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Use of aprotinin in thoracic aortic operations associated with deep hypothermic circulatory arrest: a meta-analysis

Uso da aprotinina na operação da aorta torácica associada à hipotermia profunda e parada circulatória: metanálise

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Abstract

Objective: **To evaluate complications involved in the use of aprotinin in patients after thoracic aortic aneurysm or dissection surgeries associated with deep hypothermic circulatory arrest.**

Methods: **A systematic review of literature was carried out, with a search strategy of low specificity, in the Medline® and LILACS® databases. Two independent researchers carried out article selection following the criteria adopted for inclusion of studies, grouping them into two groups, one where low doses of aprotinin were employed and the other with high doses. The results are presented as relative risk for the dichotomy variable, and as weighted mean differences for continuous variables, both with 95% confidence intervals.**

Results: **Seven articles were included in the systematic review selected from 2044 revised studies. Meta-analysis of the only randomized controlled trial did not demonstrate risks with the use of aprotinin, and presented a significant reduction in bleeding and blood transfusion requirements. Meta-analysis of the studies that used low doses of aprotinin was similar. On the other hand, meta-analysis of the studies that adopted high doses of aprotinin did not present statistical significance in any of the studied variables.**

Conclusion: **Despite of the results not showing any effective risks with the use of aprotinin, the statistical power of the meta-analysis is low. Therefore, new randomized controlled trials are required, in order to detect possible complications in the use of aprotinin in this type of operation.**

Descriptors: **Aprotinin. Aorta thoracic. Hypothermia induced. Meta-analysis.**

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Resumo

Objetivo: **Avaliar as complicações decorrentes do uso da aprotinina em pacientes submetidos à cirurgia de aneurisma ou dissecção da aorta torácica, que utilizaram hipotermia profunda e parada circulatória.**

Método: **Realizou-se uma revisão sistemática da literatura, com uma estratégia de busca de baixa especificidade, nas bases de dados da Medline® e LILACS®. Dois pesquisadores independentes realizaram a seleção de artigos, seguindo os critérios adotados para inclusão de estudos, agrupando-os em dois grupos, um em que foi empregada baixa dose de aprotinina e outro alta dose. Os resultados foram apresentados como risco relativo para as variáveis dicotômicas, e como diferença de média ponderada para as variáveis contínuas, ambos com 95% de intervalo de confiança.**

Resultados: **Sete artigos compuseram a revisão sistemática, selecionados a partir de 2044 estudos revisados. A metanálise do único ensaio clínico controlado e randomizado não evidenciou riscos no uso da aprotinina, e apresentou uma redução significativa no sangramento e requerimento de transfusão de sangue. A metanálise dos estudos que empregaram baixa dose de aprotinina foi similar. Por outro lado, a metanálise dos estudos que adotaram alta dose de aprotinina não apresentou significância estatística em nenhuma variável estudada.**

Conclusão: **Apesar de os resultados não evidenciarem riscos efetivos do uso da aprotinina, o poder estatístico da metanálise é baixo. Portanto, novos ensaios clínicos controlados e randomizados são requeridos, a fim de detectar possíveis malefícios do uso da aprotinina nesse tipo de operação.**

Descritores: **Aprotinina. Aorta torácica. Hipotermia induzida. Metanálise.**

INTRODUCTION

The conventional surgical treatment of aneurysms or dissections of the ascending or transverse aorta is indispensable to guarantee a satisfactory prognosis of the patient. It is well known that this procedure is associated with high morbimortality rates. Thus, in order to reduce the intra-operative risks, it is necessary to establish cardiopulmonary bypasses (CPB) and deep hypothermia with circulatory arrest (DHCA) [1,2]. However, it is also well known that the combination of CPB with DHCA may contribute to a greater risk of complications of the surgical procedure by triggering hemostatic dysfunction and coagulopathies [2,3].

Coagulopathies triggered by CPB have a multifactorial origin although its primary cause is exposure of the blood to the materials of the heart-lung machine [4]. Additionally, the administration of heparin and protamine cause alterations to the hemostatic balance by activation of the platelets, neutrophils and of the fibrinolytic system as well as consuming coagulation factors and reducing the platelet count [5]. Similarly, DHCA, by means of circulatory stasis, promotes the release of activated protein C and activators of tissue plasminogen, fibrinolytic agents, thereby increasing the possibility of bleeding and the necessity of re-interventions and blood transfusions [6,7].

Hence, it is necessary to attenuate these complications. Several methods have been studied including normovolemic hemodilution, intraoperative autotransfusion with pre-donation of autologous blood and the use of pharmacological agents, including protamine [8,9].

Aprotinin, a non-specific inhibitor of serin protease, was first utilized by Tice et al. [10] at the start of the 1960s, in a heart surgery procedure to prevent bleeding due to hyperfibrinolysis. Since then, it has been successfully used in hemostatic preservation in high-risk heart surgery associated with CPB, attenuated by several mechanisms including the reduction of fibrinolysis, inhibition of the activation of neutrophils and preservation of platelet function [8,11-13]. These aspects, endorsed by safety rates and the effectiveness of the drug, encouraged several medical teams to expand the use of aprotinin to procedures in which DHCA was used, mainly in cases of aortic aneurysms and dissections [14,15].

However, in spite of several retrospective series [1,15] and some controlled and randomized clinical trials [16,17] the effectiveness of aprotinin in significantly reducing postoperative bleeding and the necessity of re-interventions or blood transfusions in aortic procedures has not been proven. Westaby et al. [7], as well as Sundt et al. [18], reported controversial results. The rates of bleeding, blood transfusions, renal dysfunction, myocardial infarctions and strokes were significantly higher in a group of patients treated with aprotinin.

Despite of little clinical evidence provided by retrospective studies, these results question the effectiveness and safety of aprotinin in aortic procedures involving CPB and DHCA. Hence, a systematic review and meta-analysis of publications was performed to assess, with a high level of evidence, complications related to the use of

aprotinin in patients submitted to aortic aneurysm and dissection surgeries utilizing deep hypothermia and circulatory arrest.

METHOD

Inclusion criteria of studies

Controlled and randomized clinical trials that analyzed the effectiveness and safety of aprotinin in patients submitted to thoracic aortic aneurysm and dissection surgeries associated with CPB and DHCA were included. Although double-blind studies are possible in this type of intervention, this was not considered an inclusion criterion, but a question to be evaluated in the quality of the study.

Retrospective studies were also included however these were evaluated and grouped separately, with exceptions made due to the low evidence level provided by the results. Series of retrospective cases without control groups or in which there was a significant statistical difference between the preoperative and intraoperative parameters of the Aprotinin and Control Groups were excluded.

Participants

Patients of any age, gender or ethnic background who required a conventional surgical intervention for the reconstruction of the aorta, due to acute or chronic aneurysms or dissections of their thoracic portion were included. These aneurysms or dissections should have been diagnosed from clinical parameters and complementary imaging examinations (nuclear magnetic resonance, computed tomography or angiography).

Interventions

The use of aprotinin controlled by placebos was evaluated in the surgeries of aneurysms or dissections of the thoracic aorta associated to CPB and DHCA. However, the study groups of patients treated with aprotinin were distributed and evaluated in relation to the dose of the drug aministered, that is, high doses (2×10^6 units of kalicrein inhibiter – KIU – intravenously, 2×10^6 KIU in initial pump and 5×10^4 KIU/hour as a continuous intravenous infusion) and low doses (a dose less than or equal to half the high dose).

Clinical results

The evaluated clinical outcomes were the volume of bleeding, the necessity of blood component transfusions, myocardial infarction, strokes, reoperations, death within 30 days and renal dysfunction and failure. Renal dysfunction was defined as levels of postoperative serum creatinine 1.5 times higher than the preoperative level and renal failure was defined as the necessity of hemodialysis.

Search strategy to identify studies

The search strategy used to identify studies was by using the Medline ® database via PubMed and LILACS® database up to January 20 2006. This strategy was based on describers, synonyms and abbreviations of aprotinin, thoracic aorta aneurysm and deep hypothermia with total circulatory arrest, thus, constituting high sensitivity with low specificity. No limitations such as date, language, journal or country of origin of the published studies were imposed, reducing publication biases. The presented search strategy was used with the Medline® database and modified according to the standards required in the LILACS® database (Figure 1).

(Aprotinin OR Ferring Brand of Aprotinin OR Aprotinin Ferring Brand OR Basic Pancreatic Trypsin Inhibitor OR Trypsin Inhibitor, Basic, Pancreatic OR Bovine Kunitz Pancreatic Trypsin Inhibitor OR Bovine Pancreatic Trypsin Inhibitor OR Kallikrein-Trypsin Inactivator OR Inactivator, Kallikrein-Trypsin OR Kallikrein Trypsin Inactivator OR Kunitz Pancreatic Trypsin Inhibitor OR Trypsin Inhibitor, Kunitz, Pancreatic OR BPTI, Basic Pancreatic Trypsin Inhibitor OR Antilysin OR Contrykal OR Arzneimittelwerk Dresden Brand of Aprotinin OR Kontrikal OR Kontrykal OR Contrical OR Dilmintal OR Iniprol OR Sanofi Winthrop Brand of Aprotinin OR Pulmin OR Traskolan OR Trasylol OR Bayer Brand of Aprotinin OR Aprotinin Bayer Brand OR Zymofren) **AND** (Aortic Aneurysm, Thoracic OR Aneurysm, Thoracic Aortic OR Aneurysms, Thoracic Aortic OR Aortic Aneurysms, Thoracic OR Thoracic Aortic Aneurysm OR Thoracic Aortic Aneurysms OR Aortic Aneurysm OR Aneurysm, Aortic OR Aneurysms, Aortic OR Aortic Aneurysms OR Aneurysm, Dissecting OR Dissecting Aneurysm OR Aneurysms, Dissecting OR Dissecting Aneurysms) **AND** (randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR random allocation OR double blind method OR single blind method OR clinical trial OR clinical trials OR (clinical* AND trial*) OR single* OR double* OR treble* OR triple* OR placebos OR placebo* OR random* OR research design OR comparative study OR evaluation studies OR follow-up studies OR prospective studies OR control* OR prospectiv* OR volunteer*)

Fig. 1 – Search strategy used to Medline ® database

Standardized review method

Selection of the studies

Two researchers independently evaluated the studies identified by the search strategy, grouping the studies into selected and non-selected works according to the data in titles and abstracts. For cases in which there were doubts because the methodology used was not identifiable from the title and abstract, the complete text was evaluated and then they were selected or not. Articles related to the selected studies and their references were also verified by the same criteria (Figure 2).

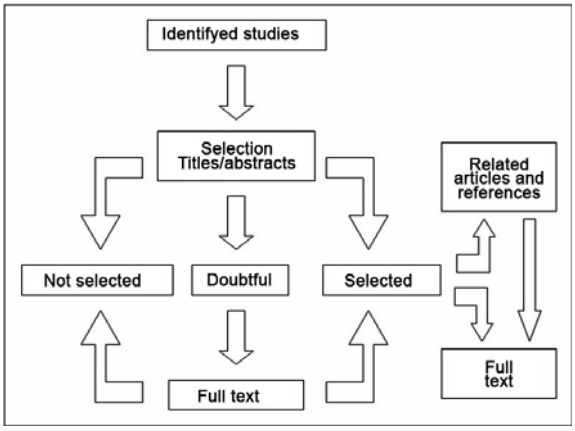

Fig. 2 – Flow chart of studies selection

The studies selected by the two researchers were compared and discrepancies determined by discussion and consensus. Following this, the entire articles were independently assessed according to the inclusion criteria. Included and excluded articles were discussed at a new consensus meeting. Finally, the articles selected by this process review were analysed to avoid duplication.

Quality of assessment

Two independent researchers assessed the quality of the methodology of the included articles, according to adequacy of the patient randomization method. This evaluation consisted in the classification of studies in categories, which varied from A to D and were closely related to the description of the randomization of patients. The studies were classified as: A – The randomization method of the study was adequately described; B - the randomization method was mentioned but was inadequately described; C - the randomization method was inadequate; D – the patients were not randomized. Any differences of opinion between researchers were decided after discussion and consensus.

To complement this method, the scale of study quality by Jadad et al. [19] was used. Again any differences of opinion between researchers were decided after discussion and consensus.

Data extraction

The necessary data to formulate the systematic review were extracted from the studies by two independent researchers. For this, a standardized questionnaire based on the required information was utilized. The authors of the studies were contacted to add information to the results of their studies when necessary.

Statistical analysis

Descriptive analysis

Clinical outcomes including renal dysfunction and insufficiency, myocardial infarction, strokes, reoperations and mortality within 30 days were considered qualitative nominal categorical variables. On the other hand, the bleeding and blood component transfusion outcomes were considered quantitative continuous numerical variables. The authors intended to analyze the sensitivity of the study, but the number of studies made this impossible.

Inferential analysis

Comparisons of the effects estimated among interventions were assessed using the Review Manager (RevMan® 4.2.8) computer program. The results were expressed as relative risks (RR) for nominal clinical outcomes and as weighted mean differences (WMD) for continuous clinical outcomes, both with 95% confidence intervals (CI). All the graphs were constructed in a random model.

RESULTS

Selected studies

Applying the search strategy in the Medline® and LILACS® databases and following the described selection method, 2044 articles were identified. From these, only 27 were selected to analyze the entire text and seven were included in the systematical review and meta-analysis (Figure 3).

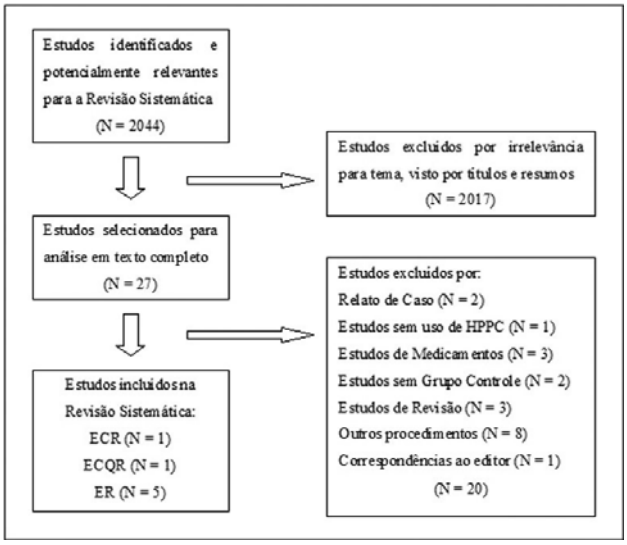

Fig. 3 - Flow chart of collect of articles
CRCT - Controlled and randomized clinical trial; QRCT- quazi-randomized clinical trial; RE- Retrospective study; DHCA- Deep Hypothermia circulatory arrest

Description of included studies

Mangano et al. [3] in 2001 published a retrospective analysis with a control group of 183 patients who underwent thoracic aortic surgery associated to DHCA. They allocated 44 patients in the Treated Group with high doses of aprotinin and 139 patients to a control group. The outcomes did not associate aprotinin to renal dysfunction or insufficiency however, the authors did not observe any reduction in bleeding or blood transfusion requirements.

Seigne et al. [11] in 2000 retrospectively compared the effects of aprotinin in blood transfusion requirements and in appearance of postoperative complications in patients

who had undergone thoracic aorta surgery associated to DHCA. They included nine patients in a group treated using aprotinin, who received low doses and ten in a control group. The outcomes showed benefits with the use of aprotinin giving statistical differences related to blood transfusion requirements and the amount of bleeding. In respect to postoperative complications, significant discrepancies were not observed between the groups.

In 1998 Ehrlich et al. [16] performed a study aiming at assessing renal complications, as well as blood loss due to the use of low doses of aprotinin in patients who were submitted to aortic aneurysm and dissection surgeries using DHCA. Utilizing a randomization method and efficient mask, the authors distributed 50 patients into two equal groups, one treated with aprotinin and the other treated with a placebo. The only preoperative discrepancy between them was a greater prevalence of diabetes in the control group. The results did not demonstrate significant differences between the assessed parameters. However, the variables, transfusion requirements and blood volume drained from thorax were significantly lower in patients treated with aprotinin.

Okita et al. [17] in 1996 performed a study comparing perioperative bleeding and the fibrinolysis system in individuals who underwent aortic surgery associated to DHCA with and without the use of aprotinin. They included 60 patients who were intentionally randomized into two groups; one group was treated with low doses of aprotinin (n=39) and the other was a control group (n=21). They used satisfactory exclusion criteria compatible with the type of study proposed. They did not find significant differences in the morbidities between groups and verified less bleeding and blood transfusion requirements in the group prescribed aprotinin. In 1995 Goldstein et al. [15] published a retrospective study with control group evaluating complications of aprotinin when used in surgeries with DHCA. Each group was formed of 23 patients who had undergone thoracic aortic aneurysm or dissection surgeries and one patient who was submitted to the resection of a renal tumor with invasion to the inferior vena cava. They administered high doses of aprotinin, and identified reductions in transfusion requirements and mortality whilst there were no significant differences in respect to strokes and myocardial infarctions. They concluded that the use of aprotinin is safe and effective in surgeries requiring DHCA.

In 1994 Westaby et al. [7] retrospectively evaluated 80 patients in two groups; one group received aprotinin in aorta surgeries using DHCA (n=53) and the other was a control group (n=27). They used high doses of aprotinin in heterogeneous operative techniques, that is, the technique was slightly changed over the assessed period. For all variables, aprotinin gave the worst results; it was associated to increases in bleeding, blood transfusion requirements and reoperations. The only variable that was similar between the two groups was the 30-day mortality rate. They concluded that aprotinin should be used with much care in aortic surgeries with DHCA.

Sundt et al. [18] in 1993 performing a retrospective study with a control group assessed the effects of aprotinin with DHCA. The group treated with high doses of aprotinin consisted of 20 patients, as did the control group. In absolutely all the morbid parameters comparing the groups, aprotinin presented the worst results, even though without significance, while bleeding and blood transfusion requirements were statistically higher with the use of aprotinin. These factors led the researchers to oppose the use of aprotinin for thoracic aortic surgery using DHCA.

Methodological quality of included studies

Table 1 summarizes all relevant information of included studies related to the evaluation of the methodology used. Seven studies were included in this systematic review; one controlled and randomized clinical trial, five retrospective studies and one quasi-randomized study.

Meta-analysis

Meta-analyses were performed considering two groups of articles. The first was composed of all studies that utilized low doses of aprotinin, that is, the studies of Ehrlich et al. [16], Okita et al. [17] and Seigne et al. [1]. The second group consisted studies that used high doses of aprotinin and included the works of Sundt et al. [18], Westaby et al. [7], Goldstein et al. [15] and Mangano et al. [3].

The studies that used low dose aprotinin did not identify significant differences in relation to the qualitative performance (Figure 4):

- Stroke – RR 0.71 [95% CI 0.11; 4.65];
- Myocardial infarction – RR 0.44 [95% CI 0.06; 3.44];
- Renal dysfunction – RR 2.00 [95% CI 0.19; 20.67];
- Renal insufficiency – RR 2.58 [95% CI 0.42; 15.99];
- Mortality at 30 days – RR 0.75 [95% CI 0.19; 3.01]

However, there were many cases of stroke, myocardial infarction and death in the placebo group, while there was a large number of renal dysfunction and insufficiency cases in the aprotinin group. Despite this, there was statistical significance in transfusion requirements and drained blood volume favoring the aprotinin group (drain of thorax – 24 hours) – WMD – 233.53 [95% CI -406.32; -60.74], transfusion requirements – WMD – 1.60 [95% CI -2.99; -0.21] (Figure 5).

There was also no significance in the analysis of qualitative outcomes of the studies that used high doses of aprotinin (Figure 6):

Table 1. Methodology and methodological quality of the included studies

Author/year	Category	Scale of Jadad	Aprotinin Group	Control Group	Aprotinin dose	Heparin dose	Test of ACT
Sundt, 1993	D	0	20	20	I	300 U/kg*	--
Westaby, 1994	D	0	53	27	I	--	--
Goldstein, 1995	D	0	24[£]	24[£]	I	300 U/kg	Celite/Kaolin
Okita, 1996	C	1	39	21	II	3 mg/kg	Kaolin
Ehrlich, 1998	A	5	25	25	II	3 mg/kg	Kaolin
Seigne, 2000	D	0	9	10	II	300 U/kg	Celite/Kaolin
Mangano, 2001	D	0	44	139	I	375 U/kg*	--

ACT = activated anticoagulation time; I= 2 x 10^6 KIU intravenous, 2 x 10^6 KIU in initial pump and 5 x 10^4 KIU/hour as continuous intravenous infusion II = dose lower than or equal to half of the Dose I (mean value; [£]A patient was submitted to the resection of renal tumor; — not described in the study)*

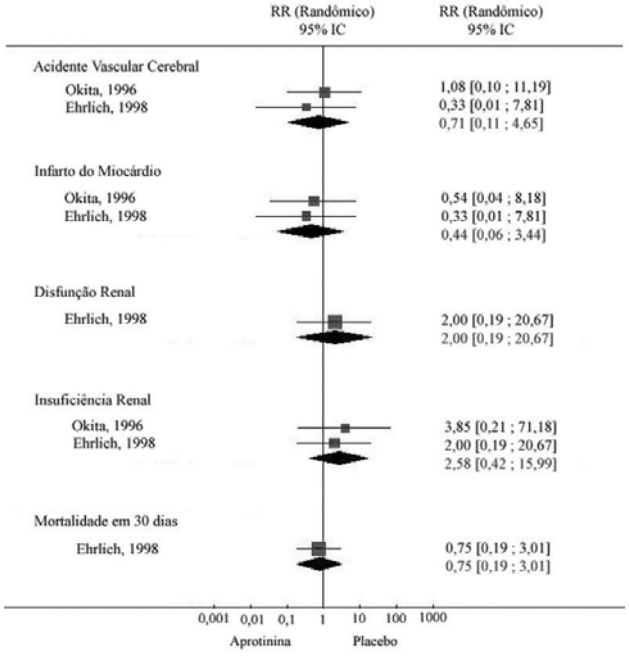

Fig. 4 – Meta-analysis of the dichotomous variables of the studies that used low doses of aprotinin; RR – Relative risk; CI - confidence interval

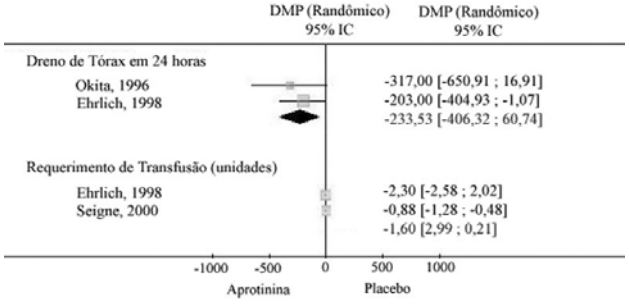

Fig. 5 - Meta-analysis of the continuous variables of studies that used low doses of aprotinin. WMD – Weighted mean difference; CI – confidence interval

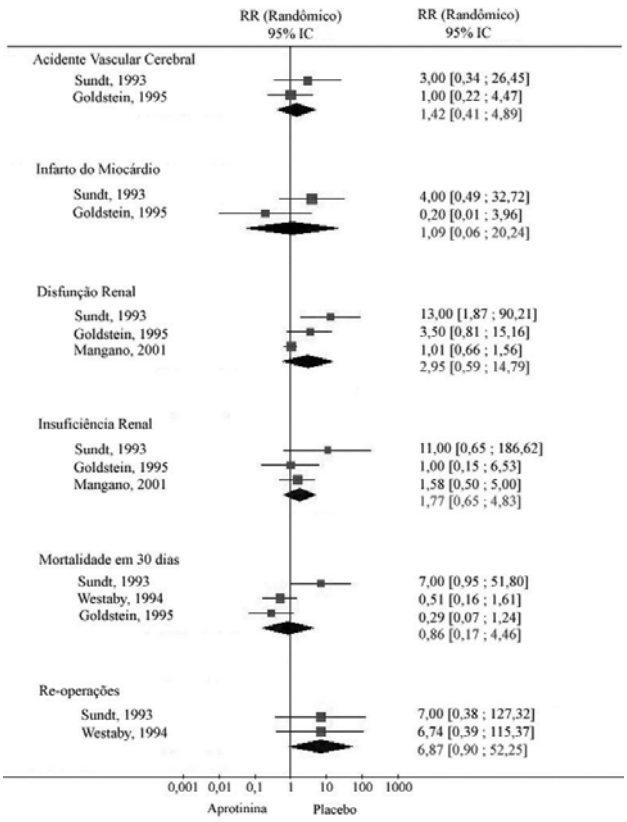

Fig. 6 – Meta-analysis of the continuous variables of the studies that used high doses of aprotinin; RR – Relative risk; CI - Confidence Interval

- Stroke – RR 1.42 [95% CI 0.41; 4.89];
- Myocardial infarction – RR 1.09 [95% CI 0.06; 20.24];
- Renal dysfunction – RR 2.95 [95% CI 0.59; 14.79];
- Renal insufficiency- RR 1.77 (95% CI 0.65; 4.83];
- Mortality in 30days – RR 0.86 [95% CI 0.17; 4.46];
- Reoperations – RR 6.87 [95% CI 0.90; 52.25].

However, there were more cases of stroke, myocardial infarction, renal insufficiency and dysfunction and reoperations in the group treated with aprotinin. The only variable that differed from the standard was the mortality rate over 30 days. Moreover, there was no statistical difference comparing the placebo and aprotinin groups in respect to drained blood volume and transfusion requirements (drain of thorax – 12 hours) – WMD -7.00 [95% CI -58.49; 44.49], transfusion requirements – WMD 2.18 [95% CI -6.05; 10.41) (Figure 7).

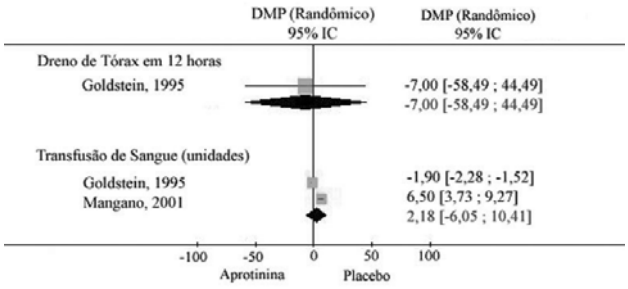

Fig. 7 – Meta-analysis of the continuous variables of studies that used high doses of aprotinin. WMD - Weighted mean difference; CI – confidence interval

DISCUSSION

Aprotinin has been used in a considerable number of surgical procedures [8-13] since it was first utilized as an antifibrinolytic agent by Tice et al. [10] in 1963. Its efficacy was observed in several studies and thus, it is routinely used in some centers, in particular in complex heart surgeries [11, 12]. Hence, it started to be utilized in operations that required the use of deep hypothermia and circulatory arrest. Nevertheless, results of studies that assessed this use are controversial [7, 15-17], in particular in respect to aneurysm and thoracic aortic dissection surgeries.

Taking this into consideration, the authors proposed a systematic review with meta-analysis of the literature aiming at clarifying the discussions over the use of aprotinin. The principal goal of this study was to evaluate complications associated to the use of aprotinin in thoracic aortic surgeries involving DHCA [7, 18].

Based on recommendations by the Cochrane Center in respect to systematical reviews [20] the inclusion of controlled and randomized clinical trials was predetermined for the statistical summaries provided by meta-analysis. The results of this type of study have lower type 1 and 2 errors (probabilities α and β, respectively), providing considerable reliability of their conclusions. However, due to the small number of studies in this case, quasi-randomized and retrospective studies were also included.

Restrictions in age, gender, ethnic background were not stipulated, nor were the dose of aprotinin utilized. These factors, together with the low specificity of the search strategy gave an ample review of publications, thereby minimizing the bias.

Seven studies were included in the review. In fact, only the study performed by Ehrlich et al. [16] in 1998 has a methodology that can be considered a controlled and randomized clinical trial. The other six studies are retrospective studies, with the exception of the work by Okita et al. [17], which has a criterion without perfect randomization and thus is not a controlled and randomized clinical trial [1,3,7, 15,18].

However, methodologically, these studies are diametrically divergent, considering that there is no standard of surgical technique used in the protocol of heparinization during CPB and the use of aprotinin. These factors cause deep methodological heterogeneity, making comparison of the results difficult and unreliable. This question is present in practically all clinical trials in surgery, as each center adopts a different operative protocol, thereby fragmenting the expected technical homogeneity. Nevertheless, in order to attenuate these methodological heterogeneities, there was a distribution and analysis of the articles in respect to the dose of aprotinin, dividing the studies in two groups: one group utilized high doses of aprotinin and the other used low doses.

The studies of Sundt et al. [18] published in 1993 and of Westaby et al. [7] published in 1994 are the most incisive in affirming that aprotinin causes greater bleeding, transfusion requirements, mortality, comorbidities and significantly contributed to the number of patients in the meta-analysis. However, despite there not being any comment on the method used to measure the activated coagulation time (ACT), it is probable that the method utilized was the Celite method, as both studies were performed between 1991 and the middle of 1993; the first descriptions of the Kaolin method to monitor anticoagulation appeared at the end of 1992 [21].

It is well known that aprotinin is closely related to ACT, as, normally, this under the effect of aprotinin is artificially prolonged, as well as with hypothermia [22]. Thus, heparin and aprotinin actuate synergistically to affect ACT, occurring, therefore, a considerable risk of having under-heparinization, if the ACT is the only method used to monitor anticoagulation [17, 23]. Moreover, the Celite method to monitor ACT is altered with greater intensity by synergistic action of the triad heparin, aprotinin and hypothermia than

the Kaolin method [24, 25]. Thus, there is a possibility that the results that were not favorable with the use of aprotinin reported in the studies of Sundt et al. [18] and Westaby et al. [7] are related to an inadequate anticoagulation level.

CONCLUSION

Taking into account these factors, it is obvious that, although there are studies that evaluate and confirm that aprotinin is an efficient and safe antifibrinolytic agent, the scarcity of solid scientific evidence in aortic surgery associated to DHCA does not allow an ample and convict affirmation for all cases. Thus, it is necessary that more studies are performed, using a standardized and well designed methodology for the surgical technique, use of aprotinin, heparinization, randomization, involving many patients to attain statistical power for the meta-analysis and to detect any possible adverse effects with the use of aprotinin.

REFERENCES

1. Seigne PW, Shorten GD, Johnson RG, Comunale ME. The effects of aprotinin on blood product transfusion associated with thoracic aortic surgery requiring deep hypothermic circulatory arrest. J Cardiothorac Vasc Anesth. 2000;14(6):676-81.

2. Bedirhan MA, Turna A, Yagan N, Tasci O. Aprotinin reduces postoperative bleeding and the need for blood products in thoracic surgery: results of a randomized double-blind study. Eur J Cardiothorac Surg. 2001;20(6):1122-7.

3. Mora Mangano CT, Neville MJ, Hsu PH, Mignea I, King J, Miller DC. Aprotinin, blood loss, and renal dysfunction in deep hypothermic circulatory arrest. Circulation. 2001;104(12 suppl 1):I276-81.

4. Wenger RK, Lukasiewicz H, Mikuta BS, Niewiarowski S, Edmunds LH Jr. Loss of platelet fibrinogen receptors during clinical cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1989;97(2):235-9.

5. Mohr R, Golan M, Martinowitz U, Rosner E, Goor DA, Ramot B. Effect of cardiac operation on platelets. J Thorac Cardiovasc Surg. 1986;92(3 pt 1):434-41.

6. Ergin MA, Galla JD, Lansman L, Quintana C, Bodian C, Griepp RB. Hypothermic circulatory arrest in operations on the thoracic aorta: determinants of operative mortality and neurologic outcome. J Thorac Cardiovasc Surg. 1994;107(3):788-99.

7. Westaby S, Forni A, Dunning J, Giannopoulos N, O'Regan D, Drossos G, et al. Aprotinin and bleeding in profoundly hypothermic perfusion. Eur J Cardiothorac Surg. 1994;8(2):82-6.

8. van Oeveren W, Harder MP, Roozendaal KJ, Eijsman L, Wildevuur CR. Aprotinin protects platelets against the initial effect of cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1990;99(5):788-97.

9. Katsaros D, Petricevic M, Snow NJ, Woodhall DD, Van Bergen R. Tranexamic acid reduces postbypass blood use: a double-blinded, prospective, randomized study of 210 patients. Ann Thorac Surg. 1996;61(4):1131-5.

10. Tice DA, Reed GE, Clauss RH, Worth MH. Hemorrhage due to fibrinolysis occurring with open-heart operations. J Thorac Cardiovasc Surg. 1963;46:673-9.

11. Cosgrove DM 3rd, Heric B, Lytle BW, Taylor PC, Novoa R, Golding LA, et al. Aprotinin therapy for reoperative myocardial revascularization: a placebo-controlled study. Ann Thorac Surg. 1992;54(6):1031-8.

12. Robinson J, Nawaz S, Beard JD. Randomized, multicentre, double-blind, placebo-controlled trial of the use of aprotinin in the repair of ruptured abdominal aortic aneurysm. On behalf of the Joint Vascular Research Group. Br J Surg. 2000;87(6):754-7.

13. Parolari A, Antona C, Alamanni F, Spirito R, Naliato M, Gerometta P, et al. Aprotinin and deep hypothermic circulatory arrest: there are no benefits even when appropriate amounts of heparin are given. Eur J Cardiothorac Surg. 1997;11(1):149-56.

14. Smith CR, Spanier TB. Aprotinin in deep hypothermic circulatory arrest. Ann Thorac Surg. 1999;68(1):278-86.

15. Goldstein DJ, DeRosa CM, Mongero LB, Weinberg AD, Michler RE, Rose EA, et al. Safety and efficacy of aprotinin under conditions of deep hypothermia and circulatory arrest. J Thorac Cardiovasc Surg. 1995;110(6):1615-22.

16. Ehrlich M, Grabenwoger M, Cartes-Zumelzu F, Luckner D, Kovarik J, Laufer G, et al. Operations on the thoracic aorta and hypothermic circulatory arrest: is aprotinin safe? J Thorac Cardiovasc Surg. 1998;115(1):220-5.

17. Okita Y, Takamoto S, Ando M, Morota T, Yamaki F, Kawashima Y. Is use of aprotinin safe with deep hypothermic circulatory arrest in aortic surgery? Investigations on blood coagulation. Circulation. 1996;94(9 Suppl):II177-81.

18. Sundt TM 3rd, Kouchoukos NT, Saffitz JE, Murphy SF, Wareing TH, Stahl DJ. Renal dysfunction and intravascular coagulation with aprotinin and hypothermic circulatory arrest. Ann Thorac Surg. 1993;55(6):1418-24.

19. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.

20. Alderson P, Green S, Higgins J: Cochrane Reviewers' Handbook 4.2.1. [updated December 2003]. Chichester, UK:John Wiley & Sons; 2004.

21. Wang JS, Lin CY, Hung WT, Karp RB. Monitoring of heparin-induced anticoagulation with kaolin-activated clotting time in cardiac surgical patients treated with aprotinin. Anesthesiology. 1992;77(6):1080-4.

22. Kawasuji M, Ueyama K, Sakakibara N, Tedoriya T, Matsunaga Y, Misaki T, et al. Effect of low-dose aprotinin on coagulation and fibrinolysis in cardiopulmonary bypass. Ann Thorac Surg. 1993;55(5):1205-9.

23. Smith CR, Mongero LB, DeRosa CM, Michler RE, Oz MC. Safety of aprotinin in profound hypothermia and circulatory arrest. Ann Thorac Surg. 1994;58(2):606-8.

24. Lemmer JH Jr, Stanford W, Bonney SL, Chomka EV, Karp RB, Laub GW, et al. Aprotinin for coronary artery bypass grafting: effect on postoperative renal function. Ann Thorac Surg. 1995;59(1):132-6.

25. Lemmer JH Jr, Stanford W, Bonney SL, Breen JF, Chomka EV, Eldredge WJ, et al. Aprotinin for coronary bypass operations: efficacy, safety, and influence on early saphenous vein graft patency. A multicenter, randomized, double-blind, placebo-controlled study. J Thorac Cardiovasc Surg. 1994;107(2):543-53.