Rev Bras Cir Cardiovasc 2013;28(4):509-17

Mortality risk is dose-dependent on the number of packed red blood cell transfused after coronary artery bypass graft

Risco de mortalidade é dose-dependente do número de unidades de concentrado de hemácias transfundidas após cirurgia de revascularização miocárdica

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DOI: 10.5935/1678-9741.20130083

RBCCV 44205-1505

Abstract

Introduction: **Transfusions of one or more packed red blood cells is a widely strategy used in cardiac surgery, even after several evidences of increased morbidity and mortality. The world's blood shortage is also already evident.**

Objective: **To assess whether the risk of mortality is dose-dependent on the number of packed red blood cells transfused after coronary artery bypass graft.**

Methods: **Between June 2009 and July 2010, were analyzed 3010 patients: transfused and non-transfused. Transfused patients were divided into six groups according to the number of packed red blood cells received: one, two, three, four, five, six or more units, then we assess the mortality risk in each group after a year of coronary artery bypass graft. To calculate the odds ratio was used the multivariate logistic regression model.**

Results: **The increasing number of allogeneic packed red blood cells transfused results in an increasing risk of mortality, highlighting a dose-dependent relation. The odds ratio values increase with the increased number of packed red blood cells transfused. The death's gross odds ratio was 1.42 (*P*=0.165), 1.94 (*P*=0.005), 4.17; 4.22, 8.70, 33.33 (*P*<0.001) and the adjusted death's odds ratio was 1.22 (*P*=0.43), 1.52 (*P*=0.08); 2.85; 2.86; 4.91 and 17.61 (*P*<0.001), as they received one, two, three, four, five, six or more packed red blood cells, respectively.**

Conclusion: **The mortality risk is directly proportional to the number of packed red blood cells transfused in coronary artery bypass graft. The greater the amount of allogeneic blood transfused the greater the risk of mortality. The current transfusion practice needs to be reevaluated.**

Descriptors: **Blood transfusion. Mortality. Myocardial revascularization. Postoperative complications.**

Resumo

Introdução: **Transfusões de uma ou mais unidades de concen-**

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No financial support.

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Article received on September 1st, 2013
Article accepted on November 4th, 2013

Abbreviations, acronyms & symbols

AF	Atrial fibrillation
AMI	Acute myocardial infarction
CPB	cardiopulmonary bypass
CHF	Congestive heart failure
CKF	Chronic kidney failure
CABG	Coronary artery bypass grafting
DM	Diabetes mellitus
COPD	Chronic obstructive pulmonary disease
EuroSCORE	European System for Cardiac Operative Risk Evaluation
RBCT	Red blood cell transfusion
SAH	Systemic arterial hypertension

trado de hemácias é estratégia amplamente utilizada em cirurgia cardíaca, mesmo após várias evidências de aumento de morbimortalidade. A escassez de sangue no mundo também já é evidente.

Objetivo: **Avaliar se o risco de mortalidade é dose-dependente do número de unidades de concentrado de hemácias transfundidas após cirurgia de revascularização miocárdica.**

Métodos: **Entre junho 2009 e julho 2010, foram analisados 3010 pacientes: transfundidos e não transfundidos. Pacientes hemotransfundidos foram divididos em seis grupos conforme receberam uma, duas, três, quatro, cinco e seis ou mais unidades concentrado de hemácias e, após um ano da cirurgia de revascularização miocárdica, avaliamos o risco de mortalidade em cada grupo. Para obtenção do *odds ratio* foi utilizado modelo de regressão logística multivariado.**

Resultados: **Transfusão crescente de unidades de concentrado de hemácias resulta em risco também crescente de mortalidade, evidenciando uma relação dose-reposta. Os valores do *odds ratio* aumentam com o acréscimo do número de unidades de hemácias alogênicas transfundidas. O risco de ocorrência de óbitos pelo *odds ratio* bruto foi 1,42 (*P*=0,165); 1,94 (*P*=0,005); 4,17; 4,22; 8,70, 33,33 (*P*<0,001) e o risco de mortalidade pelo *odds ratio* ajustado foi 1,22 (*P*=0,43); 1,52 (*P*=0,08); 2,85; 2,86; 4,91 e 17,61 (*P*<0,001), conforme receberam transfusão de uma, duas, três, quatro, cinco, seis ou mais unidades concentrado de hemácias, respectivamente.**

Conclusão: **O risco de mortalidade é diretamente proporcional ao número de unidades de concentrado de hemácias transfundidas em cirurgia de revascularização miocárdica. Quanto mais sangue alogênico transfundido, maior o risco de mortalidade. A prática transfusional atual precisa ser reavaliada.**

Descritores: **Transfusão de sangue. Mortalidade. Revascularização miocárdica. Complicações pós-operatórias.**

INTRODUCTION

Blood transfusions are a widely used medical practice in cardiac surgery, due to the occurrence of massive bleeding in this setting [1]. In some hospitals, the red blood cell transfusion (RBCT) occurs indiscriminately reaching to, in some sites, a rate of 92.8% of the surgical patients [2]. This transfusional practice has led to a blood component shortage in the blood banks worldwide [3]. In Brazil, this situation has become increasingly critical, and the noticed trend is getting worse, since that a trial performed in 2007 [4] reported that the country's demand for blood grows at a rate of 1% while the offer grows at a range of 0.5% to 0.7% per year, thus indicating that in the near future we will have to get along with the possibility of no blood available for most medical procedures.

In the literature the relationship between RBCT and increased clinical complications after cardiac surgery is already strongly established, such as infections, chronic kidney failure (CKF), congestive heart failure (CHF), atrial fibrillation (AF), stroke [5,6] malignancies [7]. In the last decade, several studies have shown reduced survival after transfusion of packed red blood cells (PRBCs) [6,8,9], especially with massive transfusions [6,10]. As evidenced in a recent study (2013), the allogeneic blood transfusion is an independent predictor of early and late mortality after coronary artery bypass grafting (CABG) [9]. These evidences help physicians to increasingly adopt a restrictive behavior regarding the RBCT [11,12].

Some authors have reported a greater mortality rate with the transfusion of a single unit of PRBC either in general surgery [13,14] and cardiac surgery [6]. However, in 2012, it was published the ACUITY study [15] demonstrating that the higher mortality rate in patients underwent CABG becomes more significant only with the transfusion of four or more units of PRBCs.

Despite these data in the national and international literature, it is still not quite clear whether the greater risk of mortality related to RBCT is really a dose-dependent on the number of units of allogeneic red blood cell transfused. The aim of this study was to assess the impact on the risk of mortality in patients undergoing CABG after one year of the increasing number of PRBCs units transfused, compared to those patients not transfused.

METHODS

We have built an electronic database, where we prospectively included the data of all the patients aged 18 or older, who underwent CABG procedure in the Hospital Beneficência Portuguesa of São Paulo from June 2009 to July 2010, and with one year follow-up after the surgery. This database contains data from 3010 patients undergoing CABG, which contemplates 69.6% of the total performed surgeries. The data collection form presented 243 variables with data collected from all the fourteen Cardiac Surgery teams of the Institution. All the information was maintained confidential, including the patients' identity.

For the objective of this study, we performed a retrospective review of this database. The total sample consisted of 3004 patients because six of them did not complete the follow-up of at least one year. The patients were divided into two groups, patients who did not receive PRBC transfusion and the patients who received PRBCs transfusion. Then, the transfused patients were subdivided into 6 groups: Group A, B, C, D, E and F, as they received one, two, three, four, five and six or more PRBCs units, respectively, in the intra and or post-cardiac surgery. After one year of postoperative, it was calculated the mortality risk (*odds ratio*) for each one of the groups.

For this study were selected the following variables from the database: age, transfusion, smoking, diabetes mellitus (DM), dyslipidemia, systemic arterial hypertension (SAH), CKF, previous stroke, chronic obstructive pulmonary disease (COPD), peripheral arterial decease, cerebrovascular disease, CHF, acute myocardial infarction (AMI), arrhythmia, coronary intervention, previous coronary angioplasty, previous CABG, previous valvar surgery, previous non-cardiac surgery, elective or urgent/ emergency surgery, type of graft (arterial/venous), use of cardiopulmonary bypass (CPB), and CABG, isolated or associated with other surgeries.

The study was approved by the Research Ethics Committee of the Hospital Beneficência Portuguesa of São Paulo, under the protocol number 136.450.

Statistics considerations

All the variables were assessed descriptively. For the quantitative variables, this analysis was performed by observing the minimum and maximum values, and the standard deviations and median, for the calculation of means. For the qualitative variables it was calculated the absolute and relative frequencies.

To obtain death prognostic factors we used the regression logistic multivariate adjusted model [16], contemplating the variables that were showed in univariate previously performed, $P<0.10$: age $\geq$ 60 years, type of graft, isolated CABG, CHF, CKF, previous stroke, elective surgery, arrhythmia, previous CABG and previous valvar surgery, DM, previous myocardial infarction, use of CPB and number of PRBCs units transfused.

Through the stepwise selection process, the selected variables were the number of packed red blood cells, isolated CABG, age, CHF, CKF, previous stroke and COPD. The significance level used for the tests was 5%.

RESULTS

A total of 4,936 units of packed red blood cells were transfused in 1888 patients during their hospital stay, which corresponds to 62.8% of the patients who underwent CABG surgery. Of those, 1,155 patients (61.2%) were male patients and 733 (38.8%) female patients. The age ranged from 31 to 89 years with a standard deviation of 9.37 years and a median of 64.01 years. The demographics data and characteristics of the transfused patients assessed in the study are described in Table 1. The average number of packed red blood cells units transfused per patient was 2.6 ± 2.4 (1-25) units. The transfusions of one, two and three units of PRBCs were the most common frequencies of the blood units transfused: 33.1%; 32.3% and 14.4%, respectively. They account for approximately 80% of the transfused patients who received 3 or less units of allogeneic blood (Figure 1). The group receiving no RBCT showed a total of 1,116 patients.

Table 1. Demographic values and characteristic description of transfused patients.

Variable	Category	Descriptive values
Age (years)		64.0 ± 9.4
Smoking		274 (14.5%)
DM		738 (39.1%)
Dyslipidemia		835 (44.2%)
CKF		145 (7.7%)
SAH		1599 (84.7%)
Previous stroke		122 (6.5%)
COPD		158 (8.4%)
Peripheral arterial disease		109 (5.8%)
Cerebrovascular disease		28 (2.0%)
Coronary Intervention		190 (10.1%)
Previous CABG		35 (1.9%)
Previous valvar surgery		8 (0.4%)
Other surgeries		4 (0.2%)
Angioplasty		137 (7.3%)
Previous AMI		867 (45.9%)
CHF		62 (3.3%)
Arrhythmia		120 (6.4%)
Surgical indication	Elective	1865 (98.8%)
	Urgent	20 (1.1%)
	Emergency	3 (0.1%)
Graft type	Arterial	264 (14.0%)
	Venous	274 (14.5%)
	Venous + Arterial	1349 (71.5%)
CPB use		1724 (91.3%)
CABG	Isolate	1636 (86.7%)
	With heart surgery	109 (5.8%)
	With other surgeries	33 (1.8%)
	With valvar	110 (5.8%)

DM – diabetes mellitus; CKF – chronic kidney failure; SAH – systemic arterial hypertension; COPD – chronic obstructive pulmonary disease; CABG – coronary artery bypass graft; AMI – acute myocardial infarction; CHF – congestive heart failure; CPB – cardiopulmonary bypass

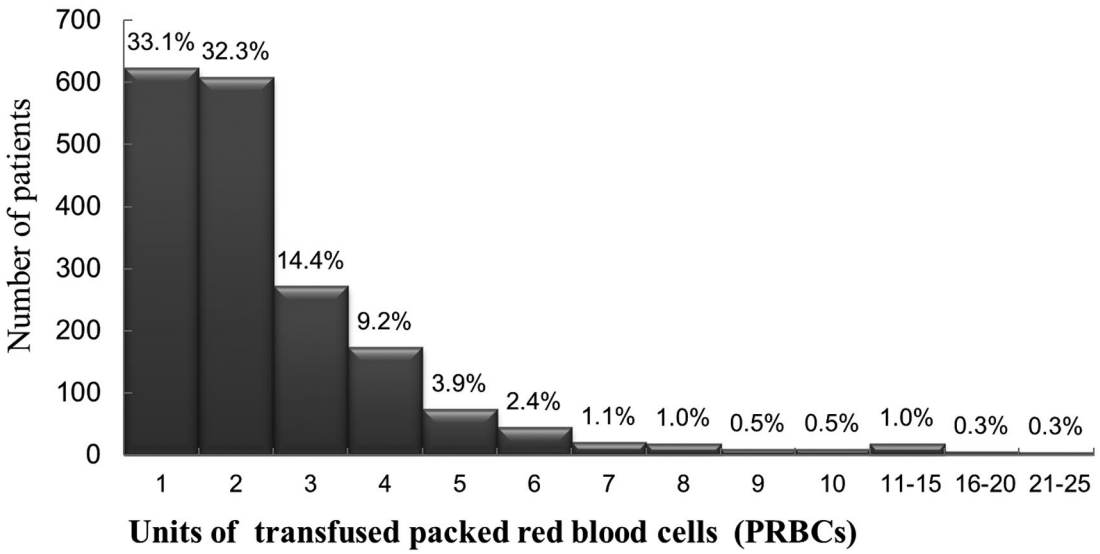

Fig. 1 - Frequency histogram of the packed red blood cells units transfused

The overall mortality rate within the transfused patients group, in the period of one year after surgery, was 11.2 % (212 deaths), compared to only 3.3% (37 deaths) among the patients who did not receive blood transfusions. It was found that there is an increasing mortality risk in the groups with increased number of allogeneic PRBCs units transfused. The group that received a single unit of PRBCs (Group A) showed a mortality risk of 4.6% (29 deaths). The group B (2 PRBCs) presented a mortality risk of 6.2 % (38 deaths). The mortality risk within the group C (3 PRBCs) and group D (4 PRBCs) was 12.5 % (34 deaths) and 12.6 % (22 deaths), respectively. Among the patients who received transfusion of 5 PRBCs (Group E) was observed a high mortality risk of 22.9% [17] of deaths. The negative impact of the allogeneic red blood cell transfusions became more evident within the group of 6 or more units of PRBCs (Group F), where occurred 72 deaths, which represents the death of more than half (53.3%) of the patients. The result of a multivariate regression model analysis confirms that the presence of red blood cell transfusion is an independent predictor of mortality in CABG surgery, increasing significantly the risk of death at one year (OR 2.31; 95% CI 1.33-4.04; *P*=0.003). Table 2 shows the other variables related to greater mortality: age, prior stroke, CKF, COPD, CHF, peripheral arterial disease, type of CABG (with other surgeries).

Through a logistic regression model, the *odds ratio* (OR) value was estimated for each one of the values of PRBCs units transfused in the univariate analysis. The risk of mortality progressively increases according to the number of packed red blood cells transfused in the patient. As shown in Figure 2, with a single unit of PRBCs transfused there is an adverse clinical outcome with a greater risk of mortality (OR 1.42; *P*=0.165). For the group that received two units of packed red blood cells, the risk of mortality was significantly greater with an *odds ratio* of 1.94 (*P*=0.005). The relationship between the risk of mortality and the number of units of allogeneic blood transfused becomes more evident when we analyze the other groups: Group C *odds ratio* of 4.17 (*P*<0.001); Group D *odds ratio* of 4.22 (*P*<0.001); Group E *odds ratio* of 8.70 (*P*<0.001); and finally, in the group that had received six or more units of packed red blood cells, we have a huge risk of mortality showing an *odds ratio* of 33.33 (*P*<0.001).

As observed in Table 3, even with the multivariate logistic regression adjusted model, the risk of mortality has also shown to be dose-dependent on the number of allogeneic PRBCs units transfused. The adjusted *odds ratio* values also increase according to the increase in the amount of packed red blood cells transfused. With one (group A) and two (group B) units of PRBCs it is also observed a greater likelihood of deaths occurrence, although not significant, yet with an *odds ratio* of 1.22 (*P*=0.435) and 1.52 (*P*=0.086), respectively. In the groups C, D and E, the risk of mortality has remained growing, with statistical significance, as exemplified by an *odds ratio* of 2.85 (*P*<0.001); 2.86 (*P*<0.001) and 4.91 (*P*<0.001), respectively. The group receiving six or more units of PRBCs transfused (Group F), resulted in a high risk of mortality with an *odds ratio* of 17.61 (*P*<0.001).

Figure 3 shows a curve which estimates the likelihood of death occurrence through the number of PRBCs units transfused. It is noted that the estimated probability of death within one year from the CABG increases progressively according to the amount of allogeneic blood transfusion, so

that, when eight units of PRBCs are transfused the patient's probability of death is 50%, and with the transfusion of 25 units of PBRCs the possibility of death is 100%.

In this study the risk of mortality has shown to be dose-dependent on the amount of allogeneic PRBCs units transfused after CABG surgery, being that, the higher the units of packed red blood cells transfused, the greater the risk of postoperative mortality at one year.

DISCUSSION

According to a study published in 2009 [17], about 85 million units of packed red blood cells are transfused annually, worldwide. This huge amount of blood used is still due to, among other factors, a 1942's concept when John Lundy published an article without scientific evidence and based only on his experience, showing that the hemoglobin level of 10 g/dL (10/30 rule) would be the lowest limit to be tolerated by humans without life-threatening, to recommend an allogeneic blood transfusion [18]. In fact, this behavior still persists in the medical community. Another factor that may explain the amount of blood transfusions performed in our study (4,936 units of packed red blood cells), is the study published in 2001 by DeFoe et al., where through a retrospective study, they found out that anemic patients (hematocrit below 22%), who underwent CABG surgery, were associated with greater operative mortality [19]. However, more recently that latter finding has been refuted, provide that, it has been demonstrated that even a hematocrit as low as 17%, in cardiac surgery, has not shown adverse impact on patients' outcome [12].

For over half a century, both in our country and in the world, it has not been questioned such transfusion practice. However, in 2002, Engoren et al. [8] published one of the first large studies questioning the real benefits of the transfusional therapy in the cardiac surgery setting. The researchers have shown that even after correction for comorbidities and other factors, the blood transfusions are associated with a 70% increase in mortality. In a recent study it was demonstrated that the RBCT is an independent predictor for both, 30 day mortality (OR 2.00; $P = 0.007$) and one year mortality (OR 2.31; $P = 0.003$), after CABG surgery. Even in low-

Table 2. Odds ratio values for the associated variables to 1 year mortality.

Variable	Category	Odds ratio	CI at 95% Lower limit	CI at 95% Upper limit	*P**
Age		1.07	1.04	1.09	< 0.001
Transfusion	No	1.00	-	-	-
	Yes	2.31	1.33	4.04	0.003
CKF	No	1.00	-	-	-
	Yes	2.98	1.65	5.38	< 0.001
Previous stroke	No	1.00	-	-	-
	Yes	3.11	1.79	5.40	< 0.001
COPD	No	1.00	-	-	-
	Yes	2.86	1.69	4.83	< 0.001
Peripheral arterial disease	No	1.00	-	-	-
	Yes	2.26	1.23	4.14	0.008
CHF	No	1.00	-	-	-
	Yes	4.26	2.12	8.56	< 0.001
CABG	Isolate	1.00	-	-	-
	With valvar	2.52	1.29	4.92	0.007
	With other cardiac surgeries	2.21	1.06	4.61	0.036
	With non-cardiac surgeries	2.54	0.87	7.44	0.089

*CI – confidence interval; CKF – chronic kidney failure; COPD – chronic obstructive pulmonary disease; CHF – congestive heart failure; CABG – coronary artery bypass graft; * probability's descriptive level of the logistic regression model*

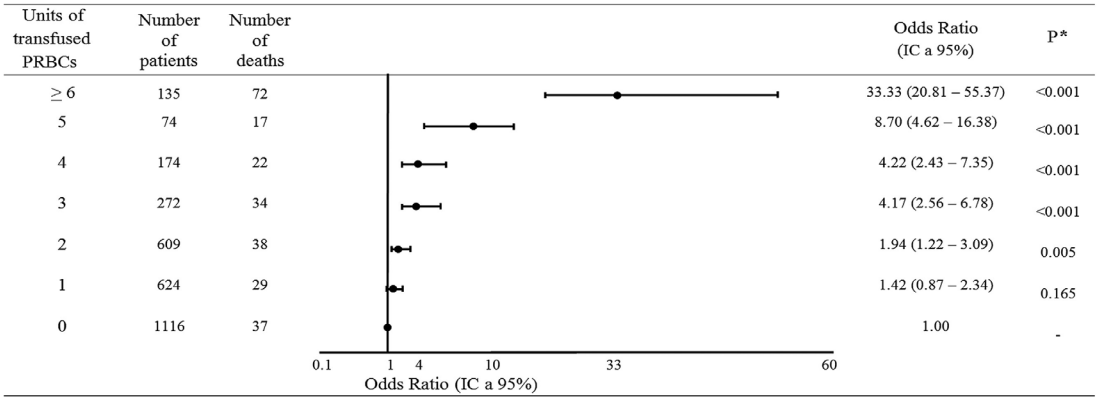

*Fig. 2 - Univariate relationship between units of transfused PRBCs and subsequent 1 year mortality. PRBCs – packed red blood cells; CI – confidence interval; * probability's descriptive level of the logistic regression model*

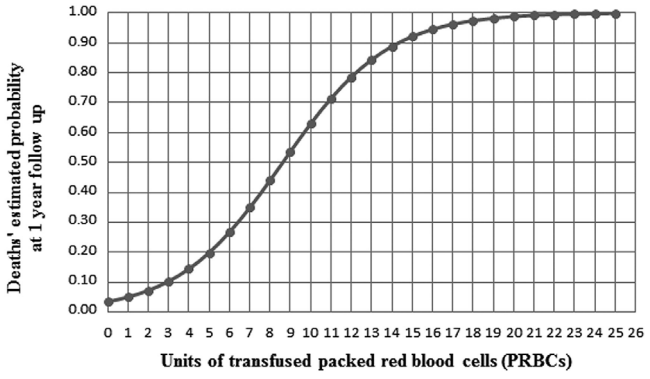

Fig. 3 - Estimated probability of death at 1 year of follow up with the number of units of PRBCs

risk patients (age <60 years and with EuroSCORE ≤ 2%), hence with fewer comorbidities, there were significantly more deaths in the transfused group within both periods 30 day (7.0% vs. 0.0%, *P*<0.001) and 1 year period (10.0% vs. 0.0%, *P*<0.001) [9]. Transfusions above four PRBCs units are associated with progressively greater mortality either in general surgery [13] and cardiovascular surgery [6,10,11,15]. In a prospective, randomized and controlled trial, it has become evident the increased mortality risk associated to the transfusions of 1-2, 3-4, 5-6 and > 6 units of packed red blood cells after cardiac surgery [11]. In the literature, there are other studies [15,20], which have also shown adverse clinical outcomes by the amount of PRBCs associated effect. Our study has shown the isolated adverse effect of every allogeneic PRBCs unit transfused in the patient's population after one year of CABG surgery.

In 2006, Koch et al. [6] by studying more than 5,000 transfused patients undergoing CABG surgery, concluded that every administered unit of PRBCs increases by 77% (OR 1.77; *P*<0.0001) the risk of post-operative mortality, thus showing a dose-dependent relationship between the amount of PRBCs units transfused and the survival's reduction. In 2012, Ferraris et al. [14] also demonstrated that there is a dose-response of adverse effects, including mortality, associated to the use of blood transfusions in 48,291 patients who underwent non-cardiac surgery. The authors have found that patients who received a single unit of PRBCs (31.4%) had presented greater morbidity and mortality, even after the use of propensity scores to control confounding variables. Similarly to the Koch et al. [6] studies, Stone et al. [15] have also found a dose-dependent relationship between the amount of PRBCs units transfused and the subsequent mortality. Although they have not observed the evidence of an impact on survival with transfusion of three or fewer units of PRBCs, Stone et al stated that one cannot rule out the occurrence of moderate adverse effect even with a smaller amount transfusion of blood.

The data from this study corroborate with those that have been published by Koch et al. [6] and Ferraris et al. [14], demonstrating a direct relationship between the amount of PRBCs transfused and greater risk of death occurrence. Furthermore, this study has demonstrated an association between PRBCs transfusions and increased mortality risk, even with a lower number of packed red blood cells units transfused, fact that was not observed by Stone et al., but found by Koch et al. [6] and Ferraris et al. [14].

It has been confirmed that the mortality risk increases with the amount of allogeneic pack red blood cells units transfused. With the transfusion of a single unit of PRBCs, an adverse clinical outcome is already demonstrated, with greater likelihood of death occurrence, showing an *odds ratio* of 1.42. However, with the transfusion of two units of PRBCs the mortality risk was significantly greater with an *odds ratio* of 1.94. This deleterious effect risk becomes more

significant as more units of PRBCs are transfused. Through the logistic regression model, we built a curve (Figure 3) to estimate the probability of death occurrence by using the number of PRBCs units transfused. It is observed that the mortality risk is progressively greater as the patient receives more allogeneic blood units.

The results of this study have shown that there is a dose-response relationship between the number of PRBCs transfused and the increased mortality risk even after the correction of comorbidities (Table 3). The adjusted *odds ratio* values increase with the increase on the number of packed red blood cells units transfused, starting at 1.22 level, for one PRBCs unit, and it gradually rises up to 4.91 (P<0.001), for five PRBCs units transfused. The group that received six or more units of packed red blood cells showed a high mortality risk with an *odds ratio* of 17.61 (P<0.001). The fact that we have not found statistical significance in groups A and B is believed to be related to the sample's size of our study (1888 transfused patients). As already mentioned, other studies were able to demonstrate statistical significance in the risk of mortality, with a single unit of PRBCs in a relatively larger patients' population undergoing blood transfusion [6].

The fact that most studies assessing the impact of blood transfusion on post-operative patient outcomes have a retrospective approach, and the concept that more severe ill patients receive more allogeneic blood, it becomes more difficult to establish a relationship between cause and effect. To establish whether a particular factor and clinical outcome is causal or merely an association, Austin Bradford Hill [21] proposed a set of nine criteria: strength of association, consistency, specificity, temporality, biological plausibility, coherence, experimental evidences, and analogy and dose-response. These criteria were employed to determine that the relationship between smoking and lung cancer is a causal relationship, since the completion of a randomized clinical trial would not be ethical for this purpose. The same approach applies to the case of blood transfusions. It would not be possible to conduct a randomized and placebo-controlled trial to assess the clinical effects of the increasing allogeneic transfusion of PRBCs. That makes the use of the Hill's criteria particularly interesting. A careful analysis on the relationship between the blood transfusion and the adverse clinical outcome based on the Hill's criteria, suggests that this is not just an association, but in fact, it is a cause and effect relationship. The data of this study corroborate to that conclusion.

Several studies have demonstrated that blood transfusions result in increased morbidity risk of AF, CKF, stroke, CHF, infections and malignancies [5-7], consequently, these pathologies contribute to the increased risk of both early and late mortality. The exact mechanisms in which the homologous blood transfusions lead to the morbidity and mortality are not fully known, and several explanations have been suggested. During the storage, the red blood cells undergo a series of chemical and structural changes, such as depletion of adenosine triphosphate, reduction of 2,3-diphosphoglycerate (2,3 DPG), and loss of elasticity. With only three hours of storage is already noted the nitric oxide's falling of bioactivity in the red blood cells, which would result in decreased oxygen delivery in the microcirculation, and hence, adverse clinical outcomes [22]. Another explanation is the similarity between blood transfusion and transplantation. According to Flohe et al. [23], as in transplantation, the

Table 3. Gross and adjusted odds ratio values for mortality risk.

	Gross			Adjusted		
	Odds ratio	CI at 95%	*P**	Odds ratio	CI at 95%	*P**
None PRBC	1.00	-	-	1.00	-	-
1 PRBC	1.42	(0.87; 2.34)	0.165	1.22	(0.74;2.03)	0.435
2 PRBCs	1.94	(1.22; 3.09)	0.005	1.52	(0.94;2.44)	0.086
3 PRBCs	4.17	(2.56; 6.78)	<0.001	2.85	(1.72;4.73)	<0.001
4 PRBCs	4.22	(2.43; 7.35)	<0.001	2.86	(1.60;5.09)	<0.001
5 PRBCs	8.70	(4.62; 16.38)	<0.001	4.91	(2.52;9.57)	<0.001
≥ 6 PRBCs	33.33	(20.81; 53.37)	<0.001	17.61	(10.65;29.13)	<0.001
Isolate CABG	0.26	(0.19; 0.36)	<0.001	0.44	(0.31;0.63)	<0.001
Age ≥ 60 years	2.78	(2.04; 3.80)	<0.001	1.91	(1.36;2.69)	<0.001
CHF	6.22	(3.87; 10.00)	<0.001	3.38	(1.92;5.96)	<0.001
CKF	4.48	(3.09; 6.49)	<0.001	2.23	(1.43;3.48)	<0.001
Previous stroke	2.62	(1.72; 3.98)	<0.001	2.37	(1.47;3.83)	<0.001
COPD	2.95	(2.03; 4.28)	<0.001	2.04	(1.32;3.15)	0.001

*PRBCs – packed red blood cells; CABG – coronary artery bypass graft; CHF – congestive heart failure; CKF – chronic kidney failure; COPD – chronic obstructive pulmonary disease; CI – confidence interval; * probability's descriptive level of the logistic regression model*

allogeneic transfusions may result in multiple inflammatory and immunological reactions. So, the greater PRBCs units transfused, the greater the charge of antigens injected into the patient's circulation. Thus, from one side we have the hemolytic reactions and the other, the even more critical, the immunomodulation [7]. Therefore, increasing transfusion units of homologous blood may result in increasing mortality risk, as it has been shown by our study.

It has still not known what is the lowest limit of hemoglobin and/or hematocrit that implies in life-threatening, to recommend a blood transfusion, without resulting in increased deleterious effects. Several strategies have been proposed to reduce allogeneic blood transfusions. Many of these measures involve optimizing the hematopoiesis; minimize the blood loss in surgeries; and mainly, to admit greater tolerance to anemia. A more restrictive approach to blood transfusion [12] can be well tolerated, and it has no adverse impact on the mortality. The acknowledgement of this fact would result in avoiding many unnecessary transfusions, since that, in most cases, is not the patient but the physician who does not tolerate the anemia. In another study it has become evident that a more conservative blood transfusion approach, in cardiac surgery with CPB, it does not alter the mortality rate among the groups of restrictive strategy (hematocrit $\geq$ 24%) and liberal strategy (hematocrit $\geq$ 30%) [11]. It is already known that patients with hematocrit below 40%, and need for cardiopulmonary bypass and multiple bypasses, have a greater likelihood to use blood in CABG surgery, therefore, to identify, treat and/or prevent these conditions will result in less use of blood products transfusion [20]. Souza & Braile [24] demonstrated that a hemoconcentration during the CPB associated to a reduced water balance, is also able to decrease the use of blood and plasma in cardiac surgery. Other interventions consist in the use of antifibrinolytic agents, such as epsilon-aminocaproic acid [25], making routine use of normovolemic hemodilution and total replacement of perfusate [26]. A study performed in patients undergoing CABG surgery without CPB, reported low rates of postoperative complications, less blood products transfusion, and lower mortality [27].

It is possible to reduce blood consumption by changing the transfusional practice. When you have the purpose and/or the multidisciplinary willingness (surgeons, physicians, anesthesiologist, and intensive care physicians) to manage and conserve the autologous blood, it is possible to perform complex cardiac surgeries, such as a cardiac retransplantation, without the use of allogeneic blood transfusion [28]. Worldwide medical centers seek to establish protocols to ration the use of blood and it has become a hospital's quality criteria to be pursued by the quality certifying agencies, such as the Joint Commission International [29]. Our study confirms the importance of achieving these goals by seeking treatment options to transfusion of blood products.

There are some limitations to our study. It is a retrospective study of a database; the blood transfusions performed on both intra- and postoperative settings did not have a hemoglobin minimum trigger, being the transfusions administered at the discretion of the patient's physician responsible for care; and the storage time of the PRBCs units transfused was not taken into account, however this study refers to the current situation of the hospitals in our environment. A final limitation is that we have not differentiated the blood transfusions given during and after surgery since intraoperatively transfusions, especially with CPB, are more triggered by hemoglobin or hematocrit levels, and not by the patient's clinical status. The advantages are: electronic database, which was filled out in a systematic way, and as well as the large number of assessed patients and the utilization of specific statistical methods to reduce the influence of confounding variables.

CONCLUSION

The mortality risk is dose-dependent on the number of allogeneic packed red blood cells units transfused after coronary artery bypass graft, therefore, as more units of PRBCs transfused, the greater the risk of postoperative mortality. It is a must to reassess the current transfusional practice and seek therapeutic options to blood products.

Authors' roles & responsibilities	
AAS	Literature research; database search, statistical analysis, analysis of results, writing of the manuscript, review of the manuscript
AGS	Database search, analysis of results; correction of the manuscript
RFP	Statistical analysis, review of the manuscript
JCMP	Bibliographic research, analysis of results, and review of the manuscript

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