5 units of RBC) had a sensitivity of 74.2

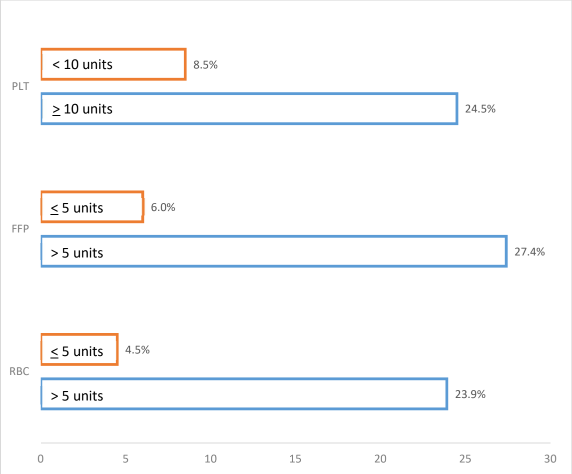

Figure 3: In hospital mortality rates according to the number of blood products transfused.

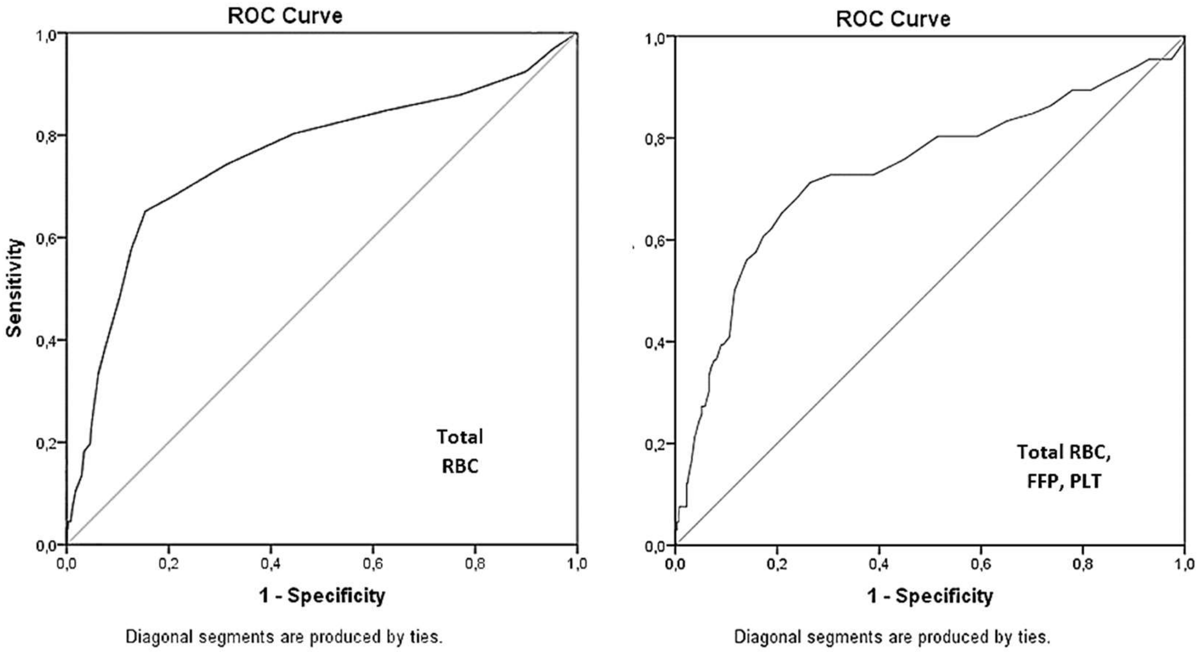

Figure 4: Receiver operator characteristics curve (ROC) for "Total red blood cells (RBC) received perioperatively" (left) and "Total RBC, fresh frozen plasma (FFP), platelets (PLT) received perioperatively" (right) as predictors of perioperative death.

% and a specificity of 68.7 % for identifying patients that would die during hospitalization [Area under the ROC curve (AUCROC): 0.756, p <0.001, Figure 4, left]. Given that 35.5 % of our patients (200 out of 562) received more than 15 units of either RBC, FFP or PLT additively and in 65 % of them (130 out of 200 patients), half of the units were PLTs, the administration of this amount of blood products (cutoff value 15.5 units) has a sensitivity of 72.7 % and a specificity of 69.5 % for identifying those that would die perioperatively (AUROC: 0.735, p <0.001, Figure 4, right).

Mortality rate according to the operation type

The mortality rate was also significantly different among different operations (p =0.0004). Off-pump CABG surgery (n =61) had the lowest associated mortality rate (8.2 %; n =5). On-pump CABG surgery (either single or two-, three- or four-vessel disease, n =319) was associated with a mortality rate of 9.7 % (n =31). Patients who underwent single valve surgery [Aortic valve replacement (AVR), Mitral valve replacement (MVR), Mitral valve repair (MVr); n =125) had a mortality rate of 10.4 % (n =13). Among patients who underwent major cardiac surgery (valve + CABG, two-valve surgery, aorta surgery, Bentall procedure), 17 of 60 patients died (28.3 %). Patients who died after having either major surgery or on-pump CABG or a single-valve operation were transfused with more RBC (12 vs 6 units, p =0.018, 10 vs 5 units, p =0.0001, and 9 vs 6 units, p =0.009, respectively) compared with those who survived these operations. In off-pump patients, the difference was not significant (p =0.156).

Discussion

Transfusion strategies differ considerably between countries and even between cardiac centers in the same country[8,9]. The most recent guidelines and clinical directives advocate restrictive transfusion policies that are supported by widely accepted techniques of blood conservation[10-13]. Generally, countries that implement patient blood management protocols tend to present significantly lower transfusion rates compared with those that do not use such protocols[8].

Frequency and volume of transfusion.

In the present study, most of the studied patients (99.5 % of the patients) were transfused with blood products perioperatively, which is only consistent with earlier studies in cardiac patients[14,15] and in contrast to percentages around 50 % which seems to be the commonest figure of transfusion rates in current cardiac surgery practices[16]. A large percentage of our patients (86.2 %) received more than two units of FFP intraoperatively, and 62 % received either two or four units of FFP intraoperatively (only 61 patients received no FFP). Three hundred and seventy-five patients (n =375, 66.4 %) received more than one unit of platelets, and 45 % received five units of PLTs intraoperatively (186 patients received no PLT intraoperatively). These data indicate high conformity with the standard order of blood products transfusion.

Multiple studies have revealed that blood product transfusion is associated with an increased, dose-dependent, perioperative morbidity and mortality rate[17-20]. Our results confirm that even a moderate amount of transfused blood products is associated with significantly increased perioperative mortality in cardiac surgery patients. In accordance with other studies, we showed increased mortality in patients receiving more than five units of RBC or FFP and ≥10 units of PLT and confirmed that low cutoff values for RBC, FFP or PLT (administered independently or additively) are associated with increased perioperative morbidity and mortality[2,18].

Given that preoperative anemia is an independent predictor of postoperative morbidity and mortality in cardiac surgery[21] and perioperative anemia might also be harmful, it seems that the ideal balance between anemia and inappropriate transfusion risk has not been definitely determined[22]. Based on current studies that compare restrictive to liberal strategies, judicious use of transfusion triggers for restrictive policies to the era of 7.5-8 g/dL is at least non-inferior to liberal practices and can probably safeguard against increased morbidity and mortality rates[16,23,24].

Our study has confirmed that increased mortality is associated with FFP administration of more than five FFP units perioperatively. Despite other publications[25], a recent study and a systematic review did not confirm increased mortality associated with FFP administration in cardiac surgery[26,27].

Platelet administration is not consistently shown to correlate significantly with increased mortality[28-30]. In our study, the increased mortality rate associated with a cutoff point of ten units of PLT was confirmed, irrespective of the administration of RBC and FFP.

In our analysis, all possible combinations of two blood products showed an increased mortality rate when administered in quantity of more than ten units. This result denotes a significant mortality effect of all blood products in our patients and challenges the safety of the "transfusing by standard orders" attitude.

All recent transfusion guidelines, based on the best evidence in the literature, advocate the use of appropriate monitoring of oxygen delivery and availability, hemostatic mechanism effectiveness, and modifications of preoperative contributors to perioperative transfusions to decrease avoidable transfusion hazards and potentially abolish transfusion-related mortality[10-13]. We are currently working on the implementation process of comprehensive, protocol-driven transfusion orders, justified by laboratory or bedside monitoring that will probably reduce the contribution of transfusions to our center's mortality rate.

There are some limitations related to the design of the current study. Its retrospective nature may have incorporated undisclosed bias and hidden confounding factors that cannot be eliminated *a posteriori*. Due to lack of data, we could not determine the post-discharge mortality of the patients studied, to examine the temporal aspect of the presumed over-transfusion approach on long-term mortality. Similarly, we could not retrieve data on perioperative blood losses, end-organ oxygen availability and coagulation parameters that would help us to comment on the necessity to administer blood product transfusions. Even though we retrieved data on most of the Euroscore II contributing factors, we could not recover the EuroScore II classification of our patients in order to present each patient's predicted mortality risk.

In conclusion, our study recorded and revealed the "old school" techniques of perioperative transfusions that were dominant at our center during the study period. Transfusions of blood products driven by standard prescriptions are currently not satisfactory and may be associated with increased mortality risk. Isolated RBC and FFP administered in an amount of more than five units, and PLT (single units) or combined administration of RBC, FFP, or PLT in amounts of more than ten units are associated with increased mortality in cardiac surgery patients. Interventions that could alleviate this mortality effect should be addressed, and their impact should be appropriately re-evaluated.

Conflict of interest

There is no conflicting of interest for any of the authors concerning the presented data.

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