

Efficacy and Safety of Aprotinin Use for Reoperative Valvular Surgery

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Background. Preservation of the hemostatic system during cardiac surgery is a main concern, primarily after repeated cardiac operations.

Methods. We compared the outcomes of adult patients undergoing isolated reoperative valvular surgery receiving full-dose of aprotinin (redo group, $n = 70$) with patients experiencing primary isolated valvular surgery not receiving aprotinin (primary group, $n = 135$).

Results. The mean age was lower in the redo group (45 ± 14 years vs 50 ± 17 years, $p = 0.036$). The redo group had more female patients (73% vs 51%, $p = 0.003$), patients in functional class IV (15% vs 4% $p = 0.009$), and patients with chronic atrial fibrillation (48% vs 24%, $p = 0.001$). The cardiopulmonary bypass duration was longer in the redo group (119 ± 50 minutes vs 103 ± 41 minutes, $p = 0.014$). However, the blood loss was significantly lower (300 ± 279 mL vs 776 ± 584 mL, $p = 0.001$) and fewer patients needed transfusions (3.0% vs 13%, $p = 0.023$) in the redo group. The

postoperative morbidity was similar in both groups. The postoperative in-hospital mortality was 7% in the primary group and 10% in the redo group ($p = 0.419$). Factors associated with postoperative in-hospital mortality were the following: age greater than 60 years ($p = 0.040$, odds ratio [OR] 3.0), New York Heart Association class IV ($p = 0.022$, OR 5.0), preoperative critical state ($p < 0.001$, OR 12), emergent operation ($p = 0.012$, OR 7.0), endocarditis ($p = 0.004$, OR 10.0), and reoperation due to mechanical mitral prosthesis dysfunction ($p = 0.009$, OR 7).

Conclusions. The mortality and morbidity in redo valve surgery with aprotinin administration was comparable with primary valve surgery without aprotinin. Bleeding and transfusion requirements were significantly lower in redo patients receiving aprotinin.

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Cardiopulmonary bypass (CPB) has profound effects on the fibrinolytic system, and it seems that fibrinolytic activity is more pronounced during CPB in cardiac valve surgery than in coronary artery bypass graft surgery [1]. Therefore, preservation of the hemostatic system during cardiac surgery is a main concern, which has stimulated strategies for management of bleeding complications after repeated cardiac operations [2–4]. Although the hemostatic effect of aprotinin is well-known [3–6], there has been concern about its safety [7], particularly with respect to hypersensitivity responses, and increased incidence of renal dysfunction, stroke, and myocardial infarction, mostly originating from repeated CABG surgery experiences.

The main cause of valve dysfunction in Brazil is still rheumatic fever. The disease usually afflicts the younger population and because many patients underwent conservative operations or received bioprostheses, which are commonly used in Brazil for social and economic reasons, repeated valvular surgery is common. However, there are few reports of aprotinin use in reoperative

valvular surgery, a cohort of patients quite different from those afflicted by coronary artery disease. Therefore, the purpose of this study was to compare hospital outcomes for patients undergoing isolated repeated valvular surgery, receiving aprotinin, with patients undergoing primary isolated valvular surgery without receiving aprotinin.

Patients and Methods

Patients and Data Collection

Our institution's Ethics Committee approved this study. This is a retrospective study of our database, and therefore the Ethics Committee waived the requirement for obtaining patient consent.

We examined all patients 18 years of age or greater who underwent isolated valve heart surgery from January 2003 to July 2006. The present study compares patients who underwent isolated reoperative valvular surgery receiving aprotinin (redo group) with patients without prior cardiac surgery history, undergoing isolated valvular surgery not receiving aprotinin (primary group). There was no randomization and the patients needing valve replacement received bovine pericardium bioprostheses (Braile Biomédica, São Jose do Rio Preto, SP, Brazil) or bileaflet mechanical mitral valve bioprostheses (St. Jude Medical,

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Inc, St Paul, MN), at the surgeon's and patient's discretion. The data were collected during the patients' admission and included age, sex, height, weight, body mass index, urgency of operation, prior cardiac surgery, diabetes, arterial hypertension, endocarditis, pulmonary arterial hypertension (systolic pulmonary pressure ≥ 50 mm Hg), renal dysfunction or failure, chronic atrial fibrillation, cerebrovascular disease, stroke, respiratory diseases, New York Heart Association (NYHA) functional class, left ventricular ejection fraction, duration of cardiopulmonary bypass (CPB), duration of aortic cross-clamping, surgery performed, hypersensitivity and anaphylactic reactions, systemic thromboembolic complications, reexploration due to postoperative bleeding, need for dialysis, wound infection, pneumonia, adult respiratory distress syndrome (ARDS), blood loss in the first 24 hours after chest closure, need for prolonged mechanical ventilation (>48 hours), need of inotropic drugs, need for transfusion of blood products, acute myocardial infarction, heart failure, acute arterial occlusion, and in-hospital mortality. Blood volume loss, the rate of patients needing transfusion and (or) reexploration for bleeding, the rate of postoperative acute myocardial infarction, renal dysfunction or failure, stroke, and in-hospital mortality were the main outcomes of interest.

Events Definition and Criteria

Postoperative myocardial infarction was diagnosed based on the following signs: appearance of a new Q wave on the electrocardiogram; postoperative severe wall motion, abnormalities in the same area as the ST segment alterations, and akinetic, dyskinetic, or severely hypokinetic segments compared with the preoperative echocardiographic findings; increased plasma concentrations of the biological cardiac marker proteins, creatine kinase and myocardial band isoenzyme (CK-MB) greater than 80 IU. It was considered renal dysfunction if the serum creatinine level was 2 mg/dL or greater preoperatively, or raised above 50% of the preoperative value. Any patient needing dialyses was considered to have renal failure. Postoperative mortality was defined as in-hospital death occurring after the operation, regardless of the time. Perioperative stroke was defined as a new focal neurologic deficit or coma, lasting more than 24 hours, associated with recent ischemic cerebral lesion as demonstrated by computed tomography, which was evident at patient awakening or occurred later in the postoperative course. Mediastinitis was defined as deep sternal wound infection with involvement of the substernal planes and systemic signs of sepsis, and associated with sternal dehiscence or instability. A critical preoperative state was defined as any one or more of the following, occurring immediately before or upon arrival in the operation room: ventricular tachycardia, fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anesthetic room, preoperative inotropic support, intraaortic balloon counterpulsation, preoperative acute renal failure (anuria or oliguria <10 mL/hour), preoperative pul-

monary edema, preoperative cardiogenic shock, or preoperative cardiac tamponade.

Operative Characteristics

Sternotomy was generally used, but some patients were operated through a right thoracotomy, at the surgeon's discretion. The CPB circuit was primed with Ringer's lactate and (or) hydroxyethyl starch. The pump flow was adjusted to 2.4 L/min/m². An infusion of norepinephrine or sodium nitroprusside was administered when necessary, to maintain a mean arterial pressure between 50 and 90 mm Hg during CPB. Arterial blood gases were managed with alpha-stat. Antegrade isothermic hyperkalemic blood cardioplegia was infused every 20 to 30 minutes (500 mL) and patients were cooled to 32° to 34°C. Anticoagulation was achieved using an initial dose of 300 units/kg of heparin (LIQUEMINE, F. Hoffmann-La Roche Ltd, Switzerland) and additional boluses when necessary to maintain a kaolin-activated clotting time greater than 400 s. After CPB, 1 mg of protamine was given for every 100 units of heparin injected before and during CPB. An additional dose of 20 mg was given if the activated clotting time was greater than 120 seconds. No corticosteroids were administered.

As an institutional policy, patients experiencing a second heart operation receive aprotinin (Trasylol; Bayer, São Paulo, Brazil). We use the full-dose regimen: loading dose of 2 million KIU after anesthesia induction, 2 million KIU added to the pump prime, and infusion of 500,000 KIU/hour after the protamine infusion. Therefore, in this study, all patients who had repeated valvular surgery received a full-dose aprotinin regimen.

Protocol for Blood Derivate Transfusion and Reexploration Due to Bleeding

Blood loss through the chest tubes was monitored hourly, starting as soon as the chest was closed. We considered it excessive bleeding when the chest tube effluent exceeded 400 mL/hour during the first two hours, 300 mL/hour during the first three hours, or 200 mL/hour during the first six hours. Additionally, sudden increases in the bleeding rate were considered excessive bleeding. Any patient presenting with excessive bleeding was screened for clotting abnormalities (platelet count $<70,000$, prothrombin time international normalized ratio >1.5). Clotting abnormalities were corrected by means of fresh-frozen plasma, cryoprecipitate and (or) platelet transfusion. If the clotting studies were normal or returned to normal, and the excessive bleeding persisted, reexploration was carried out. Reexploration was considered even if clotting abnormalities persisted after treatment.

Packed red blood cells were given for hemoglobin under 8.0 g/dL. This threshold was raised to hemoglobin under 10.0 g/dL in elderly patients with postoperative unstable hemodynamics and in patients with preoperative heart failure (class III/IV NYHA).

Statistical Analysis

Continuous variables were expressed as mean values $\pm$ standard deviation and compared using the Student *t* test

Table 1. Patient's Characteristics and Demographics

Characteristics	Primary n (%)	Redo n (%)	p Value
Gender:			
Male	67 (49%)	19 (27%)	0.003
Female	68 (51%)	51 (73%)	
Age (y)	50 ± 17	45 ± 14	0.036
Age > 60 years	44 (33%)	11 (16%)	0.012
Body mass index	25 ± 5	24 ± 4	0.990
Ejection fraction	0.60 ± 0.1	0.57 ± 0.1	0.133
Ejection fraction < 0.40	6 (4%)	4 (6%)	0.731
NYHA functional class:			
I	14 (10%)	3 (4%)	0.120
II	59 (44%)	19 (27%)	0.023
III	55 (41%)	36 (53%)	0.135
IV	5 (4%)	10 (15%)	0.009
Preoperative critical state	7 (5%)	8 (11%)	0.155
Arterial hypertension	53 (39%)	21 (30%)	0.220
Active endocarditis	8 (6%)	2 (3%)	0.498
Diabetes	9 (7%)	2 (3%)	0.337
Chronic atrial fibrillation	32 (24%)	33 (48%)	0.001
Chronic obstructive pulmonary disease	4 (3%)	4 (6%)	0.450
Stroke	7 (5%)	4 (6%)	1.000
Serum creatinina > 2 mg/dL	8 (6%)	4 (6%)	1.000
Pulmonary hypertension	32 (24%)	24 (34%)	0.137

NYHA = New York Heart Association.

or the Mann-Whitney test where appropriate. Qualitative variables were expressed as a percentage and compared using the 2-tailed Fisher exact test. Univariate analysis of the association between a perioperative variable and postoperative in-hospital death was performed using the 2-tailed Fisher exact test as well. Estimated odds ratios with their 95% confidence interval were calculated for each variable associated with death. A *p* value less than 0.05 was considered significant. Data were stored and processed in an electronic database using the SPSS 13.0 for Windows software (SPSS, Chicago, IL).

Table 2. Causes of Valvular Reoperative Surgery

Causes	n	%
Conservative mitral valve operation	28	40%
Mitral mechanical prosthesis dysfunction	12	17%
Thrombosis	6	8.5%
Perivalvular leak	6	8.5%
Mitral bioprostheses dysfunction (structural)	13	17%
Tricuspid bioprostheses dysfunction (structural)	4	6%
New native valve dysfunction	6	9%
Aortic bioprostheses dysfunction (structural)	4	6%
Conservative aortic valve operation	2	3%
Other	1	1%

Table 3. Operative Characteristics

Characteristics	Primary n (%)	Redo n (%)	p Value
Aortic cross-clamp time (min)	81 ± 35	77 ± 42	0.407
CPB duration (min)	103 ± 41	119 ± 50	0.014
Emergent operation	6 (4.4%)	7 (10%)	0.138
AVR	53 (39%)	9 (13%)	<0.001
MVR	44 (32%)	37 (53%)	0.007
AVR + MVR	11 (8%)	7 (10%)	0.795
Mitral conservative surgery	31 (23%)	3 (4%)	0.001
Tricuspid annuloplasty (De Vega)	8 (6%)	12 (17%)	0.014

AVR = aortic valve replacement; AVR + MVR = mitral and aortic valve replacement; CPB = cardiopulmonary bypass; MVR = mitral valve replacement.

Results

From January 2003 to December 2006, 205 adult patients underwent isolated heart valve surgery. No patients had previous exposure to aprotinin. One hundred thirty-five patients (66%) had not had previous heart surgery, and 70 (34%) had previous heart valve surgery and aprotinin treatment. Repeated valvular surgery represented 73% of all repeated cardiac surgeries in our institution during this period, followed by repeated coronary artery bypass grafting (CABG) (15%) and repeated valvular surgery plus CABG (5%).

Preoperative Characteristics

The preoperative characteristics of both groups of patients are listed in Table 1. Redo patients were significantly younger than primary surgery patients (45 ± 14 years vs 50 ± 17 years, respectively, *p* = 0.036). The rate of patients older than 60 years of age was significantly higher in the primary group (33% vs 16%, *p* = 0.012).

The redo group included significantly more female patients (73% vs 51%, *p* = 0.003) and functional class IV patients (15% vs 4%, *p* = 0.009). Overall, significantly more patients in the redo group were functional class III or IV (57% vs 43%, *p* = 0.004). The redo group also included more patients with chronic atrial fibrillation (48% vs 24%, *p* = 0.001). None of the patients were on dialysis preoperatively.

The causes of reoperation are listed in Table 2. Mitral

Table 4. Postoperative In-Hospital Morbidity and Mortality

Postoperative Events	Primary n (%)	Redo n (%)	p Value
Reexploration (bleeding)	8 (6%)	1 (1.5%)	0.170
Blood derivate transfusion	18 (13%)	2 (3%)	0.023
Stroke	5 (4%)	1 (1.5%)	0.666
Acute myocardial infarction	1 (0.7%)	1 (1.5%)	1.000
Renal complication	12 (10%)	5 (8%)	0.719
Renal dysfunction	10 (7%)	3 (4%)	0.549
Renal failure	2 (1.5%)	2 (3%)	0.607
Death	9 (7%)	7 (10%)	0.419

valve dysfunction after previous conservative valvular surgery (40%) and mitral prosthesis dysfunction (34%, an equal number of mechanical and bioprostheses) were the main causes of reoperation. In the primary group, the causes of valve dysfunction were rheumatic valve disease (64%), degenerative valve disease (16%), senile aortic valve calcification (10%), and endocarditis (7%). It was not possible to identify the etiology of all valve diseases leading to the primary operation in patients experiencing repeated valvular surgery, because the majority was operated in other institutions, but we found that 40% had rheumatic valve disease.

Operative Characteristics

The operative characteristics are listed in Table 3. There was no significant difference in the aortic cross-clamp duration between the groups, but the CPB duration was significantly longer in the redo group (119 ± 50 minutes vs 105 ± 43 minutes, $p = 0.014$). In the redo group, mitral valve replacement (MVR) was predominant (53% vs 32%, $p = 0.007$). In the primary group, aortic valve replacement was predominant (39% vs 13%, $p < 0.001$). Although a less frequent procedure, conservative mitral valve surgery occurred more often in the primary group (23% vs. 4%, $p = 0.001$). Tricuspid annuloplasty was performed more frequently in the redo group (17% vs 6%, $p = 0.014$).

Postoperative Course

There was no statistically significant difference between the two groups with respect to postoperative morbidity and mortality. This is evident from the data listed in Table 4. There was a difference in the volumes of blood lost through chest tubes during the first 24 hours after chest closure. The blood loss was significantly higher in the primary group (776 ± 584 mL vs 300 ± 279 mL, $p = 0.001$; Fig 1). Even though the number of patients needing reexploration for bleeding was not significantly different between the two groups (Table 4), the proportion of patients requiring transfusion of red blood cells and other blood products, due to hemostasis defects after CPB, was significantly higher in the primary group (13% vs 3.0%, $p = 0.023$). None of the patients experienced hypersensitivity reactions, prosthesis thrombosis, and (or) thromboembolism during the hospital stay.

There were no significant differences between the primary surgery and reoperation group in the other outcomes of interest (Table 4). The most frequent postoperative complication was impairment of renal function. Overall, the rate of renal dysfunction or failure was 10% in the primary group and 8% in the redo group ($p = 0.719$). When considering patients with normal preoperative serum creatinine levels, the renal complication incidence rate was 6% in the primary operation group and 4.5% in the redo group ($p = 0.751$). If only patients with preoperative serum creatinine levels of 2 mg/dL or greater are included, 50% of the patients experienced worsening in their renal function in both groups ($p = 1.0$).

The rate of in-hospital postoperative mortality was 8%. It was 7% in the primary group and 10% in the redo group ($p = 0.419$). Of the patients who died in the redo

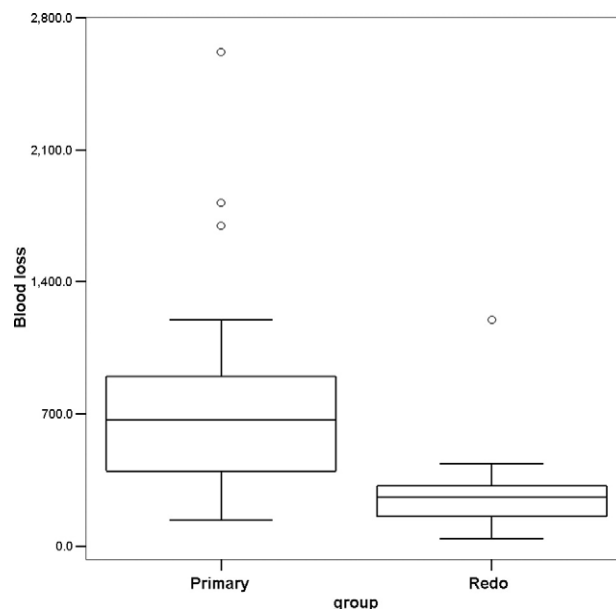


Fig 1. Postoperative blood loss. The difference was significant ($p = 0.001$).

group, 57% were NYHA class III and 43% were class IV. In the primary group, 44% of the patients were NYHA class III and 11% class IV. The number of patients in NYHA class III or IV was not significantly different between the two groups ($p = 0.088$). In the redo cohort, the primary cause of death was cardiac dysfunction in four patients (57%), ischemic stroke in one patient (14%), operated due to preoperative mechanical prosthesis thrombosis, pneumonia in one patient, and exsanguination because of brachiocephalic trunk erosion by a tracheotomy cannula one other patient. In the primary group, three (33%) patients died from respiratory complications (ARDS, chronic obstructive pulmonary disease, vomit aspiration), two (22%) from hemorrhagic stroke, one patient (11%) died of cardiac dysfunction, one from rupture of the posterior wall of the left ventricle after mitral valve replacement, one from multiple organ failure (polytrauma with endocarditis), and one of septic shock (abdominal sepsis with endocarditis).

Factors Associated With In-Hospital Mortality

The following factors were associated with postoperative in-hospital mortality. An age greater than 60 years ($p = 0.040$, odds ratio [OR] 3.0, 95% confidence interval [CI] 1.1 to 8.5), NYHA class IV ($p = 0.022$, OR 5.0, 95% CI 1.4 to 19.0), preoperative critical state ($p < 0.001$, OR 12, 95% CI 3.5 to 40.0), emergent operation ($p = 0.012$, OR 7.0, 95% CI 1.8 to 25.0), endocarditis ($p = 0.004$, OR 10.0, 95% CI 2.5 to 40.0), and reoperation due to mechanical mitral prosthesis dysfunction ($p = 0.009$, OR 7, 95% CI 2.0 to 28.0).

Comment

Our results demonstrate that patients who underwent reoperative valvular surgery and received aprotinin had

hospital courses similar to patients who had primary valvular surgery without receiving aprotinin. However, even with risk factors for increased postoperative blood loss [2, 8–10], patients in the aprotinin cohort had significantly less bleeding when compared with patients who had primary valvular surgery.

The efficacy of aprotinin as a hemostatic agent in cardiopulmonary surgery is well-accepted [11–13], but there have been safety concerns [3, 7]. The main concerns are renal function, hypersensitivity responses, and a higher incidence of strokes and myocardial infarction [7, 14].

Subclinical renal injury has been detected using beta-N-acetyl-beta-D glucosaminidase (NAG)/creatinine and α -1-microglobulin (α -1-m)/creatinine ratios [15–18] in patients who received aprotinin. However, the exact clinical significance is unclear, as it has been suggested that the reduction in reabsorptive function, which accompanies transient tubular dysfunction (as indicated by transiently increased urinary α -1-m/creatinine ratios), may be protective through diminishing tubular work and thus oxygen demand [18]. Nevertheless, from a practical point of view, it seems that aprotinin reduces intraoperative blood loss in different types of surgeries without increasing the incidence of clinically apparent renal dysfunction [19–21]. In our cohort, the renal dysfunction or failure incidence rates were not significantly different between the two groups. However, our cohort was composed of younger patients with fewer risk factors for renal complications than is usually seen in CABG surgery patients. Therefore, the use of a high-dose regimen of aprotinin in specific populations, such as elderly patients, patients with preoperative renal dysfunction, and patients with advanced atherosclerosis and (or) diabetes, should be with caution and warrants further research.

Fortunately, hypersensitivity responses are infrequent in patients without previous exposure to aprotinin. However, the incidence of anaphylactic reactions increases with repeat exposure and may range from 2.5%, for all reexposures, regardless of the time interval, to 10% if the reexposure interval is less than 6 months [22]. There was no case of hypersensitivity in our group of patients, but none had previously been exposed to aprotinin.

Recently, Mangano and colleagues [7] reported increased risk of neurological, renal, and myocardial damage with the use of aprotinin in CABG surgery, fomenting the discussion about the safety of aprotinin use [23–27]. However, other data support the safety of aprotinin use [28], and there are data that suggest that aprotinin has protective effects [29–34]. In our cohort, all cases of stroke were related to preoperative prosthesis thrombosis, acute valve endocarditis, or carotid artery atherosclerosis, and it is highly improbable that aprotinin was the cause of any of these cases of stroke.

Operative mortality in valvular reoperation has been reported to be higher than in primary procedures [35–37]. However, consistent with other studies [38], our results demonstrate that reoperative valvular surgery by itself is not a risk factor for postoperative in-hospital mortality, because the mortality in the redo cohort was similar to that observed in the primary group. However, all valvular

reoperation patients received aprotinin in this study and therefore it would be premature to suggest that aprotinin has any association with the postoperative in-hospital mortality, even when considering its beneficial effect in reducing bleeding.

The variables we have identified as associated with postoperative in-hospital mortality actually reflect decompensated hemodynamic status and (or) reduced functional reserve. These are well-known contributors to increased operative risk. Hence, our data suggest that patients undergoing isolated repeated valvular procedures, who have good functional reserves and are hemodynamically stable, face operative risks that are comparable with patients experiencing primary intervention.

Although we believe that our study contributes to the debate about aprotinin use in repeated valvular surgery, it has limitations. We observed a small cohort of nonrandomized patients that were not matched and this may lead to bias. However, even though the redo cohort consisted of younger patients, several factors usually associated with higher postoperative morbidity and mortality were more frequently observed in this group, including female gender, NYHA class IV, longer CPB duration, chronic atrial fibrillation, and prosthesis dysfunction.

The mortality and morbidity in redo valve surgery with aprotinin administration was comparable with primary valve surgery without aprotinin. Bleeding and transfusion requirements were significantly lower in redo patients receiving aprotinin.

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