on leukocytes. Compare to previous papers and to other types of infection it appears to be higher. This could inform about immune dysregulation triggered by SARS-CoV-2. The use of FC may lead to a better understanding of this response and optimize the therapies applies. Prospective studies with a higher number of cases should be conducted to confirm this observation.

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Conflict of interest

The authors have no conflicts of interest to disclose.

Bibliografía

1. Tagarro A, Epalza C, Santos M, Sanz-Santaeufemia FJ, Otheo E, Moraleda C, et al. Screening and Severity of Coronavirus Disease 2019 (COVID-19) in children in Madrid, Spain. JAMA Pediatr. 2020.
2. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71:762–8.
3. Carter MJ, Fish M, Jennings A, Doores KJ, Wellman P, Seow J, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Nat Med. 2020.
4. Hu BQ, Yang Y, Zhao CJ, Liu DF, Kuang F, Zhang LJ, et al. Accuracy of neutrophil CD64 expression in diagnosing infection in patients with autoimmune diseases: a meta-analysis. Clin Rheumatol. 2019;38:1319–28.
5. Garcia-Salido A, de Azagra-Garde AM, Garcia-Teresa MA, Caro-Patón GL, Iglesias-Bouzas M, Nieto-Moro M, et al. Accuracy of CD64 expression on neutrophils and monocytes in bacterial infection diagnosis at pediatric intensive care admission. Eur J Clin Microbiol Infect Dis. 2019;38:1079–85.
6. Gupta R, Gant VA, Williams B, Enver T. Increased Complement Receptor-3 levels in monocytes and granulocytes distinguish COVID-19 patients with pneumonia from those with mild symptoms. Int J Infect Dis. 2020.
7. de Jong E, de Lange DW, Beishuizen A, van de Ven PM, Girbes AR, Huisman A. Neutrophil CD64 expression as a longitudinal biomarker for severe disease and acute infection in critically ill patients. Int J Lab Hematol. 2016;38:576–84.
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England). 2020;395:1054–62.
9. Hyun YM, Choe YH, Park SA, Kim M. LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18) distinctly regulate neutrophil extravasation through hotspots I and II. Exp Mol Med. 2019;51:1–13.
10. Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. Lancet (London, England). 2020;395(10224):e35–6.

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https://doi.org/10.1016/j.medin.2020.09.003
0210-5691/

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 clini-

cal 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

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)

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 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.

Funding

Supported by grants (232416 and 301852) from the Canadian Institutes of Health Research (CIHR), by a grant (Kenneth J. Fyke Award, to Dr. Shehata) from the Canadian Blood Services – Health Canada, by a Miguel Servet I from the ISCCIII and European Social Fund (investing in Your Future) (CP15/00116), Spain.

Acknowledgements

To the patients who participated in the study and to all the staff who collaborated in the different clinical services involved. Dr. Mª José Martinez Zapata is funded by a Miguel Servet research contract from the Instituto de Salud Carlos III and European Social Fund (investing in Your Future) (CP15/00116).

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Bibliografía

1. Pérez-Valdivieso JR, Monedero P, García-Fernández N, Vives M, Lavilla FJ, Bes-Rastrollod M. Transfusión intraoperatoria en cirugía cardiaca Estudio retrospectivo anidado de casos y controles. Esp Anestesiol Reanim. 2013;60:79–86.
2. Basora M, Fita G, Panigua P, Litvan H, Fló A, Reverter JC. Survey of perioperative hemostasis and transfusion management in cardiac surgery: how do anesthesiologists practice? Rev Esp Anestesiol Reanim. 2010;57:3–10.
3. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med. 2017;377:2133–44.
4. Mazer CD, Whitlock RP, Fergusson DA, Belley-Cote E, Connolly K, Khanykin B, et al. Six-month outcomes after restrictive or liberal transfusion for cardiac surgery. N Engl J Med. 2018;379:1224–33.
5. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg. 1999;16:9–13.
6. Shehata N, Whitlock R, Fergusson DA, Thorpe KE, MacAdams Ch, Grocott HP, et al. Transfusion Requirements in Cardiac Surgery III (TRICS III): study design of a randomized controlled trial. J Cardiothorac Vasc Anesth. 2018;32:121–9.

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https://doi.org/10.1016/j.medin.2020.07.011