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Epsilon-aminocaproic acid influence in bleeding and hemotransfusion postoperative in mitral valve surgery

Influência do ácido épsilon aminocapróico no sangramento e na hemotransfusão pós-operatória em cirurgia valvar mitral

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Abstract

Introduction: **The epsilon-aminocaproic acid is an antifibrinolytic used in cardiovascular surgery to inhibit the fibrinolysis and to reduce the bleeding after CBP.**

Objective: **To assess the influence of the use of epsilon-aminocaproic acid in the bleeding and in red-cell transfusion requirement in the first twenty-four hours of postoperative of mitral valve surgery.**

Methods: **Prospective study, forty-two patients, randomized and divided into two equal groups: group #1 - control and group #2 – epsilon-aminocaproic acid. In Group II were infused five grams of EACA in the induction of anesthesia, after full heparinization, CPB perfusate after reversal of heparin and one hour after surgery, totaling 25 grams. In group I, saline solution was infused only in those moments.**

Results: **Group #1 showed average bleeding volume of 633.57 ± 305,7 ml, and Group #2, an average of 308.81 ± 210.1 ml, with significant statistic difference (*P*=0.0003). Average volume of red-cell transfusion requirement in Groups 1 and 2 was, respectively, 942.86 ± 345.79 ml and 214.29 ± 330.58 ml, with significant difference (*P*<0.0001).**

Conclusion: **The epsilon-aminocaproic acid was able to reduce the bleeding volume and the red-cell transfusion requirement in the immediate postoperative of patients who underwent mitral valve surgery.**

Descriptors: **Antifibrinolytic agents. Hemostasis. Blood transfusion.**

Resumo

Introdução: **O ácido épsilon aminocapróico é um antifibrinolítico usado em cirurgia cardiovascular a fim de inibir a fibrinólise e reduzir o sangramento após circulação extracorpórea (CEC).**

Objetivo: **Analisar a influência do uso do ácido aminocapróico no sangramento e na necessidade de hemotransfusão nas primeiras 24 horas em pós-operatório de cirurgias valvares mitrais.**

Métodos: **Estudo prospectivo, 42 pacientes, randomizados e divididos em dois grupos, de igual número: grupo I - controle e grupo II - ácido épsilon aminocapróico. No grupo II, foram infundidos 5 gramas de AEAC na indução anestésica, após heparinização plena, no perfusato da CEC, após reversão da heparina e uma hora após o final da cirurgia, totalizando 25 gramas. No grupo I, foi infundido apenas soro fisiológico nestes mesmos momentos.**

Resultados: **O grupo I apresentou volume de sangramento médio de 633,57 ± 305,7 ml e o grupo II média de 308,81 ± 210,1 ml, com diferença estatisticamente significativa (*P*=0,0003). O volume médio de hemotransfusão nos grupos I e II foi, respectivamente, de 942,86 ± 345,79 ml e de 214,29 ± 330,58 ml, havendo diferença significativa (*P*<0,0001).**

Conclusão: **O ácido épsilon aminocapróico foi capaz de reduzir o volume de sangramento e a necessidade de hemoderivados no pós-operatório imediato de pacientes submetidos a cirurgias valvares mitrais.**

Descritores: **Antifibrinolíticos. Hemostasia. Transfusão de sangue.**

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INTRODUCTION

Cardiopulmonary bypass (CPB), because it is an event that exposes the blood to a non-endothelial surface, provids changes to the blood crasis, determining a particular tendency to bleeding interfering with the physiology of the organism [1].

Some authors have shown that bleeding post-perfusion may be due to inadequate surgical hemostasis and/or disorders of coagulation and fibrinolysis, which justifies the need to proceed with several studies related to its effects and complications, with the purpose of that adversities of the method can be circumvented or minimized [2,3].

During CPB, due to hemodilution, hypothermia, trauma of the blood cells and the release of vasoactive substances, there are changes in platelets, proteins related to coagulation and fibrinolytic system [3-5]. About 10 to 20% of CPB patients (adults and children) have excessive bleeding in the immediate postoperative period [3,4].

The risks associated with blood transfusion and its components have encouraged the search for pharmacological agents capable of reducing blood loss as a result of CPB [6-7].

The interventions of pharmacological nature in the prevention of bleeding after infusion based on the administration of several agents, among which the most effective appear to be protease inhibitor, such as aprotinin (APT) and the lysine analogues, such as epsilon-aminocaproic acid (EACA) and tranexamic acid (TA). The effectiveness of the preventive regimen with aprotinin has been thoroughly demonstrated in literature. The high cost of the product and the various adverse effects have stimulated the search for alternatives of equal efficacy and lower costs [6-11].

Epsilon aminocaproic acid is an antifibrinolytic agent commonly used in cardiovascular surgery in order to inhibit fibrinolysis and reduce bleeding after CPB. This drug blocks the production of plasminogen and tissue plasminogen activator. The EACA combines with plasminogen and plasmin and prevents fibrinolytic enzymes bind to the lysine residues present in the molecule of fibrinogen, thereby preventing fibrinolysis [12].

The doses of epsilon-aminocaproic acid are not as well standardized as doses of aprotinin, however, it is often the administration of a loading dose of 150 mg/kg. The administration should be continued by a continuous infusion of 10 mg/kg/hour for four or five hours, the maximum dose of 24 grams, or one gram per hour [13].

Considering the need to standardize the dose of epsilon-aminocaproic acid and evidence of its effectiveness, this research aims to analyze the influence of the use of aminocaproic acid in a dose recommended by the authors in bleeding and the need for blood products in the first 24 hours postoperative of mitral valve surgery.

METHODS

A prospective study in the Department of Cardiovascular Surgery, University Hospital of the Federal University of Mato Grosso do Sul, approved by the hospital Ethics Committee, with the inclusion criteria based on patients undergoing mitral valve surgery and exclusion criteria patients with renal failure, blood, liver or digestive disease, with ischemic heart disease, lesions of two or more valves in patients in cardiogenic shock and emergency surgery, and 42 patients were enrolled in this study according to these criteria.

The mitral valve surgeries were performed by longitudinal median sternotomy with mild hypothermia at 27°C and roller pump.

Patients were randomly divided into two groups: Group I - control, Group II - epsilon-aminocaproic acid, both with 21 patients. In group I, were infused 40 ml saline (SS) 0.9% in central venous access during anesthetic induction, 80 ml in priming of the CPB circuit after full heparinization, 40 ml after heparin reversal with protamine sulfate in 1:1 ratio and 40 ml one hour after the end of surgery in the cardiac recovery in the postoperative period, in group II were infused 5 g of epsilon-aminocaproic acid at the same times in which saline was infused in group I, in a total of 25 grams of epsilon-aminocaproic acid. It should be emphasized that patients and physicians did not know who was using EACA.

The evaluation criterion for blood transfusion in cardiac output was estimated according to the metabolic needs and oxygen transport individualized, or that is, hemoglobin below 7 mg/dL, central venous oxygen saturation less than 50% and arterial oxygen pressure less than 25 mmHg, and bleeding volume greater than 200 ml/h during the first 4 hours.

The groups were similar with respect to factors that could influence postoperative bleeding and transfusion required: age, sex, weight, height, duration of CPB, valve replacement or repair, blood coagulation and platelet count. We evaluated the volumes of bleeding and infusion of packed red blood cells in the first 24 hours postoperatively. The infusions of blood products (platelets, fresh frozen plasma and cryoprecipitate) were similar between groups.

The analysis of quantitative variables was performed by comparing means (with previous verification of the normal distributions), using the Student t test and Mann-Whitney test, and for analysis of categorical variables we used the chi-square and chi-square test with Yates' correction (2x2 tables). The level of significance was $P < 0.05$.

RESULTS

Analysis of anthropometric variables showed no statistically significant difference.

The CPB time had an average of 45.48 minutes (min) in the control group and the EACA of 50.24 min ($P = 0.3447$).

The group I had a mean bleeding volume of 633.57 milliliters (ml) during the first 24 hours postoperatively, and Group II average of 308.81 ml, observing a statistically significant difference ($P = 0.0003$) - Figure 1. The mean volume of blood transfusion (Figure 2) in the first 24 hours in groups I and II were, respectively, of 942.86 ml and 214.29 ml, significant difference ($P < 0.0001$), as shown in Tables 1-4.

As to the need for blood transfusion, it was found that all patients in group I needed infusion of blood products, and only eight patients in group II required the same ($P < 0.0001$). Comparing the type of surgery performed, whether plasty or valve replacement, there was no statistically significant difference between the two groups (Tables 3 and 4).

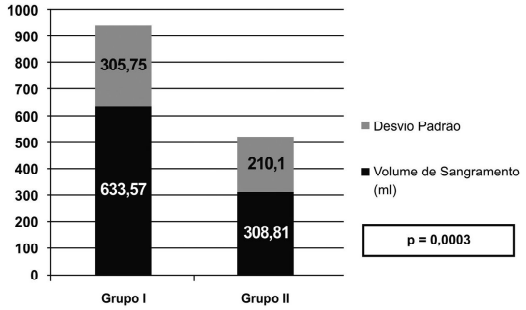

Fig.1 - Bleeding volume- Group I - control; Group II - Epsilon-aminocaproic acid

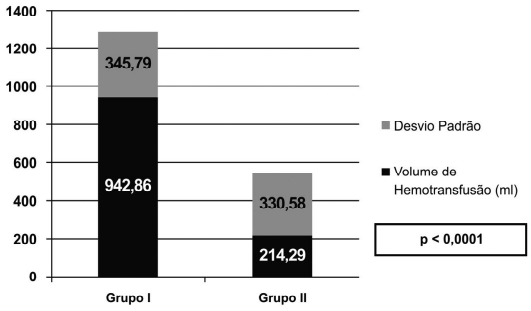

Fig. 2 - Blood transfusion volume - Group I - control; Grupo II - Epsilon-aminocaproic acid

Table 1. Variables of study of the Group I (Control).

Number	Gender	Age	Weight	Height	Time of CPB	Bleed.Volume	Hemot.Vol	Pre Hemot	Post Hemot	Pre Plat.	Post Plat.	Surgery
1	M	62	73	1.77	55	500	900	35	31	89000	106000	Plasty
2	F	80	35.2	1.5	35	500	900	43	42	155000	73000	Plasty
3	F	60	46	1.52	50	390	1200	40	39	241000	141000	Mec
4	M	73	64	1.65	30	500	1200	38	39.2	186000	56000	Plasty
5	F	59	46	1.47	35	500	900	39	34	305000	168000	Plasty
6	F	60	46.3	1.52	50	690	900	40	33	241000	124000	Mec
7	M	73	64	1.63	30	350	1200	38	37	25000	98000	Plasty
8	F	63	68	1.72	35	1530	1200	47	29	226000	122000	Plasty
9	M	72	69	1.68	30	625	900	38	38	154000	115000	Plasty
10	F	59	46.7	1.47	35	800	1200	39	39	305000	133000	Plasty
11	F	63	58.8	1.56	50	750	1800	35	30	404000	173000	Mec
12	F	64	65	1.55	45	970	300	34	33	124000	173000	Bio
13	F	47	65	1.58	55	450	300	41	27	143000	100000	Mec
14	M	43	65	1.77	60	550	900	39	38	133000	110000	Mec
15	F	53	57	1.54	60	375	600	39	28	230000	127000	Mec
16	M	72	70	1.8	45	1150	1200	40	27	263000	149000	Plasty
17	M	73	61.9	1.65	40	950	900	40	35	207000	133000	Plasty
18	M	57	55	1.68	60	400	600	42	40	176000	85000	Mec
19	F	46	50	1.52	80	575	600	37	35	2980000	159000	Mec
20	F	80	35.2	1.4	35	500	900	42	38	155000	90000	Plasty
21	F	62	95	1.65	40	250	1200	44	40	294000	177000	Plasty
Total		62.9			45.48	633.57	942.86					
dp		10.43			13.03	305.75	345.79					

CPB = cardiopulmonary bypass; bleed. = bleeding; hemot. = hemotransfusion; pre. = preoperative; post. = postoperative; Mec. = mechanical prosthesis; Bio. = Biological prosthesis; Plasty = Posterior annuloplasty; SD = Standard deviation

Table 2. Variables of the study of Group II (epsilon-aminocaproic acid)

Number	Gender	Age	Weight	Height	Time of CPB	Bleed. volume	Hemot. volume	Pre Hemot	Post Hemot	Pre Plat.	Post Plat.	Surgery
1	F	32	73	1.6	30	200	1200	32	30	187000	103000	Plasty
2	F	43	48	1.45	20	400	300	40	28	197000	157000	Plasy
3	F	53	57	1.54	60	400	600	38	28	131000	127000	Mec
4	F	41	60	1.5	55	100	0	42	34	274000	188000	Mec
5	M	65	65	1.65	45	500	600	40	42	180000	114000	Plasty
6	M	42	61	1.8	90	600	0	40	39	133000	92000	Mec
7	M	48	55	1.68	60	400	600	38	40	113000	85000	Plasty
8	M	61	80	1.8	35	250	0	38	15	217000	218000	Plasty
9	M	59	95	1.77	65	100	0	52	42	129000	85000	Mec
10	F	50	60.9	1.63	35	300	0	39	34	185000	190000	Mec
11	F	25	45	1.5	40	200	300	32	25	409000	335000	Bio
12	M	54	72	1.72	50	175	0	40	32	201000	142000	Mec
13	F	77	72.1	1.6	45	1000	0	35	32	154000	93000	Bio
14	M	68	68	1.8	35	310	0	41	35	248000	166000	Plasty
15	F	27	61	1.62	65	350	0	38	29	222000	200000	Mec
16	F	72	49.5	1.58	40	100	0	45	36	221000	148000	Plasty
17	M	81	72	1.7	35	150	0	42	36	146000	130000	Plasty
18	F	42	63.5	1.68	30	375	600	37	27	268000	164000	Plasty
19	M	56	94.5	1.67	80	150	0	44	31	261000	154000	Plasty
20	F	58	62.5	1.68	60	275	300	40	32	143000	73000	Plasty
21	F	22	65	1.66	80	150	0	41	32	170000	71000	Mec
Total					50.24	308.81	214.29					
sd					18.74	210.10	330.58					

CPB = cardiopulmonary bypass; bleed. = bleeding; hemot. = hemotransfusion; pre. = preoperative; post. = postoperative; Mec. = mechanical prosthesis; Bio. = Biological prosthesis; Plasty = Posterior annuloplasty; SD = Standard deviation

Table 3. Study variables (descriptive values and comparison between means) in groups I and II.

Variables	Group I		Group II		
	Mean	SD	Mean	SD	*P*
CPB (min.)	45.4	13.0	50.2	18.7	0.3447[(1)]
Bleeding volume (ml)	633.5	305.7	308.8	210.1	0.0003[(1)]
Blood transfusion volume (ml)	942.6	345.79	214.29	330.58	<0.0001[(2)]

Note: if P ≤ 0.05 - significant difference, [(1)]t Test; [(2)] Mann-Withney test

Table 4. Number and percentage of patients, according to study variables between groups I and II.

Variables	Group I		Group II		
	Nº	%	Nº	%	*P*
Type of Surgery					
Mitral repair	12	57.1	11	52.4	0.7565[(1)]
Valve replacement	9	42.9	10	47.5	
Need for hemotransfusion					
Yes	21	100	8	38.1	<0.0001[(2)]
No	0	0	13	61.9	

NOTE: if P ≤ 0.05 - significant difference, (1) Chi-square test (2) Chi-square test with Yates' correction

DISCUSSION

The risks associated with blood transfusion and its components have encouraged the search for pharmacological agents capable of reducing blood loss as a result of CPB [6]. The frequency of excessive bleeding is variable. It was considered, in 13% to 16% of patients observed, an abnormal bleeding, translated by the need for transfusions of 10 units of packed red blood cells, or more in the perioperative period [14].

Among the patients analyzed in this investigation, there was no bleeding exceeding 1200 ml, with a mean of 308.81 ± 210.1 bleeding ml, showing that the use of epsilon-aminocaproic acid, in this sample, in mitral cardiac surgery with use of CPB reduced bleeding and use of blood products. It should be noted the difficulty in quantifying the bleeding during surgery. It is justifiable, and in some cases and in accordance with the criteria mentioned in the method of blood transfusion, blood transfusion volumes greater than volumes of postoperative bleeding in the first 24 hours.

Karski et al. [15] reported incidence of 18% of patients undergoing surgery using CPB, with a great need for blood and blood products, increasing the risk of infection and transfusion reactions.

DelRossi et al. [16] concluded that prophylactic treatment with epsilon-aminocaproic acid in cardiac surgery requiring CPB may reduce bleeding in a safe and tolerable manner.

Montesano et al. [17] analyzed the effects of low doses of epsilon-aminocaproic acid in patients undergoing coronary artery bypass grafting. It was used 5 g of epsilon-aminocaproic acid immediately before the start of the infusion, a single dose. It was observed a lower bleeding and less need for blood transfusion, statistically significant.

Breda et al. [18] concluded that the topical use of antifibrinolytic agents in pericardial cavity of epsilon-aminocaproic acid had a favorable effect in reducing bleeding in the first 24 hours postoperatively and in the need for blood transfusion after coronary artery bypass grafting when performed.

In this study, two groups of patients were similar in all parameters except the amount of bleeding and blood transfusions. It can be verified that the group I had an average volume of 633.5 ± 305.7 bleeding ml and group II, 308.8 ± 210.1 ml, with a significance level statistically significant (P = 0.0003). There was also a decrease in the use of blood products, since in group I (control) were infused a mean of 942.8 ± 345.8 ml, whereas in group II (epsilon-aminocaproic acid), the average was 214.3 ± 330.6 ml, with a significance level less than 0.0001. With the decrease of blood products it can be reduced the risk of infection and transfusion reactions, further supporting the need for the use of EACA.

Efficacy of epsilon-aminocaproic acid, among the current options for use of antifibrinolytic agents in relation to the reduction of postoperative bleeding and the need for blood transfusions is questioned and conflicting in many studies literature [19-21].

Despite the use of antifibrinolytic is not included in consensus guidelines determining its use as mandatory everyday and in valve surgery, the results of this study, in the dose used, show that epsilon-aminocaproic acid has real importance in relation to postoperative bleeding and use of blood products in mitral valve surgery. It should be emphasized that in the dose given, in patients with normal hepatic and renal function, there is an absence of thrombosis and hypersensitivity reactions [22].

CONCLUSION

The present investigation shows that the epsilon-aminocaproic acid, in the prescribed dose, was able to reduce the amount of bleeding and need for blood products in the immediate postoperative period of patients undergoing mitral valve surgery.

REFERENCES

1. Pontes JCDV, Matos MFC, Medeiros CGS, Silva AF, Duarte JJ, Gardenal N, et al. Estudo comparativo do emprego da aprotinina em baixas doses X placebo, durante a circulação extracorpórea. Rev Bras Cir Cardiovasc. 2002;17(1):47-53.

2. Kirklin JW, Barrat-Boyes BG. Postoperative care. In: Kirklin JW, Barrat-Boyes BG, eds. Cardiac surgery. New York:Churchil Livingstone;1986.

3. Horrow JC. Management of coagulopathy associated with cardiopulmonary by-pass. In: Gravlee GP, Davis RF, Utley JR, eds. Cardiopulmonary bypass: principles and practice. Baltimore:Williams & Wilkins;1993.

4. Ellison N, Jobes D. Hemostasis during cardiopulmonary bypass. In: Tinker JH, ed. Cardiopulmonary bypass: current concepts and controversies. Philadelphia: W. B. Saunders; 1989.

5. Kucuk O, Kwaan HC, Frederickson J, Wade L, Green D. Increased fibrinolytic activity in patients undergoing cardiopulmonary bypass operation. Am J Hematol. 1986;23(3):223-9.

6. Petterson CM, Stammers AH, Kohtz RJ, Kmiecik SA, Nichols JD, Mills NJ, et al. The effects of ultrafiltration on e-aminocaproic acid: an in vitro analysis. J Extra Corpor Technol. 2002:34(3):197-202.

7. Miana, LA, Atik FA, Moreira LF, Hueb AC, Jatene FB, Auler Junior JO, et al. Fatores de risco de sangramento no pós-operatório de cirurgia cardíaca em pacientes adultos. Rev Bras Cir Cardiovasc. 2004;19(3):280-6.

8. Harmon DE. Cost/benefit analysis of pharmacologic hemostasis. Ann Thorac Surg. 1996;61(2 Suppl):S21-5.

9. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, McClelland B, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2007;(4):CD001886.

10. Rosén M. The aprotinin saga and the risks of conducting meta-analyses on small randomised controlled trials: a critique of a Cochrane review. BMC Health Serv Res. 2009;9:34.

11. Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, et al; BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med. 2008;358(22):2319-31.

12. Munoz JJ, Birkmeyer NJ, Birkmeyer JD, O'Connor GT, Dacey LJ. Is epsilon-aminocaproic acid as effective as aprotinin in reducing bleeding with cardiac surgery? A meta-analysis. Circulation. 1999;99(1):81-9.

13. Elias DO, Souza MHL. Antifibrinolíticos na profilaxia do sangramento pós-perfusão: II Ácido épsilon aminocapróico. Disponível em: www.perfline.com/artigos/artigos98/epsilon.htm

14. Despotis GJ, Skubas NJ, Goodnough LT. Optimal management of bleeding and transfusion in patients undergoing cardiac surgery. Semin Thorac Cardiovasc Surg. 1999;11(2):84-104.

15. Karski JM, Dowd NP, Joiner R, Carroll J, Peniston C, Bailey K, et al. The effect of three different doses of tranexamic acid on blood loss after cardiac surgery with mild systemic hypothermia (32 degrees C). J Cardiothorac Vasc Anesth. 1988;12(6):642-6.

16. DelRossi AJ, Cernaianu AC, Botros S, Lemole GM, Moore R. Prophylactic treatment of postperfusion bleeding using EACA. Chest. 1989;96(1):27-30.

17. Montesano RM, Gustafson PA, Palanzo DA, Manley NJ, Sadr FS. The effect of low-dose epsilon-aminocaproic acid on patients following coronary artery bypass surgery. Perfusion. 1996;11(1):53-6.

18. Breda JR, Gurian DB, Breda ASCR, Meneghine A, Freitas ACO, Matos LL, et al. Uso tópico de agente antifibrinolítico na redução do sangramento após revascularização cirúrgica do miocárdio. Rev Bras Cir Cardiovasc. 2009;24(3):341-5.

19. Henry D, Carless P, Fergusson D, Laupacis A. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. CMAJ. 2009;180(2):183-93.

20. Brown JR, Birkmeyer NJ, O'Connor GT. Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. Circulation. 2007;115(22):2801-13.

21. Souza HJ, Moitinho RF. Estratégias para redução do uso de hemoderivados em cirurgia cardiovascular. Rev Bras Cir Cardiovasc. 2008;23(1):53-9.

22. Royston D. Aprotinin versus lysine analogues: the debate continues. Ann Thorac Surg. 1998;65(4 Suppl):S9-19.