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Parreiras, Valdir Carlos; de Sá Rocha, Isabella; Martins, Antônio Sérgio; de Souza Meira, Enoch Brandão; Taniguchi, Fábio Papa

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Influence of fresh frozen plasma as a trigger factor for kidney dysfunction in cardiovascular surgery

Plasma fresco congelado como fator de risco para a disfunção renal no pós-operatório de cirurgia cardiovascular

Valdir Carlos Parreiras[1], Isabella de Sá Rocha[2], Antônio Sérgio Martins[3], Enoch Brandão de Souza Meira[4], Fábio Papa Taniguchi[5]

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Abstract

Objective: **Kidney dysfunction is a major complication in the postoperative cardiac surgery setting. Operative risk factors for its development are cardiopulmonary bypass, anemia, antifibrinolytic drugs and blood transfusion. The objective of this study was to identify the risk factors for developing kidney dysfunction in patients undergoing cardiac surgery.**

Methods: **Ninety-seven patients were studied and 84 were analyzed. The sample was stratified into two groups. A serum creatinine higher than 30% compared to the preoperative period was considered for the kidney dysfunction group (n=9; 10.71%). There also was a control group when the increase in serum creatinine remained lower than 30% (n=75; 89.28%).**

Results: **It was observed that intraoperative transfusion of fresh frozen plasma in the control group was 2.05 ± 0.78 units and 3.80 ± 2.16 units in the kidney dysfunction group with *P*= 0.032.**

Conclusion: **It was possible to associate that fresh frozen plasma transfusion is a risk factor for postoperative kidney dysfunction after cardiovascular surgery.**

Descriptors: **Renal insufficiency. Extracorporeal circulation. Plasma. Hemostasis.**

Resumo

Objetivo: **A disfunção renal é uma complicação importante no cenário de pós-operatório de cirurgia cardiovascular. Como fatores de risco conhecidos no intraoperatório para o seu desenvolvimento destacam-se a circulação extracorpórea, a hemodiluição, drogas antifibrinolíticos e a transfusão sanguínea. O objetivo deste estudo é identificar os fatores de risco na transfusão de sangue e derivados para o desenvolvimento de disfunção renal em pacientes submetidos à cirurgia cardiovascular.**

Métodos: **Noventa e sete pacientes foram estudados e 84 foram analisados. A amostra foi estratificada em dois grupos,**

1. Master in Health Sciences by IAMSPE, São Paulo, SP, Brazil.
2. Student of the Graduate Program in Health Sciences – IAMSPE, São Paulo, SP, Brazil.
3. PhD in surgery at UNESP. Department of Cardiovascular Surgery Faculty of Medicine of Botucatu-UNESP, Botucatu, SP, Brazil.
4. Director of the Department of Cardiovascular Surgery, Hosp. Serv. Public State of São Paulo – IAMSPE, São Paulo, SP, Brazil.
5. Post-Doctorate in Thoracic and Cardiovascular Surgery, USP. Cardiovascular Surgeon Hosp. Serv. Public State of São Paulo – IAMSPE, São Paulo, SP, Brazil.

Work carried out at Hospital Serv. Public State of São Paulo - IAMSPE, São Paulo, SP, Brazil.

Correspondence address:
Fábio Papa Taniguchi
Rua Itapeva 202, conj 91 – São Paulo –SP – Zip code 01332-000
E-mail: taniguchi@sbccv.org.br

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Abbreviations, acronyms & symbols	
CG	Control group
CPB	Cardiopulmonary bypass
FFP	Fresh frozen plasma
MAP	Mean arterial pressure
PreCr	Preoperative serum creatinine
RDG	Kidney dysfunction group

sendo que o incremento de 30% na creatinina sérica no pós-operatório foi considerado para o grupo com disfunção renal (n = 9; 10,71%). O grupo não disfunção renal foi caracterizado pela creatinina sérica, que permaneceu inferior a aumento de 30% no pós-operatório (n = 75; 89,28%).

Resultados: **Foi observado que a transfusão de plasma fresco congelado no grupo não disfunção renal foi de 2,05 ± 0,78 unidades e 3,80 ± 2,16 unidades no grupo disfunção renal com *P*= 0,032.**

Conclusão: **Foi possível associar, nesta série de pacientes, que a transfusão de plasma fresco congelado foi um fator de risco para disfunção renal pós-operatório de cirurgia cardiovascular.**

Descritores: **Insuficiência renal. Circulação Extracorpórea. Plasma. Hemostasia.**

INTRODUCTION

Despite recent advances in cardiovascular surgery kidney dysfunction is highly prevalent [1-8]. When dialysis is performed the mortality rate is increased by up eight times [9]. Kidney dysfunction is an independent risk factor for mortality in cardiovascular surgery and modifiable factors for its development should be monitored and performed before it occurs. Among these factors, the duration of cardiopulmonary bypass (CPB) [10] intraoperative anemia [11,12] and antifibrinolytic drugs [13,14] are variables set in the mechanism of kidney injury.

Cardiopulmonary bypass is associated with haemostatic dysfunction [15] induced by a decrease of coagulation factors. The abnormality triggered by the CPB has the potential to generate increased intraoperative bleeding that is associated with kidney dysfunction by speculative mechanisms such as hypotension and kidney ischemia [16-18].

In this scenario, transfusion of packed red blood cells, platelets and fresh frozen plasma (FFP) may be needed [19]. Transfusion of blood and blood products activate inflammatory mechanisms; increase oxidative stress; activates leukocytes and triggers the coagulation cascade [20,21]. The aim of this study is to analyze the risk factors for kidney dysfunction in cardiovascular surgery.

METHODS

We evaluated patients undergoing cardiovascular surgery with CPB from November 2008 to March 2009. The local Ethics Committee approved the study (CAAE: 0048.0.338.338-08). Exclusion criteria were age less than 18 years and preoperative kidney failure requiring dialysis.

Induction and maintenance of anesthesia were performed according to anesthesiologist assistant preference. No defined pharmacological protocol was mandatory.

In the operating room, continuous electrocardiograph was performed by monitoring by DII and V5 with oximetry and capnography (DX-7100, Dixtal, São Paulo, SP, Brazil). Mean arterial pressure (MAP), obtained by puncturing the radial artery and central venous line in the right subclavian vein were standard. We used a digital thermometer (UM62009, Braile Biomedica, São José do Rio Preto, SP, Brazil) in the evaluation of the nasopharyngeal temperature.

Anticoagulation was achieved with heparin to maintain the activated clotting time exceeding 480 seconds. The CPB circuit was filled with 1.8 L of lactated Ringer's solution, 50 ml of 20% mannitol, 10 ml of calcium gluconate 10%, 10 ml of magnesium sulfate to 10%, 500 mg of hydrocortisone, cefuroxime 750 mg and 5000 IU of heparin.

During CPB, hypothermia was performed at 32°C, non-pulsatile blood flow of 2.4 L/min/m^2 and perfusion pressure between 60 and 80 mmHg. Myocardial protection was achieved with intermittent anterograde hyperkalemic blood cardioplegia. In the process of weaning from CPB, MAP was maintained above 65 mmHg. External pacemaker supported the heart when the rate was less than 70 bpm. Dobutamine was administered routinely, with an initial dose of 3 mg/kg/min. Noradkidneyine was used if the MAP was less than 65 mmHg. Protamine was administered (1 mg per 100 IU of heparin). Prophylactic antibiotic therapy was performed with cefuroxime for 48 hours postoperatively.

The analyzed variables were age, weight, body mass index, sex, CPB time, anoxia, type of surgery, transfusion of packed red blood cells and blood products, postoperative drainage in 12 and 24 hours, presence of hypertension,

diabetes mellitus, peripheral vascular disease and myocardial infarction.

The preoperative serum creatinine (PreCr) was determined before surgery. The postoperative serum creatinine was assessed at 1, 2, 5 and 7 days post-operatively.

Group stratification

Patients were stratified into two groups, kidney dysfunction group (RDG) when the increase in serum creatinine was greater than 30% in the postoperative follow-up and control group (CG) when there was no increase in serum creatinine greater than 30% following postoperatively.

Statistical analysis

The chi-square or Fisher's exact test was used for the analysis of qualitative variables. The Mann-Whitney test was used to compare non-Gaussian distribution variables. Analysis of variance for two-factor repeated measures analysis with Bonferroni post-hoc analysis was used in serum creatinine within each group. The significance level was set at 5%. We used the statistical analysis program SPSS® version 11.0 (SPSS, Chicago, IL, USA).

RESULTS

Ninety seven patients were interviewed. Of these, one did not adhere to the study protocol. Eighty four patients were analyzed because 12 (12.5%) patients died before the end of the designed protocol and were further excluded. Patients were divided into control group (CG) (n = 75) and renal dysfunction group (RDG) (n = 9). There was a greater concentration of men (64.2%) who underwent coronary artery bypass grafting (71.43%) and with history of acute myocardial infarction (53.57%). Previous history of diabetes mellitus was reported in 36.9%, cerebrovascular accident in 10.71%, chronic obstructive pulmonary disease in 13.09% of the patients. Valvular surgery was performed in 28.57% of the patients.

Table 1 shows the characteristics of each group. Table 2 presents surgical data. Respectively, Table 3 and Table 4 present transfusion of red blood cells, FFP and platelets units intraoperatively and in the postoperative period. As presented in Table 3 the median of the number of units of FFP used intraoperatively in the control and kidney dysfunction group was 2 (p25: 2; p75: 2) units, in the control group, and 3 (p25: 2; p75: 6) units in the kidney dysfunction group ($P = 0.032$).

Table 1. Characteristics of the groups.

	CG	RDG	*P*
Age (years)	65.17±12.17	64.44±9.1	0.315
Weight (kg)	71.9±10.54	73.44±11.82	0.268
BMI	26.35±3.44	27.2±2.98	0.496
LVEF	0.53±0.16	0.51±0.27	0.452
Male	49	5	0.235
Female	26	4	
Previous MI	52%	66.6%	0.494
DM	36%	80%	0.719
CVA	13.6%	0	0.587
PVD	7.1%	0	0.955
COPD	14%	28%	0.346
High Blood Pressure	69.3%	44.46%	0.152
Valve	29.33%	22.22%	0.955
CABG	70.6%	77.7%	

CG: control group; RDG: kidney dysfunction group; BMI: body mass índex; LVEF: left ventricule ejection fraction; MI: myocardial infarction; DM: diabetes mellitus; CVA: cerebrovascular accident; PVD: peripheric vascular disease; COPD: chronic obstructive pulmonary disease; VALVE: valve surgery; CABG: coronary artery bypass graft surgery

Table 2. Surgical data.

	CG	RDG	*P*
Euroscore (%)	4.12 ± 0.82	4.28 ±0.92	0.597
CPB (mim)	82.41 ± 29.52	76.33 ± 20.74	0.379
Cross-clamp (min)	66.26 ± 24.71	59.44 ± 19.96	0.341
Hematocrit (%)	31.43 ± 4.20	29.91 ± 2.92	0,506
Troponin (ng/ml)	3.31 ± 2.65	3.12 ± 2.48	0.237
Lactate (mmol/L)	3.84 ± 3.36	2.94 ±1.47	0.186
Dobutamine(mg/kg/min)	6.62 ± 4.06	7.82 ± 3.38	0.227
Noradrenaline(mg/kg/min)	0.12 ± 0.08	0.11 ± 0.06	0.877
ICU days	3.64 ± 1.83	3.11 ± 1.27	0.192
Drainage 12h (ml)	522.86 ± 390.34	438.89 ± 207.33	0.409
Drainage 24h (ml)	827.07 ± 553.52	705.56 ± 468.67	0.114

CG: control group; RDG: kidney dysfunction group; CPB: cardiopulmonary bypass time; hematocrit: hematocrit in the immediate PO; lactate: serum lactate in the immediate PO; dobutamine: dobutamine infusion in the immediate PO; noradrenaline: noradrenaline infusion in the immediate PO; ICU: intensive care unit length stay; drainage: chest tube drainage

Table 3. Transfusion of red blood cells, fresh frozen plasma and platelets units during surgery.

	CG	RDG	*P*
Red cell	2 (1 – 2)	3 (1.75 – 6.50)	0.857
FFP	2 (2 – 2)	3 (2 – 6)	0.032
Platelets	6 (5 – 7.25)	10 (0 – 6)	0.135

Data presented as median and percentiles 25 - 75. FFP: fresh frozen plasma units; CG: control group; RDG: kidney dysfucntion group

Table 4. Transfusion of red blood cells, fresh frozen plasma and platelets units in the post-operative period.

	CG	RDG	*P*
Red cell	2 (1 – 4)	2 (1.25 – 5)	0.352
FFP	3 (1.5 – 4.5)	3 (0 – 2)	0.093
Platelets	2 (2 – 3.75)	6 (6 – 6)	0.476

Data presented as median and percentiles 25 - 75. FFP: fresh frozen plasma units; CG: control group; RDG: kidney dysfucntion group

DISCUSSION

In this study we could observe the association of transfusion of FFP as a risk factor for kidney dysfunction in cardiovascular surgery.

When kidney dysfunction occurs in the postoperative period of cardiovascular surgery it is a severe event that determines increase morbidity and mortality. It is believed that up to 30% of patients undergoing cardiovascular surgery develop kidney dysfunction [20]. In these patients the need for dialysis occurs in 1% to 2%, with a mortality rate of 30 to 70% [22,23].

Different variables are associated with kidney injury in cardiac surgery. Sex, diabetes mellitus, hypertension, age, previous kidney dysfunction, reoperation, peripheral vascular disease and left ventricular dysfunction in addition to variables related to the surgery itself as valve surgery, cardiopulmonary bypass time, hypotension and intraoperative anemia [10,12,24].

Transfusion of packed red blood cells is a relevant debate in cardiovascular surgery since indications for routine blood transfusion have been improved [12,24,25]. However, the transfusion of FFP is a topic without relevant discussion. Transfusion of blood and its products are related to preoperative anemia, weight, sex, anticoagulant or antiplatelet therapy and type of surgery. When evaluated the intraoperative factors that triggers transfusion of FFP it must be considered: previous heart surgery, thrombocytopenia, history of gastrointestinal bleeding, left ventricular dysfunction and preoperative use of heparin are noticed [26].

Transfusion of FFP is indicated when coagulopathy develops in cardiovascular surgery. However, there is no consensus for its use since cardiovascular teams depends highly in their experience and judgment for FFP transfusion. As expected, there is recognized variability transfusion rates in different surgical teams [27]. The Multicenter Study of Perioperative Ischemia Epidemiology II that was conducted in 16 countries in North America, South America, Europe and the Middle East showed that transfusion of FFP varied from 0 to 98%, platelets from 0 to 51% and red blood cells 9 to 100% among different centers [28]. The study Plasmacard, with data of French institutions, showed that 60% of patients with bleeding risk received FFP in an average volume of 7.14 ml kg to 20.87 ml/kg, in different centers. In this study, patients who developed kidney dysfunction received 3.18 ± 2.17 compared to 2.05 ± 0.78 units of FFP in those who did not. Bleeding volume, in a 24 hour period, was 827.07 ± 553.52 ml, in the control group, and 705.56 ± 468.47 ml in those who developed kidney dysfunction. One randomized clinical trial, with 40 patients, evaluated the effect of transfusion of 2 units of FFP prophylactic for bleeding in the cardiovascular surgery setting. The results showed that patients who received the two units of FFP had a postoperatively bleeding volume of 602 ± 180 ml versus 547 ± 113 ml who did not (P <0.05). Another study randomized 50 patients for 3 units of FFP or not at the end of surgery. There was no statistical difference between the groups in the postoperative period since bleeding volume averaged 896 ± 104 ml, in the group that received FFP, versus 776 ± 76 ml in the placebo group. Finally, there was no evidence that the prophylactic use of FFP in cardiovascular surgery decreased postoperative bleeding in a meta-analysis of six randomized trials involving 372 patients [29].

It must be considered that transfusion of FFP is not innocuous since infectious diseases can be transmitted and there is an increased risk for infection. Also, acute lung injury is related to the practice of blood products transfusion [29]. FFP transfusion is indicated when non-surgical bleeding occurs as a coagulation disorder induced by CPB. In this situation, FFP is able to provide coagulation factors that were consumed after CPB, such as, the Leiden factor, factor XI, factor XIII, plasminogen and S protein. Also, CPB contributes to the systemic inflammatory response since endotoxemia, ischemia reperfusion injury, surgical trauma and the non-endothelial surfaces of CPB are harmful components. These phenomena affect kidney function with consequent impact on glomerular filtration. Intraoperative bleeding in cardiovascular surgery by coagulopathy is also associated with the thrombogenic surfaces of CPB, hemodilution, hypothermia and heparin. The net result is that the complement system is activated; fibrinogen and platelets decrease with intensification of

the inflammatory phenomena. The coagulation cascade up regulates thrombin generation, intensified by the complement system, that results in a coagulation disorder associated with endothelial dysfunction by CPB and finally fibrinolysis with increased intraoperative bleeding.

FFP is indicated for coagulopathy, however bioactive substances in it such as histamine, eosinophil cationic protein, protein X, myeloperoxidase, and plasminogen activator inhibitor [30] enhance immune response and inflammatory processes. It is considered that the presence of antibodies may react with human leukocyte antigen and activation of the complement system, since endothelial damage and activation of neutrophils [31] are associated with CPB triggering kidney injury.

CONCLUSION

Although this particular scenario suggests a multifactorial etiology for kidney dysfunction in cardiovascular surgery, it was possible, in this series of patients, to associate the transfusion of FFP as a risk factor for kidney dysfunction.

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