A liberal strategy of red blood cell transfusion reduces cardiogenic shock in elderly patients undergoing cardiac surgery

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ABSTRACT

Objective: The aim of this study was to compare outcomes in patients undergoing cardiac surgery who are aged 60 years or more or less than 60 years after implementation of a restrictive or a liberal transfusion strategy.

Methods: This is a substudy of the Transfusion Requirements After Cardiac Surgery (TRACS) randomized controlled trial. In this subgroup analysis, we separated patients into those aged 60 years or more (elderly) and those aged less than 60 years randomized to a restrictive or a liberal strategy of red blood cell transfusion. The primary outcome was a composite defined as a combination of 30-day all-cause mortality and severe morbidity.

Results: Of the 502 patients included in the Transfusion Requirements After Cardiac Surgery study, 260 (51.8%) were aged 60 years or more and 242 (48.2%) were aged less than 60 years and were included in this study. The primary end point occurred in 11.9% of patients in the liberal strategy group and 16.8% of patients in the restrictive strategy group ($P = .254$) for those aged 60 years or more and in 6.8% of patients in the liberal strategy group and 5.6% of patients in the restrictive strategy group for those aged less than 60 years ($P = .714$). However, in the older patients, cardiogenic shock was more frequent in patients in the restrictive transfusion group (12.8% vs 5.2%, $P = .031$). Thirty-day mortality, acute respiratory distress syndrome, and acute renal injury were similar in the restrictive and liberal transfusion groups in both age groups.

Conclusions: Although there was no difference between groups regarding the primary outcome, a restrictive transfusion strategy may result in an increased rate of cardiogenic shock in elderly patients undergoing cardiac surgery compared with a more liberal strategy. Cardiovascular risk of anemia may be more harmful than the risk of blood transfusion in older patients. (*J Thorac Cardiovasc Surg* 2015;150:1314-20)

Cardiogenic shock occurs in elderly persons after cardiac surgery when exposed to RBC transfusion. This study illustrates that elderly patients undergoing cardiac surgery, in contrast to younger patients, have a greater risk of cardiogenic shock when exposed to a restrictive strategy of RBC transfusion.

Central Message

This study aimed to compare clinical outcomes in patients aged 60 years or more or less than 60 years undergoing cardiac surgery and submitted to a restrictive or liberal transfusion strategy. Cardiogenic shock was more frequent in patients in the restrictive transfusion group. There were no differences between groups regarding other severe complications or mortality.

Perspective

Anemia and RBC transfusions are associated with worse outcomes after cardiac surgery. Older patients are more exposed to both anemia and transfusion in this setting. Our study is a substudy from the TRACS randomized controlled trial showing that in elderly persons, a restrictive strategy of RBC transfusion is associated with higher rates of cardiogenic shock and its complications. These findings should guide the physician in the decision to administer transfusions to a sick patient at bedside.

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Abbreviations and Acronyms

ICU	= intensive care unit
RBC	= red blood cell
TRACS	= Transfusion Requirements After Cardiac Surgery

Life expectancy is increasing worldwide, and growing numbers of elderly patients are undergoing cardiac surgery. Anemia and red blood cell (RBC) transfusions are both associated with increased morbidity and mortality after cardiac surgery, especially in elderly patients.^{1,2} Recent studies have shown that a restrictive strategy of RBC transfusion is as safe and effective as a liberal one in critically ill patients.³ In a recent prospective, randomized clinical trial, Transfusion Requirements After Cardiac Surgery (TRACS), we observed that a restrictive RBC transfusion strategy was as safe as a more liberal approach to transfusion in a diverse group of patients undergoing cardiac surgery.⁴ However, these findings may not apply so readily to elderly patients who have reduced physiologic reserve and more comorbid conditions than younger patients.

A few studies have evaluated clinical outcomes in the elderly according to different strategies of RBC transfusion.⁵ The FOCUS study was a multicenter trial to determine whether a higher threshold for blood transfusion would improve recovery in elderly patients who had undergone surgery for hip fracture.⁶ The inclusion criteria were history of or risk factors for cardiovascular disease. A liberal transfusion strategy (hemoglobin threshold of 10 g/dL), as compared with a restrictive strategy (hemoglobin threshold of 8 g/dL), did not reduce rates of death or inability to walk independently on 60-day follow-up.⁶ In contrast, a recent pilot trial in 110 patients (mean age of 71 years) with acute coronary syndrome or stable angina undergoing cardiac catheterization and with a hemoglobin less than 10 g/dL showed a trend for fewer major cardiac events and deaths with a liberal than with a more restrictive RBC transfusion strategy.⁷ Thus, the risk–benefit profile of RBC transfusions remains uncertain, and more evidence is needed to guide practice in older patients with cardiorespiratory disease,⁸ such as those undergoing cardiac surgery.

Therefore, the aim of this study was to compare outcomes in patients aged 60 years or more or less than 60 years undergoing cardiac surgery after implementation of a restrictive or a liberal transfusion strategy.

MATERIALS AND METHODS

The TRACS study (ClinicalTrials.gov number NCT01021631) was designed as a prospective, randomized, controlled, noninferiority trial to study blood transfusion thresholds during elective cardiac surgery.⁴ Consecutive adult patients who were scheduled for elective cardiac surgery

with cardiopulmonary bypass between February 9, 2009, and February 1, 2010, were enrolled. We excluded patients requiring surgery in an urgency situation; undergoing ascending or descending thoracic aortic procedures; with left ventricular aneurysm resection; unable to receive blood products; who were pregnant; who had cancer, congenital heart defect, hepatic dysfunction, or end-stage renal disease; or who refused consent. The study was approved by the Heart Institute Ethics Committee of the Clinics Hospital, University of Sao Paulo, and written informed consent was obtained from all patients before enrollment. Patients were randomly assigned to be managed according to a liberal (hematocrit values maintained at $\geq 30\%$) or restrictive (hematocrit values maintained at $\geq 24\%$) transfusion strategy from the start of the operation until discharge from the intensive care unit (ICU).

The primary outcome was a composite end point of 30-day all-cause mortality and severe morbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring dialysis or hemofiltration). Cardiogenic shock was defined as the presence of tachycardia, hypotension, and poor perfusion associated with a central venous oxygen saturation less than 65%, a cardiac index 2.2 L/min/m² or less, or the presence of metabolic acidosis (base deficit >4 mmol/L) or an increase in lactate level (>18.02 mg/dL) in the absence of a cause other than heart failure.⁹ Renal injury was defined according to the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease criteria.¹⁰ Acute respiratory distress syndrome was diagnosed if patients had an acute onset of an inflammatory lung injury characterized by hypoxemia (arterial oxygen tension/inspired oxygen fraction), bilateral infiltrates on chest radiograph, and no clinical evidence of left atrial hypertension.¹¹

Statistical Analysis

In this subgroup analysis, we separated patients into those aged 60 years or more (elderly) and those aged less than 60 years (younger). We compared baseline characteristics, follow-up measures, and clinical outcomes in the 2 age groups on an intention-to-treat basis according to the randomized study group assignment. Continuous variables were compared using a *t* test or Mann–Whitney *U* test, and categorical variables were compared using the Pearson chi-square, Fisher exact, or likelihood ratio test. We compared hemoglobin levels between groups using a mixed-design analysis of variance model. We evaluated exposure to

FIGURE 1. Flowchart of the study.

TABLE 1. Baseline characteristics of study patients

Variable	<60 y		<i>P</i>	≥60 y		<i>P</i>
	Liberal n = 118 (48.8%)	Restrictive n = 124 (51.2%)		Liberal n = 135 (51.9%)	Restrictive n = 125 (48.1%)	
Age (y)	51 ± 10	49 ± 9	.131	70 ± 6	68 ± 6	.129
Sex (male)	73 (61.9)	73 (58.9)	.634	88 (65.2)	76 (60.8)	.464
BMI (kg/m ²)	26 ± 5	26 ± 5	.699	26 ± 4	26 ± 4	.782
Comorbidities						
Arterial hypertension	84 (71.2)	82 (66.1)	.397	117 (86.7)	110 (88)	.747
Diabetes	22 (18.8)	34 (27.4)	.113	57 (42.5)	52 (41.9)	.922
Dyslipidemia	52 (44.4)	66 (53.2)	.173	87 (64.4)	81 (65.9)	.812
Renal disease	9 (7.8)	7 (5.8)	.533	17 (12.9)	19 (15.3)	.574
Smoking	26 (22)	29 (23.4)	.802	8 (5.9)	9 (7.2)	.678
COPD	5 (4.3)	6 (4.9)	.823	1 (0.8)	2 (1.7)	.502
Unstable angina	34 (28.8)	32 (25.8)	.600	45 (33.3)	44 (35.2)	.751
Previous myocardial infarction	34 (28.8)	39 (32)	.595	52 (38.5)	50 (40.3)	.767
Heart failure (NYHA)			.847			.108
I	2 (3.1)	1 (1.6)		6 (10)	7 (13.2)	
II	25 (38.5)	23 (36.5)		17 (28.3)	25 (47.2)	
III	34 (52.3)	33 (52.4)		31 (51.7)	16 (30.2)	
IV	4 (6.2)	6 (9.5)		6 (10)	5 (9.4)	
Left ventricular ejection fraction			.918			.429
<40	15 (12.7)	14 (11.3)		17 (12.6)	23 (18.4)	
40-59	34 (28.8)	38 (30.6)		42 (31.1)	37 (29.6)	
>60	69 (58.5)	72 (58.1)		76 (56.3)	65 (52)	
euroSCORE, median (IQR)	3 (2-6)	3 (2-5)	.091	5 (4-7)	5 (3-7)	.661
Parsonnet, median (IQR)	8 (4-13)	8 (5-13)	.905	14 (7-21)	12 (6-20)	.398
Preoperative laboratory values						
Hemoglobin (g/dL)	13.2 ± 1.6	13.6 ± 1.8	.070	13.1 ± 1.6	13.1 ± 1.8	.844
Hematocrit (%)	40 ± 4	40 ± 5	.401	39 ± 4	40 ± 5	.710
Prothrombin time (sec)	11.1 ± 1.3	11.3 ± 2.5	.492	11 ± 1.1	11.1 ± 1.2	.707
Platelet count (1000/mm ³)	222 ± 70	230 ± 66	.391	222 ± 65	220 ± 65	.809
Creatinine concentration (mg/dL)	1.1 ± 0.4	1 ± 0.3	.547	1.2 ± 0.3	1.2 ± 0.4	.479
Leukocyte count (1000/mm ³)	7.4 ± 1.9	7.8 ± 2.1	.166	7.7 ± 2.2	7.6 ± 2	.575
Preoperative drug exposure						
Aspirin	39 (33.1)	41 (33.3)	.963	64 (47.4)	53 (42.4)	.417
Heparin	2 (1.7)	0 (0)	.239	1 (0.7)	2 (1.6)	.610

Parsonnet is the predictive score for acquired adult heart surgery; System of Units conversion factor: to convert creatinine values to $\mu\text{mol/L}$, multiply by 88.4. *BMI*, Body mass index; *COPD*, chronic obstructive pulmonary disease; *NYHA*, New York Heart Association; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *IQR*, interquartile range.

RBC transfusion through a logistic regression model for repeated measures.

Results are expressed as means with standard deviation or medians with interquartile ranges (IQRs). Statistical analyses were performed using SPSS version 18.0 (SPSS Inc, Chicago, Ill).

RESULTS

Study Population

A total of 1765 patients were assessed for eligibility in the TRACS study (Figure 1). After exclusions for various medical reasons and lack of consent, 512 patients were enrolled in the study: 257 assigned to the liberal group and 255 assigned to the restrictive transfusion strategy group. Of the 502 patients included in the TRACS study, 260 (51.8%) were aged 60 years or more and 242 (48.2%) were aged less than 60 years (Figure 1).

Baseline characteristics were well balanced between the strategies of treatment in the 2 age strata (Table 1). Procedure-related variables in the intraoperative period were also similar with the exception of RBC transfusion (Table 2).

In the elderly patients, 70% in the liberal strategy group received an intraoperative transfusion compared with 44% in the restrictive group ($P < .001$), and hemoglobin concentrations were significantly higher in the liberal than in the restrictive strategy group intraoperatively (Figure 2). In the younger patients, 68% of patients in the liberal strategy group and 36% of patients in the restrictive group received an intraoperative transfusion ($P < .001$). Hematocrit concentrations were maintained at or above the threshold for 95% of the time. Most transfusions were given in the operating room and in the first 3 days after

TABLE 2. Intraoperative data in the restrictive and liberal strategy groups

Variable	Age <60 y		P	Age ≥60 y		P
	Liberal n = 135 (51.9%)	Restrictive n = 125 (48.1%)		Liberal n = 135 (51.9%)	Restrictive n = 125 (48.1%)	
Procedure			.389			.387
CABG	62 (52.5)	68 (54.8)		93 (68.9)	84 (67.2)	
Valve replacement	53 (44.9)	49 (39.5)		26 (19.3)	31 (24.8)	
CABG + valve	3 (2.5)	7 (5.6)		16 (11.9)	10 (8.0)	
Number of grafts per patient			.716			.647
1	3 (4.6)	6 (8)		13 (11.9)	10 (10.6)	
2	20 (30.8)	22 (29.3)		33 (30.3)	24 (25.5)	
3	26 (40)	32 (42.7)		41 (37.6)	45 (47.9)	
4	13 (20)	14 (18.7)		19 (17.4)	12 (12.8)	
>4	3 (4.6)	1 (1.3)		3 (2.8)	3 (3.2)	
Cardiopulmonary bypass duration (min), median (IQR)	90 (75-113)	90 (70-114)	.536	88 (70-108)	94 (79-111)	.057
Initial hemoglobin (mg/dL)	12.7 ± 1.7	12.8 ± 1.8	.633	12.3 ± 1.6	12.6 ± 1.8	.208
Final hemoglobin (mg/dL)	10.8 ± 1.3	10.3 ± 1.7	.009	10.4 ± 1.2	9.9 ± 1.2	.001
Initial hematocrit (mg/dL)	39 ± 5.2	39.4 ± 5.4	.603	38 ± 5	39 ± 5	.228
Final hematocrit (mg/dL)	33 ± 4	32 ± 5	.007	32 ± 4	30 ± 4	<.001
Initial lactate (mmol/L)	16 ± 17	14 ± 5	.172	14 ± 5	15 ± 5	.349
Final lactate (mmol/L)	38 ± 26	35 ± 22	.282	36 ± 22	37 ± 21	.709
Initial SvcO ₂ (%)	74 ± 8	74 ± 9	.839	73 ± 8	74 ± 9	.708
Final SvcO ₂ (%)	82 ± 7	81 ± 9	.340	80 ± 8	81 ± 7	.395
Administered fluids (L), median (IQR)	3.0 (2.0-3.5)	3.0 (2.5-3.5)	.120	3.0 (2.5-3.5)	3.0 (2.5-3.5)	.110
Crystalloids (L), median (IQR)	2.5 (2.0-3.0)	2.5 (2.5-3.0)	.401	2.5 (2.0-3.0)	3.0 (2.5-3.0)	.189
Albumin	1 (0.8)	1 (0.8)	1.000	1 (0.7)	1 (0.8)	1.000
Hydroxyethyl starch 6% (130/0.4)	43 (36.4)	57 (46)	.152	57 (42.2)	60 (48)	.349
Intraoperative transfusion	79 (67.5)	45 (36.3)	<.001	95 (70.4)	55 (44)	<.001
Units of transfused RBCs			<.001			<.001
0	30 (25.4)	71 (57.3)		25 (18.5)	60 (48)	
1	25 (21.2)	25 (20.2)		16 (11.9)	19 (15.2)	
2	26 (22)	16 (12.9)		37 (27.4)	27 (21.6)	
3	12 (10.2)	3 (2.4)		25 (18.5)	11 (8.8)	
4	12 (10.2)	4 (3.2)		13 (9.6)	4 (3.2)	
>4	13 (11)	5 (4)		19 (14.1)	4 (3.2)	

Initial = samples collected after the induction of anesthesia; final = samples collected at the end of surgery. CABG, Coronary artery bypass grafting; IQR, interquartile range; SvcO₂, central venous oxygen saturation; RBC, red blood cell.

surgery, and the liberal strategy group was more exposed to RBC transfusion over time (Figure 3). There was no difference in the median storage time of RBC units between the liberal strategy and the restrictive strategy (2 days [1-2] vs 2 days [2-3], $P = .051$).

Outcome Measures

The primary end point occurred in 11.9% of patients in the liberal strategy group and 16.8% of patients in the restrictive strategy group ($P = .254$) for those aged 60 years or more and in 6.8% of patients in the liberal strategy group and 5.6% of patients in the restrictive strategy group for those aged less than 60 years ($P = .714$) (Table 3). Thirty-day mortality, acute respiratory distress syndrome, and acute renal injury were similar in the restrictive and liberal transfusion groups in both age groups. The incidence of cardiogenic shock was similar in the restrictive and liberal

transfusion groups for patients aged less than 60 years (4.8% vs 4.2%, $P = .822$). However, in the older patients, cardiogenic shock was more frequent in patients in the restrictive transfusion group (12.8% vs 5.2%, $P = .031$) (Table 3).

Patients who had cardiogenic shock compared with patients without shock needed more dobutamine (100% vs 60%, $P < .001$) and norepinephrine (32.4% vs 15.4%, $P = .01$), and presented a higher rate of mechanical ventilation over 48 hours (32.4% vs 15.4%, $P = .01$). Older patients who presented cardiogenic shock had a more severe presentation of this disease compared with patients aged less than 60 years, lasting 57 hours (IQR, 22-114) versus 34 hours (IQR, 13-75) ($P < .0003$), resulting in a higher incidence of acute kidney injury (requiring renal replacement therapy) (13% vs 5%, $P = .03$) and a greater length of hospital (13 days [10-20] vs 10 days [8-12],

FIGURE 2. Mean hemoglobin levels during the study in patients aged less than 60 years (*top*) and patients aged 60 years or more (*bottom*) according to transfusion strategy. *IO*, Intraoperative period; *IPO*, immediate postoperative period. D1-D7 indicate postoperative days. $P < .05$.

$P = .0001$) and ICU stay (6 days [4-9] vs 5 days [4-7], $P = .0001$). There were no differences between groups in the occurrence of acute kidney injury, in the duration of mechanical ventilation, and in delirium.

DISCUSSION

In this subgroup analysis of the TRACS study, a restrictive strategy of RBC transfusion was independently associated with a 2.5-fold higher rate of cardiogenic shock after cardiac surgery. These data suggest that a restrictive transfusion strategy targeting a hematocrit of 24%, as recommended in recent studies and guidelines,^{7,12,13} may be less safe than a more liberal strategy, targeting a hematocrit of 30%, in terms of cardiovascular risk in patients aged 60 years or more.

The rationale for implementing a restrictive transfusion strategy is based on many studies that have shown a lack of benefit and substantially increased costs and adverse effects associated with RBC transfusion.¹⁴⁻²⁰ These adverse effects include acute hemolytic and nonhemolytic reactions,

FIGURE 3. Percentage of patients aged less than 60 years (*top*) and patients aged 60 years or more (*bottom*) who received an RBC transfusion in the liberal and restrictive strategy groups. *IO*, Intraoperative period; *IPO*, immediate postoperative period. D1-D7 indicate days after ICU admission. $*P < .05$ (comparison between groups – logistic regression for repeated measures).

transmission of viral and bacterial diseases, transfusion-related acute lung injury, and transfusion-associated circulatory overload. Nevertheless, there is concern about the possible increased risk of adverse effects of anemia in patients with cardiovascular disease.^{21,22} One retrospective cohort study of 1958 surgical patients reported that increased severity of anemia was associated with a significant increase in mortality rates among patients with cardiovascular disease.²¹ Moreover, some studies in patients with anemia and myocardial infarction seem to suggest that transfusion may be beneficial, particularly for patients aged more than 65 years.^{23,24} A recent pilot study by Carson and colleagues⁷ showed that a restrictive transfusion strategy in older patients with symptomatic coronary disease may result in a higher rate of major cardiovascular complications. In our study, patients aged 60 years or more had an increased risk of cardiogenic shock when a hematocrit threshold of 24% was used compared with a threshold of 30%. Older patients may have reduced compensatory mechanisms after surgical trauma, making them more likely to develop mismatch between oxygen delivery and consumption and thus tissue hypoxia, and optimizing cardiac output and arterial oxygen content during cardiac surgery may reduce cardiovascular

TABLE 3. Incidence of the primary end point—composite of 30-day all-cause mortality and severe morbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring dialysis or hemofiltration)—and its individual components according to transfusion strategy in the 2 age groups

End point	Age <60 y		P	Age ≥60 y		P
	Liberal n (%)	Restrictive n (%)		Liberal n (%)	Restrictive n (%)	
Primary composite end point	8 (6.8)	7 (5.6)	.71	16 (11.9)	21 (16.8)	.25
30-d mortality	5 (4.2)	5 (4.0)	1.00	7 (5.2)	10 (8.0)	.35
Cardiogenic shock	5 (4.2)	6 (4.8)	.82	7 (5.2)	16 (12.8)	.03
ARDS	2 (1.7)	2 (1.6)	1.00	0 (0)	3 (2.4)	.11
Acute renal injury requiring RRT	3 (2.5)	4 (3.2)	1.00	10 (7.4)	6 (4.8)	.38

ARDS, Acute respiratory distress syndrome; RRT, renal replacement therapy.

complications. In our study, older patients who had cardiogenic shock had a more severe presentation of the disease, resulting in a higher incidence of acute kidney injury requiring renal replacement therapy, prolonged mechanical ventilation, and a longer ICU and hospital length of stay.

Study Limitations

Although there was a significant difference favoring the liberal arm, these data should be interpreted in the light of several study limitations. The study was single center, limiting its generalizability to other units and countries. Patients in this study experienced slightly higher rates of serious complications than those in other studies, likely because our population was a relatively high-risk group, with a median European System for Cardiac Operative Risk Evaluation of 5, and our results may not be relevant in patients with lower disease severity. Also, the sample size is small and our conclusions are based on a limited number of events. Moreover, these are results from a substudy, although this analysis was defined a priori. Future studies are needed to better characterize the outcomes of different strategies of transfusion in an older adult population undergoing cardiac surgery. Also, these should include assessments of frailty and markers of increased vulnerability to improve our understanding of this specific population.

CONCLUSIONS

Despite these limitations, a restrictive transfusion strategy resulted in an increased rate of cardiogenic shock in elderly patients undergoing cardiac surgery compared with a more liberal strategy, suggesting that in this specific population, the cardiovascular risk of anemia may be more harmful than the risk of blood transfusion.^{25,26}

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: red blood cell transfusion, cardiogenic shock, elderly, cardiac surgery

EDITORIAL COMMENTARY

Transfusion strategies in cardiac surgery: More pieces to the puzzle, more questions to be answered

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Blood management has emerged as an important aspect of perioperative cardiac surgical care and has evolved to become a key quality indicator.¹ Despite growing evidence of the risks and cost of blood transfusion, along with the physiologic rationale of improvement of oxygen delivery to tissues during hemorrhage and ischemia, the jury still out with respect to the optimal hemoglobin trigger for red blood cell transfusion in cardiac surgical patients, specifically in elderly patients, and how we define the concept of physiologic reserve, possibly to modify the transfusion threshold.

It is important, however, to recognize, that both anemia and transfusion are associated with poor outcomes and that both of these conditions are common among cardiac surgical patients. These patients frequently are seen with a myriad of comorbidities in different states of compensation and physiologic reserve that are difficult to control

for in large-scale studies. Moreover, the variability of the hemoglobin value in the perioperative care episode, as well as the frequency of rapid changes in blood volume during this period, make the issue of transfusion “trigger”

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Central Message

Elderly patients may benefit from a more liberal transfusion strategy. Studies are needed to balance benefit-risk-cost of transfusion.

See Article page 1314.

See Editorial page 1032.