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The authors have no conflicts of interest to disclose.

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Restrictive or liberal transfusion for cardiac surgery: Spanish results of a randomized multicenter international parallel open-label clinical trial

Transfusión Restrictiva o liberal en cirugía cardiaca: Resultados españoles de un ensayo clínico aleatorizado, multicéntrico, internacional, paralelo y abierto

Dear Editor,

In cardiac surgery, red blood cell (RBC) transfusion is very frequent. Although transfusion is useful to treat anemia and avoid its complications, it represents a potential risk of acute kidney damage at 72 h after surgery, prolonged mechanical ventilation, need for hemodynamic support, increase-hospital mortality, as well as longer hospital stays.[1] Finding the optimal threshold of hemoglobin for indicating the transfusion with maximal benefit and minimal risk is an aim of the clinical practice. However, a survey in 34 Spanish centers performed in 2007 showed that 70% centers did not have homeostasis protocols and 75% of patients undergoing cardiac surgery were transfused.[2]

Because of the wide variability in transfusion practices and high rates of transfusion in cardiac surgery in Spain, we participated in the Transfusion Requirements in Cardiac Surgery (TRICS) III trial. This is a randomized, multicentre, international, controlled, open-label clinical trial to assess whether a restrictive transfusion strategy, in which lower hemoglobin concentrations for RBC transfusion, applied throughout the perioperative period, would be non-inferior, in terms of major morbidities and mortality, to a liberal approach among 5243 patients undergoing cardiac surgery.[3,4] This study was funded by national peer-review organizations from Australia, Canada, Spain (ISCIII and European Social Fund, CP15/00116) and New Zealand.

We present the results of the Spanish included patients followed up to 6 months after surgery.

Ethics approval was provided by each institutional review boards. All patients consented to participate in the clinical trial. An independent data and safety monitoring board provided trial oversight.

The inclusion criteria were patients undergoing cardiac surgery with cardiopulmonary bypass at moderate to high predicted risk for death, as defined by the European System for Cardiac Operative Risk Evaluation

(EuroSCORE) I[5] ≥6 on a scale from 0 to 47, with higher scores indicating a higher risk of death after cardiac surgery.

Using interactive web-based randomization, patients were allocated to receive restrictive or liberal transfusion strategy. Patients assigned to restrictive strategy received a RBC transfusion when hemoglobin concentration was <7.5 g/dl. Patients assigned to liberal strategy received a RBC transfusion when hemoglobin concentration was <9.5 g/dl intraoperatively or postoperatively in the Intensive Care Unit (ICU), and it was <8.5 g/dl when the patient was in the non-ICU ward. The treating physicians followed the transfusion protocol until 28 days after surgery or hospital discharge, whichever came first.

The main outcome was a composite outcome including death from any cause, myocardial infarction, new focal neurologic deficit (stroke), or new-onset renal failure with dialysis occurring within 6 months after the cardiac

Table 1 Characteristics, hemoglobin concentration, and in-hospital transfusion outcomes (intent-to-treat) in Spanish patients.

		Restrictive transfusion threshold N = 77		Liberal transfusion threshold N = 78	*p* value
	N	*No. (%) or mean ± SD*	*N*	*No. (%) or mean ± SD*	
Baseline characteristics					
Age (y)	77	75.17 ± 6.33	78	75.93 ± 6.88	0.474
Male sex – no. (%)	77	37 (48.1)	78	40 (51.3)	0.809
Body-mass index	77	28.01 ± 4.70	78	28.51 ± 4.32	0.495
EuroSCORE I	77	7.83 ± 2.04	78	8.03 ± 2.08	0.557
Previous cardiac surgery – no. (%)	77	8 (10.4)	78	8 (10.3)	1.000
Myocardial infarction in previous 90 days – no. (%)	77	4 (5.2)	78	4 (5.1)	1.000
Diabetes mellitus – no. (%)	77	19 (24.7)	78	19 (24.4)	1.000
Treated hypertension – no. (%)	77	67 (87.0)	78	58 (74.4)	0.073
Operative characteristics					
Emergency surgery – no. (%)	77	3 (3.9)	78	1 (1.3)	0.603
CABG surgery only – no. (%)	77	1 (1.3)	78	2 (2.6)	1.000
CABG and valve surgery – no. (%)	77	12 (15.6)	78	17 (21.8)	0.432
CABG and other, non-valve surgery – no. (%)	77	0 (0)	78	0 (0)	NA
Valve surgery only – no. (%)	77	63 (81.8)	78	56 (71.8)	0.198
Other, non-CABG surgery – no. (%)	77	1 (1.3)	78	3 (3.8)	0.622
Duration of cardiopulmonary bypass – min	77	98.27 ± 32.58	78	114.35 ± 51.55	0.022
Intraoperative tranexamic acid – no. (%)	77	77 (100.0)	78	76 (97.4)	0.482
Hemoglobin concentration (g/l)					
Preoperative	77	128.56 ± 16.39	78	128.22 ± 14.46	0.891
Nadir Intraoperative	77	83.81 ± 12.65	78	83.00 ± 11.31	0.677
ICU Admission	77	95.65 ± 14.33	78	100.23 ± 13.85	0.045
Pre-discharge	77	96.14 ± 13.24	78	101.46 ± 11.46	0.008
In-hospital transfusion outcomes					
≥1 unit of red cells transfused after randomization – no. (%)	77	35 (45.5)	78	61 (78.2)	<0.001
Number of red cell units transfused after randomization	77	1.23 ± 2.26	78	2.38 ± 2.49	0.003
Protocol suspension at any time – no. (%)	35	4 (11.4)	61	6 (9.8)	1.000
Plasma – no. (%)	77	7 (9.1)	78	11 (14.1)	0.470
Platelets – no. (%)	77	11 (14.3)	78	11 (14.1)	1.000
Cryoprecipitate – no. (%)	77	0 (0)	78	0 (0)	NA
Prothrombin complex concentrate – no. (%)	77	3 (3.9)	78	3 (3.8)	1.000

Table 2 Odds ratios for primary and secondary 6-month outcomes in Spanish patients.

	Per-protocol			Intent-to-treat		
	Restrictive transfusion threshold *N* = 74	Liberal transfusion threshold *N* = 74	Unadjusted OR (95% CI)	Restrictive transfusion threshold *N* = 77	Liberal transfusion threshold *N* = 78	Unadjusted OR (95% CI)
Primary outcome						
Composite-outcome	9/73 (12.3)	12/74 (16.2)	0.73 (0.28–1.84)	10/76 (13.2)	14/78 (17.9)	0.69 (0.28–1.66)
Secondary outcomes						
Death	4/74 (5.4)	5/74 (6.8)	0.79 (0.19–3.10)	4/77 (5.2)	5/78 (6.4)	0.80 (0.19–3.14)
Myocardial infarction	1/72 (1.4)	1/69 (1.4)	0.96 (0.04–24.54)	1/75 (1.3)	1/73 (1.4)	0.97 (0.04–24.92)
Stroke	1/72 (1.4)	1/69 (1.4)	0.96 (0.04–24.54)	1/75 (1.3)	1/73 (1.4)	0.97 (0.04–24.92)
New-onset renal failure with dialysis	5/72 (6.9)	9/72 (12.5)	0.52 (0.15–1.60)	6/75 (8.0)	11/76 (14.5)	0.51 (0.17–1.43)
Expanded composite-outcome	37/73 (50.7)	32/74 (43.2)	1.35 (0.71–2.59)	39/76 (51.3)	34/78 (43.6)	1.36 (0.72–2.58)
Coronary revascularization	0/72 (0)	0/69 (0)	Non estimable	0/75 (0)	0/73 (0)	Non estimable
Hospital readmission or emergency department visit after index surgery	34/71 (47.9)	24/69 (34.8)	1.72 (0.88–3.43)	35/74 (47.3)	25/73 (34.2)	1.72 (0.89–3.37)

surgery. The secondary outcomes included the individual components of the composite outcome. We included in an expanded composite outcome hospital readmission, emergency department visit, or coronary revascularization. More details about the trial protocol can be obtained from the published version.[6]

For this subgroup analysis of Spanish patients we calculated mean and standard deviation (SD) for continuous variables and percentage for categorical variables. Due to the low number of patients analyzed, one unadjusted analysis was performed. The incidence, odds ratios (OR) and confidence interval of 95% (95% CI) were calculated for the outcomes of interest. We also calculated whether the effect of the transfusion strategy varied according to pre-specified subgroups like age, sex, diabetes, creatinine level, chronic pulmonary disease, surgery category, left ventricular function and preoperative hemoglobin concentration. The analysis was done by Intention to treat (ITT) including all patients randomized and per protocol (PP).

From the total of the TRICSIII trial, 155 patients were included in four Spanish centers. Seventy seven patients were assigned to restrictive strategy and 78 to liberal strategy. Three patients in the restrictive strategy and four patients in the liberal strategy were excluded from the PP analysis. There were no differences between groups in baseline and surgery characteristics (Table 1). Duration of cardiopulmonary bypass was significantly shorter in the experimental group than in the control group. Preoperative hemoglobin concentration was similar in both compared groups, but hemoglobin concentration at ICU admission and pre-discharge, was significantly lower in the restrictive strategy group than in the liberal strategy group. The percentage of patients transfused was also significantly lower in the restrictive strategy group and the number of RBC units administered.

The primary composite outcome was not different between assessed interventions in both the ITT analysis and the PP analyses (Table 2). In the secondary outcomes there were not differences in number of deaths, myocardial infarction, stroke and new-onset renal failure with dialysis between restrictive and liberal strategy. Similarly, the expanded composite outcome or its components (hospital readmission or emergency department visit after index surgery) were not significantly different between groups. The effect of the transfusion strategy did not vary according to pre-specified subgroups like age, sex, diabetes, chronic pulmonary disease, surgery category, left ventricular function and preoperative hemoglobin concentration. However, in the subgroup analysis by sex, OR for women was 0.29 (95% CI 0.06−1.11) and for men was 1.81 (95% CI 0.47−7.66) ($p = 0.059$).

The Spanish population had a higher incidence of some risk characteristics in respect to the overall TRICSIII[3] trial including an older age (mean 75 versus 72 years old) and the percentage of males were lower (50% versus 65%). Furthermore, the Spanish patients presented more hypertension (81% versus 74%), less background of myocardial infarction (5% vs 23%), the type of cardiac surgery was mainly valve surgery (74% versus 29%) and the duration of cardiopulmonary bypass was shorter (106 min vs 120 min).[4] In addition, there was a greater difference in likelihood of transfusion between liberal and restrictive groups (33% vs 20%).[4] Unlike in the Spanish subgroup analysis by age in TRICSIII study, younger patients (<75 years) obtained more benefits with a liberal transfusion. Furthermore, in the subgroup analysis by sex, unlike in the TRICSIII study, Spanish women seemed to benefit more with a restrictive strategy. Despite these differences in patient characteristics, this analysis ratifies that restrictive RBC transfusion strategy reduced RBC transfusion but was as safe as a liberal RBC transfusion liberal strategy with no differences in main composite outcome and its individual components in Spanish patients undergoing cardiac surgery.

Contributions of authors

Conceived the study: Galan J, Martinez-Zapata MJ, Mazer CD

Acquisitions of data: Galan J, Mateo E, Carmona P, Gajate L, Martinez-Zapata MJ

Analysis: Mistry N, Mazer CD, Martinez-Zapata MJ

Interpretation of the data: All authors

Draft the first version of the manuscript: Martinez-Zapata MJ

Revised critically the manuscript and accepted the last version: All authors

Conflict of interest

The authors have not conflict of interests.

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