Timing of Recombinant Factor VIIa Administration for Severe Bleeding in Cardiac Surgery: Does It Make Any Differences?

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ABSTRACT

Introduction: Perioperative severe bleeding remains a frequent complication in cardiac surgery with high incidence of morbidity and mortality. Recombinant activated factor VII (rVIIa) is administered for the management of many cases of severe bleeding in cardiac surgery with improvement of outcome. We hypothesize that there may be differences in the efficacy and safety of early versus late administration of rVIIa.

Methods: A retrospective descriptive analytic study involved all patients who received rFVIIa in cardiac surgery department over 6 year’s duration with a total number of 50 patients. The studied population was divided into two groups according to timing of rFVIIa administration, early group who received rVIIa within the first 2 hours of onset of bleeding (23 patients) and late group if rVIIa was given after 2 hours of onset of bleeding (27 patients). Preoperative, intraoperative and postoperative data were collected and statistically analyzed.

Results: There were no significant statistical demographic or surgical differences between the identified groups. Postoperatively we noted statistically significant lower postoperative blood loss (p = .001), blood transfusion (p = .02), Fresh frozen plasma P (p = .02), platelets transfusion (p = .02) and incidence of re-exploration (p = .02) in the early rVIIa administration group. There was no difference in the lengths of mechanical ventilation or hospital stay but length of ICU stay was significantly longer in the late rVIIa administration group.

Conclusion: In this analysis, Early administration of rFVIIa in the management of severe bleeding following cardiac surgery was associated with decreased blood loss, decreased the need for blood and blood products transfusion and decreased Incidence of Re-exploration. Long-term safety remains unclear.

Keywords: Cardiac Surgery, Postoperative bleeding, Recombinant factor VIIa.

Introduction

Perioperative severe bleeding remains major cause of morbidity and mortality in cardiac surgery [1], with relatively high incidence 10%-15% [2]. Many factors are responsible for the complex hemostatic defects including hypothermia, hemodilution, and activation of the coagulation, fibrinolytic, and inflammatory pathways [3,4]. Recombinant activated factor seven (rFVIIa) was administered for management of many cases of severe bleeding in cardiac surgery when conventional therapy has failed with reported improvement of outcome [5-8]. Most of rFVIIa administrations (95%) were off-label as FDA approval for rFVIIa was only for hemophilic patients [9]. Recombinant FVIIa is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues (MW 50 K Dalton) and structurally similar to human plasma-derived Factor VIIa [10]. Recombinant FVIIa acts by increasing the activity of extrinsic tissue factor [11], also rFVIIa binds to the surface of activated platelets promoting factor X activation and thrombin generation [12].

Decision of rFVIIa administration in our institute is variable in timing of administration or even excluding rFVIIa use. The
dynamicity and multiple factors affecting coagulation makes some physicians delay or hesitate to give rFVIIa in addition to possible thromboembolic complications and off-label state [13]. The hypothesis of this research was to find out if there is difference in the efficacy and safety of early versus late administration of rFVIIa.

**Methods**

Our study was a retrospective, descriptive, single-center study with purposive sampling that examined the effect of rFVIIa administration timing differences in management of severe bleeding in cardiac surgery. Approval for the study was obtained from the Hamad Medical Corporation ethical committee (reference number MRC 0198 /2017). After institutional research ethics board approval was obtained, Patients were identified from hospital administrative databases from September 2011 TO December 2017. We collected detailed perioperative, operative and postoperative data (including demographics, laboratory results, ejection fraction and Euroscore II (Tables 1 & 2). Descriptive statistics in terms of mean and standard deviation as well as median (inter quartile range) for interval variables and frequency with percentage for categorical variable were performed. Student t tests for normal distributed interval variables and Mann Whitney U tests for non-normal variables were used to see significant mean difference between early admission and late admission group. Chi-square tests were applied for categorical variables to see association between the two groups. Graphical presentation was made for important variables according to two groups. P value was used for the statistically significant level. SPSS22.0 statistical package was used for the statistical analysis.

Fifty patients were recruited in our sample as their cardiac surgery was complicated with severe bleeding and they got administered rFVIIa during the management course. They were subsequently classified into two groups according to the timing of administration of rFVIIa.

Early administration group: 27 patients who had administered rFVIIa within two hours from the onset of bleeding management course.

Late administration group: It included 23 patients who had administered rFVIIa after 2 hours from the onset of bleeding management course.

Data were retrieved using Cerner Data System hospital Cerner System, (Cerner Corporation, Kansas City, MO, USA) and Dendrite Clinical Systems (London, UK).

**Statistical analysis**

Descriptive statistics in terms of mean and standard deviation as well as median (inter quartile range) for interval variables and frequency with percentage for categorical variable were performed. Student t tests for normal distributed interval variables and Mann Whitney U tests for non-normal variables were used to see significant mean difference between early admission and late admission group. Chi-square tests were applied for categorical variables to see association between the two groups. Graphical presentation was made for important variables according to two groups. P value 0.05 (two tailed) was considered for the statistically significant level. SPSS22.0 statistical package was used for the analysis.

**Results**

On comparing data between two groups we found no statistical differences regarding demographic characteristics, preoperative laboratory results, ejection fraction and Euroscore II (Tables 1 & 2).

| Variable          | Early Group | Late Group | P value |
|-------------------|-------------|------------|---------|
| Gender male       | 17 (77.3)   | 22 (68.6)  | 0.63    |
|                   | 6 (22.7)    | 5 (17.9)   |         |
| Age               | 52 ± 14.2   | 54 ± 14.1  | 0.65    |
| Weight            | 78.8 ± 19.8 | 72.8 ± 16  | 0.25    |
| Height            | 169.3 ± 5.3 | 167.1 ± 9.2| 0.24    |
| Smokers           | 6 (27.3)    | 6 (21.4)   | 0.50    |
| Serum creatinine  | 114.59 ± 39.9 | 106.7 ± 45.7 | 0.53    |
| Normal liver enzymes | 21 (95.5)  | 23 (82.1)  | 0.18    |
| ≤double normal    | 1 (4.5)     | 2 (3.6)    | 0.86    |
| >double normal    | 1 (0)       | 2 (14.3)   | 0.09    |
| Ejection fraction | 50 ± 11.8   | 44 ± 11    | 0.17    |
| Hemoglobin        | 12.99 ± 1.9 | 12.7 ± 2.7 | 0.73    |
| Platelets count   | 221.18 ± 49.6 | 192.4 ± 58.7 | 0.07    |
| Fibrinogen level  | 2.314 ± .38 | 2.15 ± .24 | 0.08    |
| Euroscore II      | 11.5 ± 4.8  | 12.4 ± 6.6 | 0.15    |

Table 1: Patients demographics and preoperative variables among the studied groups.

| Variable               | Early Group | Late Group | P value |
|------------------------|-------------|------------|---------|
| Elective               | 12 (50)     | 18 (64.3)  | 0.18    |
| Urgent                 | 7 (31.8)    | 3 (10.7)   |         |
| emergency              | 4 (18.2)    | 6 (25)     |         |
| Redo surgery           | 6 (27.3)    | 8 (28.6)   | 0.92    |
| CABG                   | 13 (59.1)   | 10 (35.7)  |         |
| Valve surgery          | 5 (22.7)    | 9 (32.1)   | 0.06    |
| CABG + valve           | 2 (4.5)     | 7 (28.6)   | 0.33    |
| Other                  | 3 (13.6)    | 1 (3.6)    |         |
| Non-anticoagulant      | 16 (68.2)   | 20 (75)    | 0.50    |
| Heparin                | 6 (27.3)    | 7 (25)     | 0.41    |
| Warfarin               | 1 (4.5)     | 0 (0)      | 0.43    |
| Non-antiplatelet       | 11 (45.5)   | 10 (35.7)  | 0.76    |
| Aspirin                | 11 (50)     | 15 (57.1)  | 0.76    |
| Clopidogrel            | 1 (4.5)     | 2 (7.1)    | 0.46    |
| Preoperative IABP      | 2 (9.1)     | 3 (17.9)   | 0.32    |
| Preoperative inotropic | 2 (9.1)     | 3 (14.3)   | 0.46    |
| Preoperative CCU admission | 2 (9.1)  | 4 (14.3)   | 0.46    |

Table 2: Preoperative surgical characteristics among the studied groups. CABG: Coronary artery bypass grafting surgery, IABP: Intra aortic balloon pump, CCU: Coronary care unit.

Also there was no statistical significate difference in data collected for the intraoperative period between early and late group as cardiopulmonary bypass time was (189 ± 29.9 min) in early group and was (201.7 ± 86) in late group, We found statistically significant differences when we compared postoperative blood loss. Data showed less postoperative blood loss 1700 ml (825-1800) in the early group versus 2427ml (1200-3875) in the late group P value 0.25.
Early group
1 (4.5)
Late group
1.55 ± .59
0.02
0.045
1.6 ± .5
o.98
--
0 (0)
4.36 ± 2.77
0.56
6.39 ± 9.98
0.12
14 ± 11.6
P value
0 (0)
1.2 ± .4
0 (0)
1.68 ± .77
0 (0)
13.7 ± 6.7
units in late group with P value 0.02. Rate of re-
exploration in the early group was 1.2 ± 0.4 in early group and 1.6
± 0.5 in late group with P value 0.02 (Table 3).

Figure 1: Comparison of total amount of postoperative blood loss in ml
in both groups.

There was no difference in the length of mechanical ventilation or
length of hospital stay but length of intensive care unit stay was
longer in the late group 9.39 ± 9.98 days in late group and 4.36 ±
2.77 days in early group p value 0.045 (Table 3).

| Variable               | Early group   | Late group   | P value |
|------------------------|---------------|--------------|---------|
| Re-exploration         | 1.2 ± .4      | 1.6 ± .5     | 0.02    |
| Thrombo-embolic
complication           | 0 (0)         | 0 (0)        | --      |
| Neurologic complication| 0 (0)         | 1 (3.6)      | 0.56    |
| Length of ventilation  | 1.55 ± .59    | 1.68 ± .77   | 0.12    |
| Length of ICU stay     | 4.36 ± 2.77   | 6.39 ± 9.98  | 0.045   |
| Length hospital stay   | 14 ± 11.6     | 14.2 ± 21.7  | 0.98    |
| Mortality              | 1 (4.5)       | 2 (8.4)      | 0.19    |

Table 4: Postoperative outcomes among the studied groups.

Discussion
Severe bleeding is one of the most common complications
following cardiac surgery. It can be due to one or more contributing
factors. Incomplete surgical hemostasis, residual heparin
effect after cardiopulmonary bypass, clotting factor depletion,
hypothermia, hemodilution (dilutional thrombocytopenia and
coagulopathy), or platelet abnormalities (platelet dysfunction and
thrombocytopenia) were known as the most common causes [16].
Massive transfusion, historically defined as the replacement by
transfusion of 10 units of packed red blood cells over
one hour.

It is more sensitive in identifying patients who need more concerns
of transfusing blood products because of uncontrolled hemorrhage
[17]. Massive transfusion involves the selection of the appropriate
amounts and types of blood components to be administered and
requires consideration of a number of issues during management
strategies including volume status, tissue oxygenation, management
of bleeding and coagulation abnormalities, as well as changes in
ionized calcium, potassium, and acid-base balance.

Massive transfusions are in a subset analysis of a large randomized
controlled trial of complex cardiac surgeries requiring repeat
midline sternotomy, patients receiving transfusion of more than
5 units of RBCs had a threefold excess mortality if they did not
also receive 5 units of plasma [18]. All efforts should be done to
minimize massive transfusions to avoid the associated hemostatic
and metabolic complications [19].

The transfusion practice varies widely in cardiac surgery as
reported by Australian and New Zealand society of cardiac and
thoracic surgeons, PRBCs were used in 22- 67 % of patients,
platelets 11-39%, FFP 11-48% and cryo 1-20% [20]. In our study,
there was statistically significant less postoperative blood loss
1700 ml (825-1800) in the early group and 2427ml (1200-3875)
in the late group P value 0.001. Miskolczi et al. found that the
effect of rFVIIa may be enhanced if it is given early in the course
of blood loss.

Significant delay in the use of rFVIIa can be avoided because a
temporary reduction in bleeding does not reduce mortality [21].
Safani et al. in their analysis of outcomes of a low-dose rFVIIa
protocol, they found that chest tube output declined from a mean
of 350 to 85 mL/h within 60–90 min of rFVIIa administration [22].
Romagnoli et al. in two reports showed that small dose rFVIIa
significantly reduced postoperative bleeding and patients needed
less packed red cells, fresh frozen plasma, and platelet transfusion,
and they had a reduced re-exploration rate [23-24]. There was
statistically significant less postoperative need for blood and blood
products transfusion (PRBCs given in the postoperative period
was 3.67 ± 3.1 units in the early group and 6.29 ± 4.3 units in the
late group P value 0.02. Early group was transfused 4.58 ± 1.8
units of FFP while late group transfused 8.9 ± 6.3 units P value
0.02. Platelets given in the postoperative period in the early group
were also significantly less than the late group 8.8 ± 5.2 units for
early group and 13.7 ± 6.7 units in late group with P value 0.02).
Andersen et al compared low-dose rFVIIa administration (<60
mcg/kg) to propensity-matched control patients during complex
thoracic aortic operations. Their findings suggest that rFVIIa
led to fewer postoperative transfusions and no requirement for
postoperative rFVIIa administration or re-exploration for bleeding
[25]. Andersen and his colleagues study matches with our study
as regard less bleeding and less transfusion of blood products if
rFVIIa given early, in the same time the need of rFVIIa repeated
doses was higher if FVII give late (Table 4).
In a survey of UK practice in using rFVIIa in management of intractable hemorrhage, Biss and Hanley found wide variability in dose regimen [26]. In our study we found that dose of rFVIIa was 3.83 ± 1.3mg in early group and 3.53 ± .84 in late group with P value 0.33. FVII was give twice in one patient of the early group while in late group three patients given a second dose of FVII and one patient was given 3 doses (Table 4).

| Variable                  | Early group       | Late group       | P value |
|---------------------------|-------------------|------------------|---------|
| FVII dose in mg           | 3.83 ± 1.3        | 3.53 ± .84       | 0.33    |
| One dose FVII             | 21 (95.5)         | 25 (89.3)        | 0.61    |
| Two doses FVII            | 1 (4.5)           | 3 (7.1)          | 0.50    |
| Three doses FVII          | 0 (0)             | 1 (3.6)          | 0.34    |
| Re-exploration            | 1.2 ± .4          | 1.6 ± .5         | 0.02    |

Table 3: Postoperative rVII administration.

Conclusion
Early administration of rFVIIa in the management of severe bleeding following cardiac surgery was associated with decreased blood loss, decreased the need for blood and blood products transfusion and decreased Incidence of Re-exploration. Long-term safety remains unclear.

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