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

Ricardo Adala BENFATTI¹, Amanda Ferreira CARLI², Guilherme Viotto Rodrigues da SILVA³, Amaury Edgardo Mont’serrat Ávila Souza DIAS⁴, José Anderson GOLDIANO⁵, José Carlos Dorsa Vieira PONTES⁶

Abstract

Introduction: The epsilon-aminocaproic acid is an antifibrinolytic used in cardiovascular surgery to inhibit the fibrinolysis and to reduce the bleeding after cardiopulmonary bypass (CPB).

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 (EACA). 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.
INTRODUCTION

Cardiopulmonary bypass (CPB), because it is an event that exposes the blood to a non-endothelial surface, provides changes to the blood crisis, 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).

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   | 35          | 500          | 900       | 35        | 31        | 890000    | 1060000   | Plasty   |
| 2      | F      | 80  | 35.2   | 1.5    | 35          | 500          | 900       | 43        | 42        | 155000    | 730000    | Plasty   |
| 3      | F      | 60  | 46     | 1.52   | 50          | 390          | 1200      | 40        | 39        | 241000    | 141000    | Plasty   |
| 4      | M      | 73  | 64     | 1.65   | 30          | 500          | 1200      | 38        | 39.2      | 186000    | 560000    | 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        | 250000    | 980000    | 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    | 850000    | 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    | 900000    | 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

![Fig. 1 - Bleeding volume- Group I - control; Group II - Epsilon-aminocaproic acid](image1)

![Fig. 2 - Blood transfusion volume - Group I - control; Grupo II - Epsilon-aminocaproic acid](image2)
Table 2. Variables of the study of Group II (epsilon-aminocaproic acid)

| Number | Gender | Age | Weight | Height | Time of CPB | Bleed. volume | Hemat. volume | 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    | Plasty  |
| 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    | Bio     |
| 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       |
| 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(2) |
| 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-Whitney test

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

| Variables              | Group I | Group II |
|------------------------|---------|----------|
|                        | Nº      | %        | Nº      | %        |
| 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

|            | Nº | %  |
|------------|----|----|
| Yes        | 21 | 100|
| No         | 0  | 0  | 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 Acido epsilon 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, Cernaianau 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.