Intraoperative use of recombinant activated factor VII during complex aortic surgery

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Objective: Postoperative bleeding is a major cause of morbidity and mortality after complex aortic surgery. Intraoperative coagulopathy is a well-known culprit in this process. Recombinant activated factor VII is increasingly used for the postoperative management of such bleeding. We report our experience with the intraoperative use of this agent.

Methods: We performed a propensity-matched analysis on 376 retrospectively identified patients who underwent aortic root, arch, or ascending aortic replacement surgeries from 1999 to 2010. We matched a total of 58 patients: recombinant activated factor VII–treated group (n = 29) and nonrecombinant activated factor VII–treated group (n = 29). We compared the matched patients on re-exploration, mortality, bleeding-related events, use of blood and blood products, length of intensive care unit stay, duration of hospitalization, and thrombotic complications.

Results: Propensity-matched patients had similar preoperative and intraoperative characteristics. The mean dose of recombinant activated factor VII group was 23 ± 12 μg/kg. We found significantly lower rates of surgical re-exploration ($P = .004$), fewer prolonged intubations ($P = .004$), less total chest tube output ($P = .01$), and fewer units of packed red blood cells ($P = .01$) and fresh-frozen plasma ($P = .04$) transfused postoperatively in the recombinant activated factor VII group. There was no significant difference in mortality ($P = 1$), duration of intensive care unit stay ($P = .44$) or hospital stay ($P = .32$), or thrombotic complications between the groups ($P = .5$).

Conclusions: We recommend the intraoperative administration of low-dose recombinant activated factor VII but limited to the management of persistent, nonsurgical, mediastinal bleeding in aortic surgery. Further prospective randomized studies and larger cohorts are needed to verify these findings. (J Thorac Cardiovasc Surg 2012;143:1198-204)

Repair of aortic root, ascending aorta, and aortic arch aneurysms is associated with significant postoperative bleeding that often requires transfusion of large volumes of blood and blood products.[1] This is a well-known risk factor for postoperative morbidity and has been reported to cause an 8.1-fold increase in mortality rates.[2] In patients undergoing re-exploration for postoperative bleeding after cardiac surgery, it has been demonstrated that only 50% have a grossly identifiable surgical source of bleeding.[3] This identifies microvascular bleeding caused by coagulopathy as a major risk factor for postoperative bleeding. Strategies to prevent coagulopathic bleeding are essential for the successful management of patients undergoing complex aortic operations.

Recombinant activated factor VII (rFVIIa; NovoSeven, NovoNordisk, Copenhagen, Denmark) was initially developed for management of bleeding in hemophiliacs.[4,5] Over the last decade, rFVIIa has been increasingly used in the postoperative management of intractable bleeding after cardiac and aortic surgery.[6] Of note, the precise dose required to control bleeding without causing thrombotic complications is controversial.[7] Dose recommendations in the current literature have ranged from 30 to 200 μg/kg, which can be administered in multiple doses.

Currently, there are a paucity of data regarding the intraoperative use of rFVIIa as a measure to minimize postoperative bleeding and associated complications.[8] We report our clinical experience with off-label intraoperative use of low-dose rFVIIa for inadequate hemostasis in patients undergoing complex aortic repair procedures.

MATERIAL AND METHODS

Study Population

Patients were retrospectively identified from our aortic aneurysm research registry. From 1999 to 2010, 488 patients underwent repair of the aortic root, ascending aorta, and arch (Table 1). Excluded from the study were the patients undergoing concomitant coronary artery bypass grafting, mitral or tricuspid valve surgery, and congenital surgery. We further excluded patients who had abnormalities in the preoperative coagulation panel (prothrombin time, partial thromboplastin time, bleeding time, and platelet count [if < 150 k/mL]). The above exclusion criteria narrowed the pool to 376 patients. In February 2009, we started administering

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Abbreviations and Acronyms

DHCA = deep hypothermic circulatory arrest
FFP = fresh-frozen plasma
ICU = intensive care unit
POD = postoperative day
PRBC = packed red blood cell
rFVIIa = recombinant activated factor VII

intraoperative off-label rFVIIa to patients who met our clinical criteria as outlined below. We identified 37 such patients. The remaining patients served as a control pool for the propensity-matched analysis.

Study End Points

The primary end points of our study were major bleeding requiring surgical re-exploration and postoperative in-hospital death. Secondary end points were the use of blood and blood products, delayed chest closure, postoperative tamponade, chest tube output, duration of intensive care unit (ICU) stay, prolonged intubation (>48 hours), duration of hospitalization, and any complication that might be related to thrombosis.

Data Collection

Preoperative and intraoperative data are listed in Table 2. The institutional review board approved the use of these data for the purposes of this study. All patients undergoing aortic surgery after 2009 were informed in advance that they might receive factor VII.

Surgical Technique

After endotracheal intubation and administration of appropriate anesthetic agents, radial arterial, central venous, and Swan–Ganz catheters were introduced per routine. Median sternotomy was performed followed by arterial and venous cannulations as outlined below. Standard cardiopulmonary bypass technique was carried out using membrane oxygenators. Of note, 152 patients (40%) received right axillary cannulation for arterial access. Venous access was obtained via cannulation of the right atrium or the femoral vein. Depending on the complexity of the procedure, moderate to deep systemic hypothermia was used. Mean arterial blood pressure was kept between 50 and 70 mm Hg during cardiopulmonary bypass. Myocardial protection was achieved by antegrade and retrograde cold blood cardioplegia. Heparin was administered to achieve an activated clotting time more than 480 seconds. This was neutralized with appropriate use of protamine administered within 10 minutes after the end of cardiopulmonary bypass. All patients received aminocaproic acid (AMICAR; Lederle Parenterals, Carolina, Puerto Rico) perioperatively. Generally accepted criteria were used for re-exploring patients with postoperative bleeding.[9]

Management of Intraoperative Bleeding

Figure 1 summarizes the algorithm we used to treat intraoperative bleeding. Beginning in February 2009, rFVIIa was added to this regimen as described below. If bleeding persisted after routine attempts at surgical hemostasis, coagulation parameters were measured to rule out any existing correctable measures. If none existed or corrected, rFVIIa was administered at 1 to 2 mg/dose (10–30 μg/kg), which was repeated once if bleeding persisted. If the surgeon was not satisfied with the degree of hemostasis despite these measures, the chest was left open and packed with continuous negative pressure suction dressing for delayed closure. The patient was subsequently transferred to the ICU for observation and brought back to the operating room within 24 to 72 hours for definitive closure.

Statistical Analysis

Demographic, perioperative, and intraoperative continuous variables were compared using the unpaired or paired t test for the prematch and propensity-matched groups, respectively. Accordingly, dichotomous variables were compared using the Fisher exact or McNemar test.

Because of the absence of preoperative randomization, a propensity-matched analysis was performed.[10] Propensity scores were generated through a logistic regression procedure using the following risk factors observed to be significant in the univariate prematch group comparisons and deemed likely to cause postoperative bleeding: gender, total body surface area, emergency status of the operation, total pump time, redo sternotomy, and use of deep hypothermic circulatory arrest (DHCA). Once generated, propensity scores were addressed as proposed by Austin.[11] Matching without the replacement method was used to pick up a match from the control group. Finally, patients were matched by an identical 5-digit propensity score. If this could not be done, we then proceeded to a 4-, 3-, 2-, or 1-digit match. Five-digit matches were 11, and 4-3-2-1 matches were 6, 6, 4, and 2, respectively. We were unable to match 8 patients who had rFVIIa; therefore, we excluded those from further analysis.

Values are expressed as mean ± standard deviation, median (minimum–maximum), or percentage. All analyses were performed with SPSS 13.0 software (SPSS Inc, Chicago, Ill).

RESULTS

Total Prematch Group

The mean age was 63 ± 13 years (19–88), and 64% were male. The mean intraoperative dose of rFVIIa in 37 patients was 23 ± 14 μg/kg (10–60). Nineteen patients received 1 mg of rFVIIa (51%), 13 patients (35%) received 2 mg of rFVIIa, 4 patients (10%) received 3 mg of rFVIIa, and 1 patient (2%) received 4 mg of rFVIIa before leaving the operating room. Of note, none of the patients received additional doses of rFVIIa after leaving the operating room. The patient who required 4 mg of rFVIIa had had an acute type A dissection requiring replacement of the aortic root, arch, and ascending aorta. Furthermore, the patient was anticoagulated with argatroban because of a standing diagnosis of heparin-induced thrombocytopenia with a preoperative platelet count of 155×10^3/mL.

Prematch Comparison

All performed operations are listed in Table 1. The ascending aorta was involved in 195 patients (51%), the aortic root was involved in 94 patients (25%), and the aortic arch was involved in 105 patients (28%). Prematch baseline variables are shown in Table 2. In the prematch analysis, there were significantly more male patients in the control group ($P = .02$). The rFVIIa group had longer total pump time ($P = .008$) and aortic crossclamp time ($P = .006$). Redo sternotomy was performed in 10 patients (27%) in the rFVIIa group and in 39 patients (11%) in the control group ($P = .01$). Other preoperative variables were not statistically different.

Postmatch Comparison

The propensity-matched analysis yielded 58 patients available for analysis. All variables before administration of rFVIIa were similar between the 2 groups (Table 2).

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