

Impact on early and late mortality after blood transfusion in coronary artery bypass graft surgery

Impacto na mortalidade precoce e tardia após transfusão de hemácias em cirurgia de revascularização miocárdica

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DOI: 10.5935/1678-9741.20130003

RBCCV 44205-1436

Abstract

Objective: To assess the 30-day and 1-year mortality associated to the red blood cell transfusion after coronary artery bypass grafting surgery. This procedure has been questioned by the international medical community, but it is still widely used in cardiac surgery. Therefore, it is needed more evidence of this medical practice in our country.

Methods: We retrospectively analyzed 3,004 patients who underwent coronary artery bypass grafting surgery between June 2009 and July 2010. Patients were divided into two groups: non-transfused and transfused.

Results: The transfused group totaled 1,888 (63%) and non-transfused 1,116 (37%). There were 129 deaths in 30 days, with 108 (84%) in the transfused group and 21 (16%) in the non-transfused ($P<0.001$). One year mortality totaled 249 distributed in 212 (85%) among transfused patients and 37 (15%) in non-transfused ($P<0.001$). The adjusted odds ratio for mortality in patients transfused was 2.00 ($P=0.007$) in 30 days and 2.31 ($P=0.003$) in 1 year. Even in low risk patients (age < 60 years and EuroSCORE ≤ 2 points), and so with fewer comorbidities, both outcomes, 30 day and 1 year mortality were significantly higher in the transfused patients (7.0% vs. 0.0%, $P<0.001$) and (10.0% vs. 0.0%, $P<0.001$), respectively.

Conclusion: The perioperative red blood cell transfusions after coronary artery bypass grafting surgery increased significantly the 30-day and 1-year mortality, even after the adjustments for comorbidities and other factors. So, new therapeutic options and autologous blood management and conservation strategies should be encouraged to reduce blood products transfusions.

Descriptors: Blood transfusion. Mortality. Blood cells. Coronary artery bypass. Myocardial revascularization. Postoperative complications.

Resumo

Objetivo: Avaliar a mortalidade em 30 dias e em 1 ano associada à transfusão de glóbulos vermelhos após cirurgia de revascularização miocárdica. Esse procedimento já vem sendo questionado pela comunidade médica internacional, mas ainda é utilizado em grande escala em cirurgias cardíacas. Portanto, faz-se necessário mais evidência dessa prática médica em nosso meio.

Métodos: Analisamos retrospectivamente 3004 pacientes submetidos à cirurgia de revascularização miocárdica entre

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Article received on June 29th, 2012

Article accepted on July 30th, 2012

Abbreviations, Acronyms & Symbols

AF	Atrial fibrillation
CABG	Coronary artery bypass grafting
CPB	Cardiopulmonary bypass
EuroSCORE	European System for Cardiac Operative Risk Evaluation
HF	Heart failure
ICU	Intensive care unit
KF	Kidney failure
RBCT	Red blood cells transfusion

junho de 2009 e julho de 2010. Os pacientes foram divididos em dois grupos: Transfundidos e Não transfundidos.

Resultados: O grupo de pacientes transfundidos totalizaram 1888 (63%) e o grupo não transfundidos 1116 (37%). Foi observado 129 óbitos em 30 dias, sendo 108 (84%) no grupo transfundidos e 21 (16%) no grupo não transfundidos ($P<0,001$). Os óbitos em um ano totalizaram 249 distribuídos

em 212 (85%) hemotransfundidos e 37 (15%) sem transfusão ($P<0,001$). O odds ratio ajustado para mortalidade nos pacientes transfundidos foi de 2,00 ($P=0,007$) em 30 dias e 2,31 ($P=0,003$) em 1 ano. Mesmo em pacientes de baixo risco (idade <60 anos e com EuroSCORE $\leq 2\%$), portanto com menos comorbidades, temos significativamente mais óbitos no grupo transfundidos em 30 dias (7,0% vs. 0,0%; $P<0,001$) e também em 1 ano (10,0% vs. 0,0%; $P<0,001$).

Conclusão: A transfusão de glóbulos vermelhos após cirurgia de revascularização miocárdica aumenta significativamente a mortalidade em 30 dias e em um ano, mesmo após correção de comorbidades e outros fatores. Novas opções terapêuticas e estratégias de gerenciamento e conservação do sangue autólogo devem ser estimuladas para reduzir as transfusões de hemoderivados.

Descritores: Transfusão de sangue. Mortalidade. Células sanguíneas. Ponte de artéria coronária. Revascularização miocárdica. Complicações pós-operatórias.

INTRODUCTION

Blood transfusions are among the greatest scientific discoveries of medical history. Since the nineteenth century they are used on a large scale worldwide. In Brazil, for example, about four million units of blood and derivatives are transfused annually [1]. The reason for this clinical practice is that the anemic patients have adverse outcomes due to reduced capacity to transport oxygen to the tissues, and hence the replacement of red cells through transfusion could prevent these deleterious outcomes [2].

Other indications, such as getting volemic expansion and blood pressure restoration, have no scientific support [3]. However, as evidenced in the worldwide medical literature, the blood transfusions have been questioned for several reasons. Firstly, we still do not have a specific, safely and effectively hemoglobin level able to set the trigger to indicate a blood transfusion [4], moreover there is a huge discrepancy of its use among physicians and hospitals [5]. Another worrying factor is the increased risk of heart failure (HF) [6], atrial fibrillation (AF), kidney failure (KF), stroke, respiratory infection, severe sepsis, and longer hospital stays [7], in the postoperative cardiac surgery, besides the malignant diseases [8], potential transmission of 68 infectious agents [9], multiple organ failure [10].

But what really has concerned the medical community according to recent studies is the mortality increase in general [11] and cardiac surgery [6,12,13]. Another important factor is the reduction of blood donations, leading to blood bank stocks below than what would be the ideal in Brazil [14] and abroad [15].

Based on these findings the use of homologous blood has been proposed more narrowly in cardiovascular surgery [16]. Therefore, it is necessary to have more evidence of this medical practice in our country. Thus, the aim of this study is to assess the 30-day and 1-year mortality associated with the red blood cells transfusion (RBCT) after coronary artery bypass grafting (CABG).

METHODS

We performed a retrospective cohort study using data from the cardiac surgery service of the Beneficência Portuguesa Hospital of São Paulo. The CABG surgeries database is powered by 14 teams, composed of 3,004 patients who were followed-up during the period of June 8, 2009 to July 26, 2010.

For the study, were considered patients undergoing CABG with or without associated procedures, age ≥ 18 years; with no restriction on gender or race. We excluded patients who underwent any other surgery, including cardiac, without CABG.

The data collection form presented a total of 243 variables. For this study were assessed nine: age, gender, comorbidities, European System for Cardiac Operative Risk Evaluation (EuroSCORE), type of surgery, packed red blood cells transfusion, length of stay (in hospital and Intensive Care Unit - ICU), acquired comorbidities after surgery, and intraoperative and postoperative complications.

We present in Tables 1 and 2 the variables assessed in this study in each group.

Table 1. Mean values and standard deviation (for age) and absolute frequencies (%), according to group of death (30 days)

Variable	Category	Group		P
		30-days mortality (n=129)	No death (n=2755)	
Age		66,9 ± 9,6 51 (40)	61,7 ± 9,4 1099 (40)	< 0,001
Smoker	Former			
	No	59 (46)	1230 (45)	0,961
	Yes	19 (5)	426 (16)	
Transfusion		108 (84)	1676 (61)	< 0,001
DM		55 (43)	981 (36)	0,111
Dyslipidemia		39 (30)	1247 (45)	< 0,001
CKF		22 (17)	126 (5)	< 0,001
SAH		109 (85)	2271 (82)	0,564
Previous Stroke		10 (8)	137 (5)	0,161
COPD		16 (12)	168 (6)	0,004
Peripheral arterial disease		10 (8)	118 (4)	0,062
Cerebrovascular disease		5 (4)	41 (1)	0,052
Coronary intervention		13 (10)	301 (11)	0,762
Previous CABG		3 (2)	41 (1)	0,446
Previous valvar surgery		1 (1)	7 (0,3)	0,307
Other surgeries		0 (0)	3 (0,1)	1,000
Angioplasty		9 (7)	243 (9)	0,469
Previous AMI		52 (40)	1299 (47)	0,128
CHF		13 (10)	55 (2)	< 0,001
Arrhythmia		15 (12)	134 (5)	< 0,001
Surgical indication-Urgent		2 (2)	22 (1)	0,323
	Arterial	13 (10)	484 (18)	
Graft type	Venous	34 (26)	309 (11)	< 0,001
	Venous + Arterial	82 (64)	1961 (71)	
CPB use		8 (6)	337 (12)	0,039
	Isolate	89 (69)	2503 (91)	
CABG	With heart surgery	9 (7)	138 (5)	< 0,001
	With other surgeries	10 (8)	27 (1)	
	With valvar	21 (16)	87 (3)	

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

Table 2. Mean values and standard deviation (for age) and absolute frequencies (%), according to group of death (1 year)

Variable	Category	Group		P
		1-Year mortality (n=249)	No death (n=2755)	
Age		67,5 ± 9,1	61,7 ± 9,4	< 0,001
Smoker	Former	101 (40)	1099 (40)	0,749
	No	114 (46)	1230 (45)	
	Yes	34 (14)	426 (16)	
Transfusion		212 (85)	1676 (61)	< 0,001
DM		117 (47)	981 (36)	< 0001
Dyslipidemia		89 (36)	1247 (45)	0,004
CKF		44 (18)	126 (5)	< 0,001
SAH		214 (86)	2271 (82)	0,160
Previous Stroke		30 (12)	137 (5)	< 0,001
COPD		40 (16)	168 (6)	< 0,001
Peripheral arterial disease		28 (11)	118 (4)	< 0,001
Cerebrovascular disease		13 (5)	41 (1)	< 0,001
Coronary intervention		26 (10)	301 (11)	0,814
Previous CABG		6 (2)	41 (1)	0,278
Previous valvar surgery		1 (1)	7 (0,3)	0,500
Other surgeries		1 (1)	3 (0,1)	0,293
Angioplasty		18 (7)	243 (9)	0,393
Previous AMI		109 (44)	1299 (47)	0,307
CHF		28 (11)	55 (2)	< 0,001
Arrhythmia		31 (13)	134 (5)	< 0,001
Surgical indication-Urgent		6 (2)	22 (1)	0,024
Graft type	Arterial	32 (13)	484 (18)	< 0,001
	Venous	54 (22)	309 (11)	
	Venous + Arterial	163 (65)	1961 (71)	
CPB use		21 (8)	337 (12)	0,076
CABG	Isolate	180 (72)	2503 (91)	< 0,001
	With heart surgery	18 (7)	138 (5)	
	With other surgeries	15 (6)	27 (1)	
	With valvar	36 (14)	87 (3)	

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

The patients were divided among two groups: 1) transfused, patients who received one or more units of packed red blood cells during and / or after surgery, and 2) non-transfused.

We adjusted two models for assessing the mortality in these two groups: a model for 30-day mortality and another for the 1-year mortality.

Quantitative variables were described as means and standard deviations or medians, and qualitative variables by absolute and relative frequencies. For the data analysis in both groups we used the t-Student test and Mann-Whitney nonparametric test. For checking homogeneity between ratios we used the chi-square or Fisher's exact test.

To obtain mortality prognostic factors the multivariate logistic regression model [17] was used with "stepwise" variable selection process, based on variables that presented $P < 0.25$ in the univariate analysis. The significance level used for the tests was 5%.

This study was assessed and approved by the Ethics Committee in Research of the Hospital Beneficência Portuguesa of São Paulo, under N° 700-11, according to the Helsinki Declaration.

RESULTS

The group of transfused patients was 1,888 (63%) and non-transfused 1,116 (37%). There was a predominance of male patients (69.9%) and whites (84.6%) with mean age of 62.2 ± 9.5 years. The survival rate was 94.4% at hospital discharge (in four cases to another hospital) and only 0.2% (seven cases) of intraoperative death.

Firstly, we found that the RBCT proved to be a predictor of 30-day mortality. The adjusted odds ratio for 30-day mortality in transfused was 2 (95% CI 1.21 to 3.31, $P=0.007$). The study showed a total of 129 deaths in 30 days, with 108 (84%) in transfused group and 21 (16%) in non-transfused ($P < 0.001$). Thus, the transfusion group showed a significantly greater percentage of deaths in 30 days when compared to non-transfused (Table 3). On the other hand, we observed a mortality rate of 5.7%

in the group receiving RBCT, against only 1.9% deaths among non-transfused group ($P < 0.001$). So we have a risk reduction of 3.8%, which is equivalent to state that every 26 RBCT restrictions we avoid one death in 30 days. As shown in the Figure 1, the difference between the two groups became well evident when assessed the adjusted Kaplan-Meier survival curves of 30-day mortality ($P < 0.001$).

According to this study, the RBCT also showed to be a predictor of 1-year mortality. After a follow up period of 1 year deaths totaled 249 distributed in 212 (85%) in transfused group against 37 (15%) in non-transfused group ($P < 0.001$) (Table 3). The adjusted odds ratio for 1-year mortality after red blood cell transfusion was 2.31 (95% CI 1.31 to 4.04, $P=0.003$). So, we also observed differences between groups for RBC transfusion in relation to the presence of death at 1 year, being significantly higher in the transfused group. In terms of percentage, we observed a 1-year mortality rate of 11.2% in the group receiving RBCT against only 3.3% in non-transfused group ($P < 0.001$). Thus, we have a reduced risk of 7.9%, which is equivalent to say that, every 13 RBCT restrictions we avoid a death in one year.

Another data analysis in our study allows us to conclude that in both outcomes 30-day and 1-year, the non-transfused group presents significantly greater percentage of alive patients when compared to the transfused group (log-rank test $P < 0.001$), as shown in Figure 2.

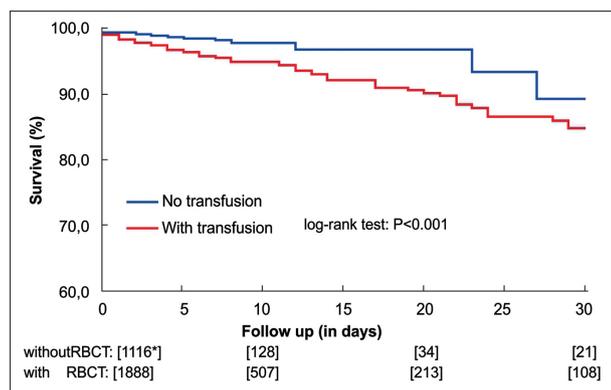
Even in low risk patients (expected mortality by EuroSCORE $\leq 2\%$) we have significantly more deaths within 30 days in the transfused group (5% vs. 1%, $P=0.007$). In one year we also observed survival reduction in patients with low euroSCORE in transfused group (7% vs. 1%, $P=0.001$) (Table 4). When we separate a specific group of younger patients (< 60 years) and EuroSCORE $\leq 2\%$, and hence less comorbidity, we also have significantly more deaths among transfused, as shown in Table 5.

Based on these results, our study objectively shows that the RBCTs are associated with a reduction, adjusted risk, on survival in patients undergoing CABG in both 30-day and 1-year outcomes.

Table 3. Association between transfusion and death at 30 days and 1 year

	Total	30-day Mortality	%	1-year Mortality	%	No Death	%
Non-transfused	1116	21	16	37	15	1079	39
Transfused	1888	108	84	212	85	1676	61
Total	3004	129	100	249	100	2755	100

30-day Mortality vs. No Death: chi-square test, $P < 0.001$; 1-year Mortality vs. No Death: chi-square test, $P < 0.001$



[*] Number of patients at risk at the time of evaluation; RBCT – red blood cell transfusion.

Fig. 1 – Kaplan-Meier survival curve in the study of death at 30 days (y-axis starts at 60%)

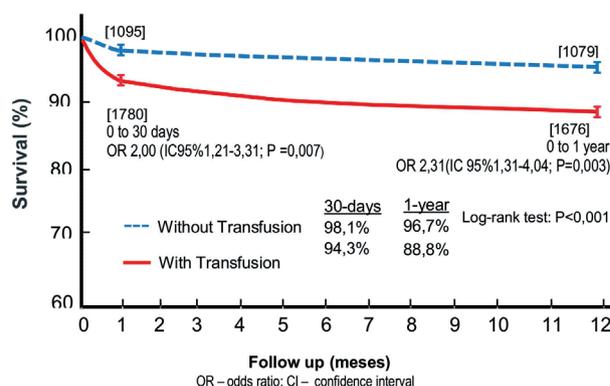


Fig. 2 – Adjusted survival risk after coronary artery bypass grafting (y-axis starts at 60%)

Table 4. Mortality study in patients with low risk (EuroSCORE ≤ 2)

Mortality	Transfused		P*
	No (n=308)	Yes (n=317)	
30-days	1 (1%)	14 (5%)	0,007
1-year	3 (1%)	22 (7%)	0,001

(*) descriptive level of the chi square probability

Table 5. Mortality study in patients with low risk (EuroSCORE ≤ 2) and age less than 60 years

Mortality	Transfused		P*
	No (n=188)	Yes (n=154)	
30-days	0 (0,0%)	11 (7%)	< 0,001†
1-year	0 (0,0%)	15 (10%)	< 0,001‡

* significant difference; † descriptive level of the Fisher's exact test probability.

‡ descriptive level of the chi-square test probability.

DISCUSSION

The real purpose of the red blood cell transfusion is to maintain adequate tissue oxygenation. Blood is a living tissue that circulates through the body delivering oxygen and nutrients to all organs. The blood has its classification into groups with the presence or absence of an antigen on the red blood cells surface. Although the ABO and Rh groups (positive and negative) are the most important, there are countless others. A transplant is the transfer of cells, tissues or organs from a living individual (donor) to another (recipient) with the aim at restoring a lost function. Thus, we can say that blood transfusions are the most common type of transplantation [18]. As it occurs with any

transplant, there is an acute immune reaction and it also occurs in long term.

We have evidence to support a role of immunomodulatory effect on the transfusion with changes in the blood cells (such as a reduction in the number of circulating lymphocytes, modification in T-cells and activation of immune cells) [19]. The cardiac surgery related traumas together with RBCTs promote a noninfectious inflammatory response reflected by an increase in the inflammatory mediator concentrations. In these circumstances cytokine levels are very high. Other limitations in respect to the blood transfusions is related to the stored blood that have a reduced tissue oxygen delivery and as the storage time increases, the

red cells undergo to cellular, biochemical, hormonal and inflammatory structural changes, resulting in the inability of the stored blood to perfuse the microcirculation [20]. Recently, a study reported an association between blood transfusions and the pulmonary coagulation activation, as well as intraoperative thromboembolic complications [11]. These and other still unknown factors, respond largely the negative outcomes associated with blood transfusions, specifically the early mortality of patients undergoing CABG.

This study showed that the death risk presented a most influential early impact of the blood transfusion for the first 30 days after surgery, as we can see by comparing the survival curves (Figures 1 and 2). When assessing the graphs it is possible to observe an association between the RBCT and reduced survival, statistically and significantly different, from those who did not receive a RBCT at 30 days ($P < 0.001$). The RBCT effect on the risk of early mortality (first 6 months after surgery) was also found by Koch et al. [13]. Thus, though, an analysis of survival curve in one year it is also possible to observe higher mortality among the transfused group (Figure 2).

The long-term mortality related to red blood cell transfusions is still speculative. Some of the mechanisms responsible for this effect would be the systemic inflammatory response and the immunomodulation [19]. But, we also can state that comorbidities (such as: HF, AF, stroke, KF, infectious agents transmission, pulmonary thromboembolism, and other malignancies) [6-11], caused by the transfusions also influence the late mortality.

The higher early mortality increase is believed to be related with cardiopulmonary dysfunction, and as well as the infections increase, higher inflammatory response, and the transfusion immunomodulatory effect.

With respect to different response we found with a large increase in short term mortality, and then, a sustained increase in long-term mortality in transfused patients, suggesting two distinct processes. One of these processes is the hypothesis that a transfused patient is sicker. However, the increased mortality, also in long term, discards the argument that transfusion is an indicator of hospitalized patients (Figure 2). Other information from our study, contrary to the idea that the higher mortality after a RBCT is due to the patient's more severe condition, was provided by the EuroSCORE calculation, a simple and objective index, but it has been shown as a satisfactory predictor of mortality in patients undergoing CABG [21]. When we have an EuroSCORE $\leq 2\%$, the mortality is low, but in our study when we provide RBCT the death risk increased significantly in both at 30-day and 1-year mortality (Table 4). Interestingly, when we have patients younger than 60 years and an EuroSCORE $\leq 2\%$, and so with fewer comorbidities and/or aggravating risk factors for heart

surgery, we had no deaths in the non-transfused group (Table 5), unlike the group that received RBCT, where we had a significant mortality, in both early and late period. It is known that intraoperative allogeneic transfusion, which is usually based on hemoglobin levels and not on the patient's clinical status (symptoms and signs), is also a risk factor for the increased mortality [12]. Thus, we can state that the blood product transfusion is not necessarily an indicator factor of sicker patient, but it is an independent factor of early and late mortality.

The potential adverse influence of blood transfusions on early and long term survival is indeed alarming, as was also demonstrated by Kuduvali et al. [22]. Our findings were also evidenced by Michalopoulos et al. [23], which reported an independent association of blood transfusions with early and late mortality after CABG.

Engoren et al. [12] also studying the effects of blood transfusions in patients undergoing CABG alone, also reported that transfused patients had twice the mortality of non-transfused. Even after the adjustment for comorbidities and other factors, the blood transfusion was still independently associated with an increase of 70% in mortality.

Other authors also reported an association between RBCT and increased mortality in a series of clinical scenarios, both in cardiac and general surgery [6,11,12].

There is a global real need in making more decisions based on evidence, in relation to the RBCTs. The proposal to maintain certain hemoglobin level via blood transfusions has no strong support in the medical literature. Several randomized and controlled studies have shown that lowering the hemoglobin threshold for recommending a blood transfusion in cardiac surgery [16] and in critically ill patients [4] do not adversely affect patient outcome.

In 2010 was published a large study that identified a dramatic variability on RBCT rates (7.8% to 92.8%) in patients undergoing CABG in several hospitals [5], demonstrating thereby that is often the physician and not the patient who does not tolerate low hemoglobin and/or hematocrit levels during or after a surgery [24]. Researchers have found that a hematocrit level between 17% and 21% during CABG together with moderate hypothermia, are well tolerated and have no adverse impact on the outcomes. In our study, even within a single center (hospital) we also recorded a wide variation in blood transfusion rates. Among the fourteen teams that perform CABG, the team who most indicated transfusion had 85.7% of their patients receiving RBCT and that who less indicated transfusion had 54.1%. This demonstrates that blood products are still used on a large scale in our country, hence the relevance of this study that adds itself to several others in highlighting the adverse effects of this medical practice.

Various techniques and strategies to reduce the blood

use have been studied; one of these is the blood products during cardiopulmonary bypass (CPB) associated with a reduced hydric balance, proposed by Souza & Braile [25]. Other proposed measures are the use of antifibrinolytic agent, aminocaproic acid [26], minimum use of CPB, especially in relation to its duration [27]. Others relevant care include preoperative patient meticulous assessment, implementation of intraoperative and postoperative measures for reducing blood loss and transfusion, active involvement of the surgeon, physician, anesthesiologist and intensivist, and as well as the use of algorithms for patients assessment and treatment, can significantly reduce transfusion need and prove to be lifesaving in cases of serious bleeding. This was evidenced by previous studies that reported a reduction of up to 50% in transfusion rates with the implementation of the cardiac surgery multidisciplinary protocols [28].

The tolerance of anemia in the perioperative period is one of the three main pillars of the blood conservation, and it does not increase the risk of complications and death in cardiac surgery [29]. Another important pillar is to optimize the erythrocyte mass by stimulating the red blood cell production through specific medication (ferrous sulfate, folic acid, vitamin B12, and erythropoietin). The third pillar, also equally important, involves the blood loss reduction by using all available resources such as electrocautery, argon beam coagulation, heparin-coated circuits, leukocyte filter, anti-fibrinolytic drugs, buffer fibrin glue, hemostatic agents, normothermia, induced hypotension, meticulous hemostasis, phlebotomy, acute normovolemic hemodilution [27], and especially the intraoperative cell salvage (cell saver).

The allogeneic blood is expensive, difficult to obtain, transport and store. The local and global shortages are imminence [14,15]. Currently, there are no demonstrated real benefits of blood transfusions, and adverse effects are increasingly described. Thus, alternatives to this procedure provide many advantages, and its use is likely to improve the outcomes, as the safer and more effective agents are developed. Therefore, they should be encouraged worldwide.

There are some limitations in our study. The first is that by being a retrospective database study, by its nature, we can only find associations between variables and outcomes, without however showing the causality. A second limitation is the fact that there was not a well-established rule for transfusion in both intra and postoperative period, and the transfusion triggers were dependent on the physician responsible for the patient. Another limitation is that we use all-cause of mortality as a final outcome, not differentiating causes of cardiac and non-cardiac death. A final limitation is that we have no data to differentiate transfusions, both from intraoperative

data to the postoperative period, since intraoperative transfusions, especially in surgery with CPB, are more triggered by levels of hemoglobin or hematocrit rather than patient's clinical status, and having added this parameter in our study probably would reinforce our conclusion.

CONCLUSION

The red blood cell transfusion after coronary artery bypass grafting surgery increases significantly the 30-day and 1-year mortality, even after the adjustment for comorbidities and other factors. Other therapeutic options and strategies for autologous blood management and conservation should be encouraged to reduce the transfusion need of blood products.

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