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Aprotinin in Cardiac Surgery: A Different Point of View

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ABSTRACT

Aprotinin is widely used in cardiac surgery to reduce postoperative bleeding and the need for blood transfusion. Controversy exists regarding the influence of aprotinin on renal function and its effect on the incidence of perioperative myocardial infarction (MI) and cerebrovascular incidents (CVI). In the present study, we analyzed the incidence of these adverse events in patients who underwent coronary artery bypass grafting (CABG) surgery under full-dose aprotinin and compared the data with those recently reported by Mangano et al [2006]. For 751 consecutive patients undergoing CABG surgery under full-dose aprotinin (>4 million kalikrein-inhibitor units) we analyzed in-hospital data on renal dysfunction or failure, MI (defined as creatine kinase–myocardial band > 60 iU/L), and CVI (defined as persistent or transient neurological symptoms and/or positive computed tomographic scan). Average age was 67.0 ± 9.9 years, and patient pre- and perioperative characteristics were similar to those in the Society of Thoracic Surgeons database. The mortality (2.8%) and incidence of renal failure (5.2%) ranged within the reported results. The incidence rates of MI (8% versus 16%; $P < .01$) and CVI (2% versus 6%; $P < .01$) however, were significantly lower than those reported by Mangano et al. Thus the data of our single center experience do not confirm the recently reported negative effect of full-dose aprotinin on the incidence of MI and CVI. Therefore, aprotinin may still remain a valid option to reduce postoperative bleeding, especially because of the increased use of aggressive fibrinolytic therapy following percutaneous transluminal coronary angioplasty.

INTRODUCTION

Aprotinin (Trasylol®, Bayer, Zurich, Switzerland) is widely used in cardiac surgery to reduce perioperative bleeding. Several large multicenter trials have shown that aprotinin is associated with a more than 45% reduction in blood transfusion compared to placebo [Levy 1995; Aldermann 1998]. These observations are very important, because many patients undergoing coronary artery bypass grafting (CABG) surgery are receiving fibrinolytic medication and, consequently, at higher risk for peri- and postoperative bleeding. Reducing or even eliminating the need for a blood transfusion is important because the number of red blood cell transfusions and the storage duration of red blood cells before transfusion have been associated with adverse outcomes in cardiac surgery [Basran 2006]. However, the use of aprotinin in cardiac surgery has been controversial because of the early published data on a dose-dependent influence on renal function [Sundt 1993; Feindt 1995; D'Ambra 1996]. Microvascular platelet-fibrin thrombi have also been described postmortem in patients undergoing cardiac surgery under deep hypothermic circulatory arrest [Sundt 1993]. In 2004, a metaanalysis of randomized clinical trials revealed that there is no evidence that aprotinin is associated with a higher incidence of mortality, myocardial infarction, or renal failure in patients undergoing cardiac surgery [Sedrakyan 2004]. In fact, this review showed a decreased incidence of perioperative stroke and a trend toward reduced postoperative atrial fibrillation in patients treated with aprotinin [Sedrayan 2004]. However, the debate was recently reactivated after an observational multicenter study of 4374 patients was published by Mangano et al [2006]. In this study—involving 69 institutions in North and South America, Europe, the Middle East, and Asia—patients were prospectively enrolled according to a systematic sampling scheme to receive either aprotinin, aminocaproic acid, or tranexamic acid. High-dose aprotinin appeared to be associated with a 55% increase in the risk of myocardial infarction or heart failure, and a 181% increase in the risk of stroke or encephalopathy [Mangano 2006]. Although this report has several limitations, including the flaw of study design (the assessed variables are barely defined and selection bias may have occurred during patient selection), such reports may have important consequences on the cardiological community. In addition to the immediate reactions provoked by this publication [Dietrich 1995; Ferraris 2006; Levy 2006], we performed the present study to analyze our single-center experience on the incidence of adverse events in nonselected CABG surgery patients undergoing surgery under full-dose aprotinin during a 12-month period and to compare our results with those reported by Mangano et al [2006].

PATIENTS AND METHODS

All consecutive patients who underwent surgical revascularization between January and December 2005 were

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included in the current analysis. According to our institutional organization, patients' written informed consent for data analysis were obtained before the in-hospital data were prospectively collected in a database. Perioperative mortality (until 30 days following surgery) and the following morbidities were assessed: myocardial infarction, indicated by postoperative creatine kinase–myocardial bound (CK-MB) >60 iU/L; cerebrovascular accident, indicated by reversible neurological effects (within 72 hours) or permanent neurological effects (stroke) with confirmed alteration in the computed tomographic scan; renal dysfunction, indicated by a >50% increase of postoperative serum creatinine compared to the preoperative value; and renal failure, indicated by the need for postoperative temporary or permanent hemodialysis. All patients underwent on-pump surgery under moderate hypothermia (32°C). Unless contraindicated, aprotinin is routinely administered in our surgical patients, using a high-dose regimen of 2 Mio units in the priming volume, 2 Mio units given by the anesthesiologist, and 500,000 units/h as a continuous perfusion.

Statistical Analysis

All data analysis and statistical analysis were performed by our system administrator (BG). Data are presented as mean ± SD. A Mann-Whitney *U* test and a χ^2 test were used to compare continuous and nominal variables, respectively. A *P* value <.05 was considered significant.

RESULTS

Pre- and perioperative patient characteristics are reported in the Table. During a 12-month period, 751 patients underwent a CABG procedure under full-dose aprotinin; the average age was 67.0 ± 9.9 years (median, 68.1 years); 77% of patients were male, 157 (21%) had diabetes, and 591 (80%) had arterial hypertension. Seventy-nine patients (11%) had a preoperative history for a cerebrovascular accident, and 33 (4.4%) of these 79 patients suffered from persistent neurological symptoms. The average EUROScore was 5.5 ± 3.9. An isolated CABG procedure was performed in 481 patients (64%), whereas 122 (16%) of CABG surgeries were combined with valve surgery. In the remaining 148 patients (20%), CABG surgery was combined with other procedures (ligation of the left atrial appendage, aortic surgery). Average aortic cross-clamping time was 55.2 ± 25.7 minutes. Death occurred in 21 patients (2.8%), and 39 patients (5.2%) developed postoperative renal dysfunction and/or failure. These data are not significantly different from the 4% mortality rate and 5% postoperative renal insufficiency reported by Mangano et al [2006]. A postoperative increase of CK-MB >60 iU/L was found in 58 patients (7.7%), and 18 patients (2.4%) suffered from a postoperative neurological event, of which 7 patients (0.9%) had a stroke with persistent neurological deficit at time of discharge. These results are significantly better than the 16% risk of post-operative MI and 6% risk of neurological complications reported by Mangano et al [2006] (Figure).

Patient Characteristics (N = 751)*

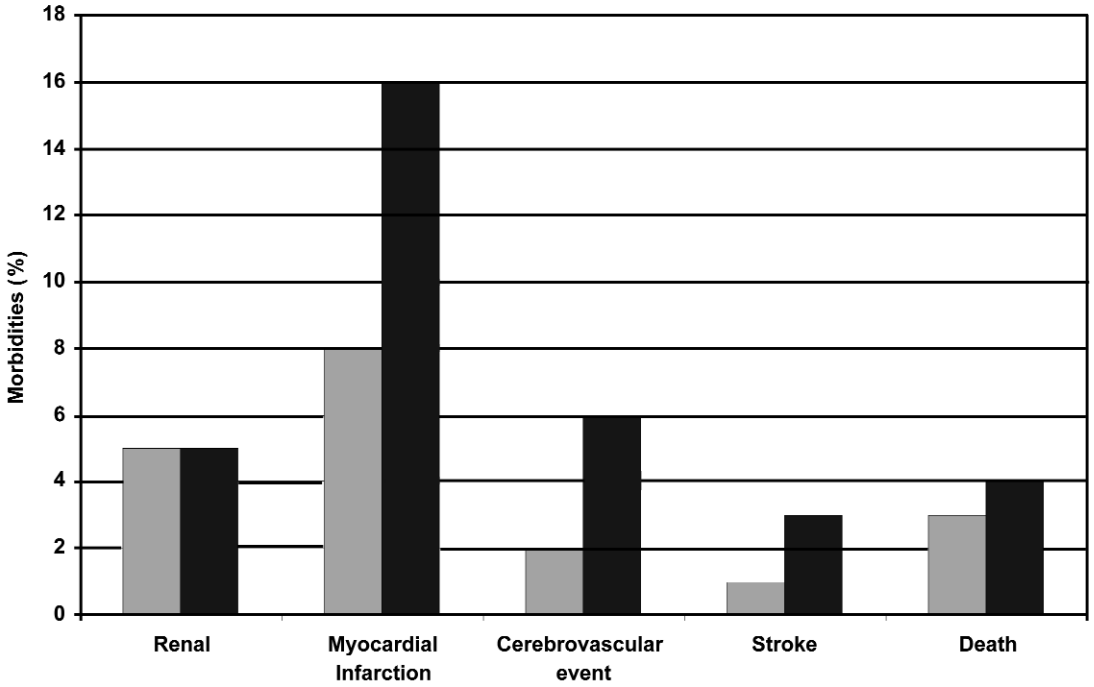
Male sex	575 (76.6%)
Age, y	67.0 ± 9.9
Risk factors	
Diabetes	157 (20.9%)
Cholesterol	517 (68.9%)
Arterial hypertension	591 (78.7%)
History of smoking	392 (52.5%)
Concomitant diseases	
History of cerebrovascular incident	78 (10.4%)
Persistent neurological symptoms	33 (4.4%)
Chronic obstructive pulmonary disease	114 (15.2%)
Renal insufficiency	31 (4.1%)
Perioperative data	
EUROscore	5.5 ± 3.9
Elective	446 (59.8%)
Semielective	250 (33.3%)
Urgent	55 (7.3%)
Aortic cross-clamping, min	55.2 ± 25.7
Postoperative data	
Mortality	21 (2.8%)
Renal insufficiency	39 (5.2%)
Myocardial infarction	58 (7.7%)
Cerebrovascular incident (reversible)	18 (2.4%)
Stroke	7 (0.9%)

*Data are n (%) or mean ± SD.

DISCUSSION

We report the results of a prospective single-center trial, including data of 751 consecutive patients undergoing myocardial revascularization. All patients underwent surgery under a high-dose regimen of aprotinin (>4 Mio units). Patient characteristics were quite similar to the typical profile in patients undergoing cardiac surgery—especially to data recently published by Mangano et al [2006]. Our analysis of clinical endpoints could not confirm that a perioperative high dose of aprotinin was associated with a higher incidence of myocardial infarction or cerebrovascular events. In fact, our results show a significantly lower incidence of both these events compared to the results reported by Mangano et al [2006]. More importantly, our results are for patients who underwent surgery before the publication of the report by Mangano et al, and their data were already collected in our database. Consequently, no special pre-, peri-, or postoperative precautions were taken, and none of our patients who underwent surgery during the chosen period were excluded from the analysis.

The data presented by Mangano et al may have had a detrimental effect on the opinion of the medical community and we suggest therefore, according to our experience, that these data be reconsidered. Indeed, even though we do not question the data from Mangano et al's multicentric observational study, we propose some explanations for the higher incidence of postoperative myocardial infarction and/or neurological events they observed.



Comparison of morbidity in patients treated with full-dose aprotinin. Data of the present single-center (gray bars) (N = 751), compared to the multicenter data reported by Mangano [2006] (black bars) (N = 1295).

In our opinion, close monitoring of coagulation status is crucial in patients undergoing on-pump surgery if a high-dose aprotinin regimen is chosen. Indeed, aprotinin is known to artificially increase the activated clotting time (ACT) [Dietrich 1995], and therefore may potentially lead to nonsufficient heparinization of the patient, with possible microembolization. In the report by Mangano and colleagues [2006], the high incidence of myocardial infarction and cerebrovascular incidents in patients receiving aprotinin may therefore be partially explained by potential underheparinization; the lower incidence of those complications in patients receiving tranexamic acid [Bechtel 2002] and aminocaproic acid support this hypothesis because these 2 chemicals do not affect the activated clotting time.

Our current study highlights a possible effect of the patients' critical mass. We report a single-center experience that included 751 patients in a 12-month period, a significantly higher number compared to the 15 patients/center (1016 patients included from 69 centers) from the analysis of Mangano et al. Indeed, several reports have now confirmed the relationship between the annual operation numbers per surgeon and the complication rate reported by Mangano et al. This aspect was addressed in the report by Mangano et al [2006], and may therefore constitute a bias in the analysis of his results.

In addition, because patients were not clearly randomized, it is possible that high-dose aprotinin was administered by many surgeons only in patients in more critical situations; for instance those under antifibrinolytic therapy, with a critical ischemia or an ongoing infarction.

However, our data, although encouraging, may not reflect the reality of several other cardiosurgical centers, and aprotinin might remain a drug with known adverse effects. For instance, the incidence of renal insufficiency in our patients was 5%, similar to that reported by Mangano et al as well as by others [Sedrakyan 2004]. However, the current analysis does not compare aprotinin to other treatments and/or placebo. Therefore, we cannot conclude from our data that aprotinin increases this incidence. The main perioperative risk of using aprotinin is a hypersensitivity reaction, especially in reexposure situations. The incidence of such events is reported to be 2.8%; however, 72% of the documented hypersensitivity reactions occurred within the first 3 months after initial exposure [Beierlein 2005]. At our institution, aprotinin is therefore administered only when the patient is ready to go on cardiopulmonary bypass.

On the other hand, aprotinin has been shown to reduce a transfusion requirement in patients undergoing cardiac surgical procedures [Sedrakyan 2004]. This aspect is critical because a transfusion requirement is known to increase the risk of postoperative adverse events; because more patients are under antifibrinolytic therapy until the time of surgery, the risk of peri- and postoperative bleeding is increased. Therefore, aprotinin offers an attractive means to counteract the anticoagulation effect of antifibrinolytic drugs.

In conclusion, compared to the recent report by Mangano et al [2006], the analysis of our single-center experience demon-

strates significantly better results in terms of adverse events following a surgical myocardial revascularization procedure under cardiopulmonary bypass and full-dose aprotinin. In our opinion, aprotinin continues to represent a valid option to reduce postoperative bleeding, providing ACT is monitored closely to prevent perioperative underheparinization.

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