Rev Bras Cir Cardiovasc 2009; 24(3): 341-345

Topical use of antifibrinolytic agent to reduce postoperative bleeding after coronary artery bypass surgery

Uso tópico de agente antifibrinolítico na redução do sangramento após revascularização cirúrgica do miocárdio

João Roberto BREDA[1], Danilo Bortoloto GURIAN[2], Ana Silvia Castaldi Ragognetti BREDA[3], Adriano MENEGHINE[4], Andréa Cristina de Oliveira FREITAS[5], Leandro Luongo de MATOS[6], Luiz Carlos de ABREU[7], Adilson Casemiro PIRES[8]

RBCCV 44205-1098

Abstract

Objective: **Antifibrinolytic agents reduce bleeding after cardiac surgery, but there are adverse effects after their systemic use. These effects are avoided by topical application of antifibrinolytic agents in pericardial cavity. We compared the effects of topically applied epsilon-aminocaproic acid (EACA) and placebo on postoperative bleeding and transfusion requirements after coronary artery bypass surgery.**

Methods: **In this single center prospective, randomized, double-blind trial, 53 patients were randomized into two groups to receive EACA (24 g in 250 ml of saline solution) or placebo (250 ml of saline solution) before sternal closure. Groups were compared according the preoperative and intraoperative variables. Postoperative bleeding, transfusion requirements and hematologic parameters were evaluated.**

Results: **Postoperative bleeding within first 24 hours (h) period (EACA group 154.66±74.64 x Placebo group 220.21±136.42 ml; *P*=0.031) showed statistically significant inter-group difference, within 48 h (EACA group 259.14±420.07 x Placebo group 141.67±142.58 ml; *P*=0.614), as well as cumulative blood loss (EACA group 832.07±576.86 x Placebo group 827.50±434.12 ml; *P*=0.975), not showed statistically inter-group differences. Inter-group difference of blood product requirements was statistically significant (EACA group 185.90±342.07 x Placebo group 439.42±349.07 ml; *P*=0.016). Laboratory analyses showed no differences between the two groups postoperative (hematologic characteristics: hemoglobin (g/dl)- EACA group 9.18±0.92 x Placebo group 8.85±1.48 g/dL; *P*=0.11; hematocrit (%)-EACA group 28.15±3.35 x Placebo group 26.67±4.15%; *P*=0.06).**

Conclusion: **Topical use of epsilon aminocaproic acid reduces postoperative bleeding in the first 24 hours and requirements of blood transfusion after coronary artery bypass graft surgery.**

Descriptors: **Coronary Artery Bypass. Antifibrinolytic Agents. Hemorrhage.**

Resumo

Objetivo: **Verificar o efeito do uso tópico do ácido epsilon-aminocapróico (AEAC), aplicado na cavidade pericárdica, na redução do sangramento e necessidade de transfusão sanguínea no pós-operatório de revascularização cirúrgica do miocárdio.**

Métodos: **Entre outubro de 2007 e outubro de 2008, 53 pacientes da mesma instituição foram alocados em um estudo prospectivo, randomizado e duplo-cego. Foram selecionados portadores de insuficiência coronariana crônica com indicação para revascularização cirúrgica do miocárdio. Os**

1. PhD. in Medicine (Professor)
2. Medical Resident in Cardiology
3. Cardiologist
4. Master in Cardiology
5. Cardiovascular Surgeon
6. Medical Resident in General Surgery
7. PhD. (Professor of Physiology)
8. PhD. (Head Professor)

Work performed at the Cardiovascular Surgery Discipline of the Faculdade de Medicina do ABC and Serviço de Cirurgia Cardiovascular of the Hospital Estadual Mário Covas, Santo André, SP, Brazil.

Correspondence address:
João Roberto Breda. Rua Antonio Bastos, 755 - Apto. 31. Santo André/SP, Brazil. ZIP Code: 09040-220.
E-mail: jrbreda@hotmail.com

Article received on January 5th, 2009
Article accepted on July 20th, 2009

pacientes foram divididos em dois grupos: grupo AEAC e grupo Placebo, comparados de acordo com as características clínicas, demográficas e variáveis operatórias. Foram avaliados o volume de sangramento pelos drenos, a necessidade de transfusão e os níveis de hemoglobina e hematócrito de pós-operatório.

Resultados: **O sangramento pós-operatório pelos drenos nas primeiras 24 horas (grupo AEAC 154,66±74,64 x grupo placebo 220,21±136,42 ml; *P*=0,031) foi menor no grupo AEAC, porém, em 48 horas (grupo AEAC 259,14±420,07 x grupo placebo 141,67±142,58 ml; *P*=0,197) e a perda acumulada até a retirada dos drenos (grupo AEAC 832,07±576,86 x grupo placebo 827,50±434,12 ml; *P*=0,975) não apresentou diferença estatística significante. Houve menor necessidade de transfusão no grupo AEAC, com diferença estatística significante (grupo AEAC 185,90±342,07 x grupo placebo 439,42±349,07 ml; *P*=0,016). Os valores de hemoglobina (grupo AEAC 9,18±0,92 x grupo placebo 8,85±1,48 g/dL; *P*=0,331) e hematócrito (grupo AEAC 28,15±3,35 x grupo placebo 26,67±4,15%; *P*=0,162) não mostraram diferença estatística significante na comparação entre os grupos.**

Conclusões: **O uso tópico do ácido epsilon-aminocapróico apresentou efeito favorável na redução do sangramento nas primeiras 24 horas de pós-operatório e na necessidade de transfusão sanguínea após revascularização cirúrgica do miocárdio.Trabalhos adicionais com maior número de pacientes serão necessários para confirmar estes resultados.**

Descritores: **Revascularização Miocárdica. Antifibrinolíticos. Hemorragia.**

INTRODUCTION

The systemic use of antifibrinolytic agents remains controversial, with conflicting evidences in terms of benefits and adverse events [1]. Therefore, the topical use of these agents, in the pericardial cavity, started to be considered as an alternative for reducing bleeding after cardiovascular surgeries [2,3].

Nevertheless, similarly to the systemic use, the topical application of antifibrinolytics in the pericardial cavity is not a routine procedure in cardiac surgeries [4]. The topical application of tranexamic acid (TA) and aprotinine have already been tested in previous works and, one of the main reasons not to recognize the regular use of these agents is the lack of evidences of their potential benefits [3,4].

In 2000, De Bonnis et al. published a randomized study demonstrating a small clinical benefit favorable to the topic use of TA when compared to a placebo [5]. More recently, in 2007, Baric et al. compared the effects of topical application of TA, aprotinine and placebo over postoperative bleeding of 300 patients submitted to cardiac surgery, concluding the benefits in the topical use of antifibrinolytic agents [6].

The objective of this work is verifying the effect of the topical application of EACA in the pericardium of patients submitted to myocardial revascularization surgery, comparing the postoperative bleeding volume and the need for hemoderivative transfusion, between the antifibrinolytic and placebo groups.

METHODS

Between October 2007 and October 2008, 53 patients of the same institution were assigned to a prospective randomized double-blind study. The selected candidates were patients holding chronic coronary insufficiency referred to myocardial revascularization surgery, performed with the aid of extracorporeal circulation (ECC).

The criteria for exclusion were: previous diagnosis for coagulation disorder, associated operations (in addition to myocardial revascularization), minimally invasive myocardial revascularization, reoperations, urgent or emergency procedures.

The clinical and demographic characteristics of both groups of patients are described in Table 1.

The protocol of the study was approved by the Ethics and Research Commission of the Faculdade de Medicina do ABC (FMABC) and the patients agreed in participating of the study by signing an agreement term.

Surgical technique

The operation started with hemodynamic monitoring with mean blood pressure measurement, central venous pressure and urinary debt, as well as pulse oximetry control.

The operation was performed in a conventional manner; the method of access in all cases was mean sternotomy. It was used an aortic cannula from the inferior vena cava through the right atrium after the endovenous administration of heparine (400 UI/Kg) in order to obtain activated coagulation time (ACT) higher than 480 seconds, with mild hypothermia and myocardial protection by controlled hypoxia with intermittent aortic clamping. In all cases it was used protamine sulfate for complete reversion of anticoagulation (proportion of 1:1).

At the end of the operation, the patients in normothermia were conveyed to the Postoperative Unit and kept under continuous monitoring.

All patients were followed-up during hospital evolution

by the same member of the surgical group, filling out a protocol for analysis of the preoperative and postoperative data.

Pharmacologic protocol

After the selection, the patient was randomized in one of the two study groups. A paramedic not directly involved in the research prepared the medication that was used topically in the patient, in an appropriate place and outside the operation room, containing 24g of EACA diluted in salty solution (in a total volume of 250 ml) or simply salty solution (also 250 ml). The solution was sent to the operation room containing only an identification number; none of the members of the surgical group or the postoperative unit were aware of the liquid content to be applied in the pericardial cavity.

In all patients the anti-aggregating therapy was interrupted 5 days prior to the operation and restarted 24 hours after the surgical procedure with the introduction of an acetylsalicylic acid (ASA) dosage of 100 mg/day.

Statistical analysis

The choice for central tendency measures and value dispersion of which the samples are composed, as well as the statistical tests for their comparison was based on the distribution type by the Kolmogorov-Smirnof test. For all the analysis it was used the program SPSS® version 13.0 (SPSS Inc®, Illinois, U.S.A.).

The values obtained by the study of each quantitative variable were organized and described by the mean and standard deviation. For the qualitative variables there were used absolute and relative frequencies.

Comparisons of frequency events between qualitative variable groups were performed by the application of the exact test of Fisher and qui-square. For the comparison between the averages of two sample populations there were used the "t" test of Student and the "U" test of Mann-Whitney for parametric and non-paramedic variables, respectively.

RESULTS

Both groups were compared according to their preoperative clinical and demographical characteristics not presenting differences between them (Table 1). In the laboratory comparison between the preoperative hematological characteristics no statistically significant difference in the hemoglobin values was noticed (EACA group 12,9±2,41 x placebo group 12,2±3,36 g/dL; *P*=0,100) and the hematocrit values (EACA group 39,7±4,02 x placebo group 38,7±4,73%; *P*=0,163) in the comparison between the groups (Table 2). Similarly, in the postoperative no statistically significant difference between the groups was observed, in the hemoglobin values (EACA group 9,18±0,92 x placebo group 8,85±1,48 g/dL; *P*=0,331) and hematocrit values (EACA group 28,1±3,35 x placebo group 26,6±4,15%; *P*=0,162) (Table 3). No patient was reoperated for hemostasia review. The time of anoxia and perfusion are described in Table 4.

The postoperative bleeding through the drains in the first 24 hours (EACA group 154,66±74,64 x placebo group 220,21±136,42 ml; *P*=0,031) it was lower in the EACA group, although, in 48 hours (EACA group 259,14±420,07 x placebo group 141,67±142,58 ml; *P*=0,197) and the accumulated loss until the removal of the drains (EACA group 832,07±576,86 x placebo group 827,50±434,12 ml;*P*=0,975), no statistically significant difference was observed. The need for transfusion in the EACA group was lower with statistically significant difference (EACA group 185,90±342,07 x placebo

Table 1. Demographical and clinical characteristics of the patients

Variables	EACA Group	Control Group	*P* descriptive
Gender (%)			
Female	17.2	37.5	0.124
Male	82.8	62.5	
Age (years)	57.83±9.33	60.0±8.07	0.802
High blood pressure (%)	93.3	83.3	1.000
Diabetes mellitus (%)	36.7	50	0.051
Left coronary trunk disease (%)	20.7	24.5	0.942
Three vessel disease (%)	55.2	56.6	0.287
Two vessel disease (%)	20.7	15.1	0.287
One vessel disease (%)	3.4	3.8	0.287
Ventricular function %			0.223
Good >50	51.7	58.5	
Moderate [30 - 50]	37.9	28.3	0.223
Bad < 30	10.3	13.2	0.223
Dislipidemia (%)	40	33.3	0.650

Table 2. Preoperative hematological characteristics

Variables	EACA Group	Placebo Group	*P* descriptive
Hemoglobin (g/dl)	12.9±2.41	12.2±3.36	0.100
Hematocrit (%)	39.7±4.02	38.7±4.7	0.163
Platelets (10^3/mm^3)	216±69	225±82	0.453
Time of protrombine (seconds)	12.9±2.29	13.5±3.10	0.949
Activity of protrombine(%)	91.3±14.1	88.7±17.2	0.348
Time of parcial tromboplastine activated (seconds)	29.1±4.51	30.5±5.65	0.093
INR (International Normatized Relation)	1.07±0.20	1.12±0.28	0.708

Table 3. Postoperative hematological characteristics

Variables	EACA Group	Placebo Group	*P* descriptive
Hemoglobin (g/dl)	9.18±0.92	8.85±1.48	0.331
Hematocrit (%)	28.1±3.35	26.6±4.15	0.162
Platelets (10^3 /mm^3)	128±57	151±64	0.180
Time of protrombine (seconds)	17.4±8.17	16±2.44	0.262
Activity of protrombine (%)	62.4±15.7	60.9±14.9	0.739
Time of parcial tromboplastine activated (seconds)	42.1±16.8	40.2±15.8	0.686
INR (International Normatized Relation)	1.35±0.35	1.43±0.50	0.540

Table 4. Operative data

Variables	EACA Group	Placebo Group	*P* descriptive
Time of anoxia (minutes)	34.5±12.4	38.1 ±11	0.269
Time of perfusion (minutes)	51.3±17.1	56.3 ±16.3	0.286

group 439,42±349,07 ml; *P*=0,016). The hemoglobin (EACA group 9,18±0,92 x placebo group 8,85±1,48 g/dL; *P*=0,331) and hematocrit (EACA group 28,15±3,35 x placebo group 26,67±4,15%; *P*=0,162) no statistically significant difference was evidenced when comparing both groups (Table 5).

DISCUSSION

This study revealed a positive effect of the topical application of the antifibrinolytic agent tested for bleeding reduction, evaluated by the volume drainage by the drains. When comparing both groups it was noticed a decrease of approximately 30% in the drain debt. Blood transfusion was less required with positive results for the EACA group. The cumulative loss of blood during the first 24 hours was lower in the EACA group than in the placebo group (with significant difference). The absence of difference in the accumulated drainage volume until the removal of the drains was expected and had already been identified in previous works, that demonstrated that the best haemostatic effect of these agents lasts up to 6 hours of its introdution [5,7].

In 1993, Tatar et al. published the first work on the topical use of antifibrinolytic agents, demonstrating a positive effect in reducing bleeding and the need for transfusion in 25 patients holding coronary disease, using aprotinine [2]. This result was later confirmed in a randomized and double-blind study, in 100 patients submitted to myocardial revascularization surgery (MRS) [3].

In 1995, Ciçek et al. verified that after the topical application of aprotinine in the pericardium there was no evidence of this substance in the blood of the operated patients and this factor could indicate a decrease in the fibrinolytic "state" of the patients submitted to surgery with the aid of extracorporeal circulation (ECC) [7].

De Bonnis et al. published a randomized double-blind study, with 40 patients submitted to myocardial revascularization surgery and observed a reduction of 25% in the drainage volume in the first 24 hours, although, it did not occur reduction in the transfusion of hemoderivatives [5].

In 2007, Baric et al. Published an analysis of 300 patients submitted to open heart surgery, that were randomized in three group: placebo, tranexamic acid and aprotinine. In this double-blind and prospective study, it was verified a positive effect in the topical application of antifibrinolytic agent: both agents tested (tranexamic acid and aprotinine) reduced in approximately 20% a cumulative blood loss compared to the placebo group. Nevertheless, the work did not revealed significant reduction in the blood and hemoderivative transfusion in the comparison between groups [6].

Starting in 1990, the parenteral use of antifibrinolytic agents was broadly adopted in the cardiovascular operations; this fact was followed of increasing preoccupation with the efficiency and security of these agents. Amongst the three main available drugs, the aprotinine was the most used and tested [8-10]. In 2007, Ferraris et al. published a recommendation based on the evidences available in the literature as class I (evidence level A): 1. Aprotinine in high doses is indicated for reducing transfusion, the total loss of blood and the need of re-exploration in high risk patients submitted to cardiac surgery. The benefits of this application need to be evaluated against the risk of renal adverse effects. 2. Aprotinine in low doses is indicated for reducing the number of patients that require blood transfusion and still

Tabela 5. Postoperative data

	EACA Group	Placebo Group	*P* descriptive
Debit of drain (ml)-24hours	154.66±74.64	220.21±136.42	0.031
Debit of drain (ml)-48hours	259.14±420.07	141.67±142.58	0.197
Debit of drain (ml)-cumulative until removal	832.07±576.86	827.50±434.12	0.975
Transfusion of erythrocyte concentration (ml)	185.90±342.07	439.42±349.07	0.016

reduce the total loss of blood in cardiac operations. 3. Analogous of the lisine, such as the EACA and tranexamic acid, are indicated for reducing the need of transfusion and reducing the total loss of blood.

These agents are less effective than the aprotinine and its security requires additional studies [11]. Recently, the sales of aprotinine were temporarily suspended by the laboratory responsible for its production, and this decision was based on the information supplied by the Canadian Study Executive Commission BART (The Blood Conservation Using Antifibrinolytics in a Randomized Trial), whose preliminary results demonstrated that the benefits of the drugs administration in blood reduction were not sufficient for maintaining the continuity of the study [12].

Regarding the uncertainties about the security of the parenteral application of antifibrinolytic agents, its topical application in the pericardial cavity could be a better alternative, with the possibility of reducing the adverse effects of these medications (including renal risk of graft acute thrombosis after myocardial revascularization surgery). We have used the routine parenteral EACA in cardiac operations. However, after reading the article from Baric et al., that analyzed the topical effect of the aprotinine and of the tranexamic acid, we decided to test the efficiency of the EACA applied topically in the pericardium, once this agent was not previously evaluated. Therefore, despite the number of patients included, the results obtained in this work imply a positive effect of the EACA applied topically in the pericardium, possibly representing an acceptable alternative with reduction of the collateral effects of the systemic use of antifibrinolytic agents. A possible complication of the topical use would be the increase of pericardial adherence, thus, causing further complications in an eventual reoperation, however, this situation was suggested in a work that tested the aprotinine and needs additional confirmation [13].

Therefore, based on the results achieved, we concluded that the topical use of the epsilon-aminocaproic acid presented a positive effect in reducing bleeding, particularly in the first 24 hours of postoperative, with a lesser requirement of blood transfusion when compared with the use of placebo. Additional prospective works with a larger number of patients will be necessary to confirm these results.

REFERENCES

1. Levi M, Cromheecke ME, de Jonge E, Prins MH, de Mol BJ, Briët T, et al. Pharmacological strategies to decrease excessive blood loss in cardiac surgery:a meta-analysis of clinically relevant endpoints. Lancet. 1999; 54(9194):1940-7.

2. Tatar H, Ciçek S, Demirkilic U, Ozal E, Süer H, Oztürk O, et al. Topical use of aprotinin in open heart operations. Ann Thorac Surg. 1993; 55(3):659-61.

3. O'Regan DJ, Giannopoulos N, Mediratta N, Kendall SW, Forni A, Pillai R, et al. Topical aprotinin in cardiac operations. Ann Thorac Surg. 1994;58(3): 778-81.

4. Hanif M, Nourei SM, Dunning J. Does the use of topical tranexamic acid in cardiac surgery reduce the incidence of post-operative mediatinal bleeding? Interact Cardiovasc Thorac Surg. 2004;3(4): 603-5.

5. De Bonis M, Cavaliere F, Alessandrini F, Lapenna E, Santarelli F, Moscato U, et al. Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study. J Thorac Cardiovasc Surg. 2000;119(3):575-80.

6. Baric D, Biocina B, Unic D, Sutlic Z, Rudez I, Vrca VB, et al. Topical use of antifibrinolytic agents reduces postoperative bleeding: a double-blind, prospective, randomized study. Eur J Cardiothorac Surg. 2007;31(3): 366-71.

7. Ciçek S, Tatar H, Demirkiliç U, Kuralay E. Topical use of aprotinin in cardiac surgery. J Thorac Cardiovasc Surg. 1995;110(2): 568-9.

8. Souza HJB, Moitinho RF. Estratégias para redução do uso de hemoderivados em cirurgia cardiovascular. Rev Bras Cir Cardiovasc. 2008; 23(1): 53-59.

9. Mangano DT, Tudor IC, Dietzel C. Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. N Engl J Med. 2006; 354(4):353-65.

10. Karkouti K, Beattie WS, Dattilo KM, McCluskey SA, Ghannam M, Hamdy A, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. Transfusion. 2006;46: 327-38.

11. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA 2nd, Haan CK, Hoyston BD, et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. Ann Thorac Surg. 2007; 83(5 Supp): S27-86.

12. 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.

13. Cicek S, Theodoro DA. Topical aprotinin in cardiac operations: a note of caution. Ann Thorac Surg. 1996; 61(3): 1039-40.