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Safety and Efficacy of Recombinant Factor VIIa (NovoSeven) Use during ECMO Support in Patients after Cardiac Surgery

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Abstract

Background: Acute postoperative bleeding in cardiac surgical patients is a major cause of morbidity and mortality. Substitution of coagulatory factors may not always provide optimal hemostasis and off label, use of recombinant FVIIa has been proposed. When on ECMO, extra care must be taken during coagulatory substitution as clotting of the system may cause cardiovascular complications and possible ECMO failure, leading to death. In this paper, we examined the safety and efficacy of rFVIIa during ECMO support in postoperative cardio-surgical patients.

Methods: We retrospectively examined all patients receiving rFVIIa postoperatively from December 2005 and January 2020. Clinical characteristics, demographics, bleeding, thrombotic complications, mortality, and rFVIIa administration were analyzed.

Results: A total of 74 patients received rFVIIa postoperatively due to uncontrollable bleeding after cardiac surgery on our ICU. Of these patients, 23 patients were on ECMO treatment. Twelve patients received rFVIIa during, but not prior to the initiation of ECMO therapy. Six patients (50%) were male; mean age was 46 years (30-72 years). Eleven patients (91.7%) were on veno-arterial ECMO, one patient was on central ECMO (8.3%). Dose of administered rFVIIa was corrected for body weight; mean dosage was 82μg/kg. We saw a significant reduction in need for red packed cells, fresh frozen plasma and thrombocyte transfusion after rFVIIa administration. There was no impact on the functionality of the ECMO system, especially regarding the oxygenator after rFVIIa administration. One patient suffered a stroke due thromboembolism (8.3%). One patient developed late thromboembolism in the leg (8.3%), and two cases of pulmonary embolism (16.7%) were recorded. Overall survival was 25% and there was no significant difference in survival between ECMO and non-ECMO patients. Weaning from ECMO could be achieved successfully in 41.7% of our patients.

Conclusion: Recombinant Factor VIIa is an effective agent in reducing blood loss during ongoing ECMO therapy in patients with refractory bleeding. Although no direct relation between rFVIIa application and thromboembolic events could be established, its use should be done with the utmost care and in selected patients. However, rFVIIa therapy did not impact ECMO function in our cohort.

Keywords: Extracorporeal membrane oxygenation; NovoSeven; Recombinant FVIIa; Hemostasis

Introduction

Extracorporeal Membrane Oxygenation (ECMO) support after cardiac surgery is an established technique for patients with respiratory and/or cardiac failure. Patients with fulminant respiratory failure are classically treated with a veno-venous cannulation, whereas hemodynamic stabilization is achieved with veno-arterial extracorporeal support [1]. Causes for increased risk of bleeding in patients on prolonged ECMO therapy have been contributed to thrombocytopenia, hyperfibrinolysis, disseminated intravascular coagulation and acquired von Willebrand syndrome [2]. Furthermore, consumption of coagulation factors and anticoagulant therapy contribute to the increased risk of bleeding [2,3]. In the acute postoperative patient however, the origin of bleeding while on ECMO is multifactorial and an independent risk factor for postoperative mortality [4,5]. Strategies for postoperative hemostasis in cardiac surgery patients include substitution of blood products, coagulation factors and desmopressin [6]. In few patients however, these methods solely do not suffice in establishing adequate hemostasis, and refractory postoperative bleeding remains a potentially life-threatening situation. As ultima ratio, off label use of recombinant activated coagulation factor VII (rFVIIa; NovoSeven, Novo Nordisk,

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Copenhagen, Denmark) has been proposed for these patients [7]. Recombinant FVIIa was initially developed in the 1970s and was intended for the treatment of bleeding in hemophilia A and B patients [8]. Its working mechanism involves increased FXa expression and thus increasing thrombin production. This leads to increased platelet aggregation and Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) and FXIII activation, resulting in the production of a tight fibrin plug [9]. Although use of rFVIIa has significantly reduced bleeding rates in the hemophilia population, adverse effects such as severe thromboembolic events have been reported [8]. Furthermore, the use of rFVIIa in coronary artery bypass patients with refractory postoperative bleeding led to increased risk of cerebral ischemia, myocardial infarction and pulmonary embolisms [10]. The use of rFVIIa during ECMO support has been published as singular case reports and case series [11,12]. The purpose of this study was to retrospectively examine the effect of rFVIIa use due to refractory bleeding in patients on ECMO support.

Patients and Methods

This retrospective study was performed in the Intensive Care Unit (ICU) of our cardiac surgery department. The ethics committee at our institution (Hannover Medical School, Hannover, Germany) waived the need for patient consent for this study. All data were retrieved by retrospective review of patient's records.

Patients

This retrospective study was done using medical records of cardiac surgery patients receiving rFVIIa for refractory bleeding between 2005 and 2020 at our cardiac surgical intensive care unit (ICU). All patients >18 years receiving rFVIIa were included. Refractory bleeding was defined as ongoing loss of blood despite the optimal medical and surgical hemostatic measures. Thrombotic events were determined through review of progress notes and discharge summary of cases receiving rFVIIa. The patient's demographics, type of surgery, bleeding site, need for mechanical support and stability of ongoing mechanical support after administration of rFVIIa were collected. Furthermore, the amount of blood- and coagulation products was examined prior and post rFVIIa substitution. Primarily, the effect of rFVIIa administration in ongoing ECMO patients was examined. Goal was to determine the efficacy and safety of rFVIIa, determined as thromboembolic events on ECMO and need for system exchange due to coagulation or diminished function of the oxygenator. Impaired oxygenator function was determined when pO_2 <350mmHg under 100% FiO_2.

Assessment of rFVIIa efficacy in reducing transfusion requirements was the secondary endpoint. Various blood products administered, including packed Red Blood Cells (RBCs), Fresh Frozen Plasma (FFPs) and Thrombocyte Concentrates (TCs) were collected in the 24h before and after injecting rFVIIa to observe its effect on reducing transfusion requirements. Furthermore, need for coagulation factors such as Fibrogammin® (Factor XIII), Haemate® (Factor VIII/von Willebrand-Factor), Beriplex® (Prothrombin complex concentrate), Fibrinogen, Kybernin® (anti-thrombin III) and Cyklokapron® (tranexamic acid) were evaluated.

Statistical analysis

Summary statistics were presented as medians with ranges. Categorical variables are presented as counts and percentages. Group comparisons were done using student t-test for continuous variables. For categorical analysis both Fisher exact test and Pearsons χ^2 test was used depending on the sample size. A p-value<0.05 was considered significant in all tests. SPSS version 25 (SPSS Inc., Chicago, IL, USA) software was used to analyze the data.

Results

Between 2005 and 2019, a total of 74 cardiac surgical patients were treated with rFVIIa due to uncontrollable postoperative bleeding. In this population, 13 patients were on ECMO therapy while receiving rFVIIa therapy. One patient (8.3%) was on central ECMO, the other patients (91.7%) were on veno-arterial ECMO at time of rFVIIa substitution. Cannulation of the central ECMO was done using an arterial cannula in the ascending aorta and a venous cannula in the right atrium. The veno-arterial ECMO was cannulated typical using the femoral artery and vein. As it was not per standard at the time, only 3 patients (25%) received antegrade distal leg perfusion during veno-arterial ECMO. Patient characteristics are shown in Table 1.

Indications for postoperative ECMO therapy were graft failure

Table 1: Patient characteristics.

Total population n=74 (100%)	ECMO n=13 (17.6%)	no ECMO n= 62 (82.4%)	P-value
Gender (male), n (%)	6 (8%)	50 (68%)	0.071
Age in years (mean ± SD)	47.54 ± 13.68	53.2 ± 16.9	0.277
ECMO Type			
Veno-arterial (n; %)	12 (92.3%)		
Central (n; %)	1 (7.7%)		
Antegrade distal leg perfusion (n; %)	3 (23.1%)		
Indication (n; %)			
Heart transplantation (n; %)	2 (15.4%)	7 (11.5%)	0.654
Combined heart-lung transplantation (n; %)	2 (15.4%)	6 (9.8%)	0.624
Bilateral lung transplantation (n; %)	3 (23.1%)	7 (11.5%)	0.366
Postcardiotomy (n; %)	5 (38.5%)	32 (52.5%)	0.543
LVAD (n; %)	1 (7.7%)	9 (14.8%)	0.68
Bleeding Site			
Mediastinal (n; %)	10 (83.3%)	54 (87.1%)	0.661
Lung (n; %)	1 (8.3%)	3 (4.8%)	0.515
Brain (n; %)	1 (8.3%)	2 (3.2%)	0.417
Other (%)	0	3 (4.8%)	1
Hemoglobin (g/dl) (mean ± SD)	10.9 ± 2.2	10.0 ± 2.3	0.65
Platelet count (103/µl) (mean ± SD)	154 ± 43	150 ± 101	0.914
Fibrinogen in g/l (mean ± SD)	3.21 ± 1.99	2.93 ± 1.41	0.656
INR (mean ± SD)	1.84 ± 0.76	1.57 ± 0.74	0.27
APTT in sec (mean ± SD)	68 ± 51	48 ± 34	0.102
Quick in % (mean ± SD)	49.8 ± 19.2	69.8 ± 30.9	0.043
Factor II (mean ± SD)	70.0 ± 30.2	76.3 ± 40.3	0.675
Factor V (mean ± SD)	60.4 ± 33.4	75.7 ± 49.8	0.411

Patient characteristics of all patients at time of rFVIIa administration. LVAD left ventricular assist device, INR International Normalized Ratio, APTT activated partial thromboplastin time, ECMO extracorporeal membrane oxygenation.

Table 2: Complications after admission of rFVIIa.

Complications	ECMO	no ECMO	P-value
Total population n=74 (100%)	**n=13 (17.6%)**	**n=62 (82.4%)**	
Thromboembolic event (n; %)	4 (33.3%)	9 (14.5%)	0.206
Pulmonary embolism (n; %)	2 (16.7%)	1 (1.6%)	0.067
Brain embolism (n; %)	1 (8.3%)	2 (3.2%)	0.417
Femoral artery embolism (n;%)	1 (8.3%)	0	0.162
Mesenterial embolism (n;%)	0	3 (4.8%)	1
Myocardial embolism (n;%)	0	3 (4.8%)	1
Cardiac tamponade (n; %)	4 (25%)	24 (38.7%)	1
Postoperative dialysis (n; %)	8 (66.7%)	35 (56.5%)	0.75
Stay at ICU in days (mean ± SD)	13 ± 16	25 ± 35	0.26

Complications after rFVIIa administration were mainly thromboembolic. However, there was no significant increase of thromboembolic events in the ECMO population. ICU intensive care unit, ECMO extracorporeal membrane oxygenation.

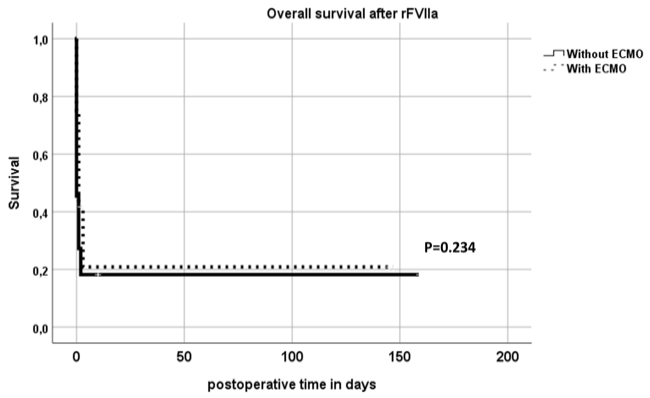

Figure 1: Kaplan-Meier table of survival, depicting no significant difference in survival between patients receiving rFVIIa during ECMO therapy vs patients without ECMO therapy.

after transplantation (53.8%, n=7/13), right heart failure after LVAD implantation (7.7%, n=1/13) or post-cardiotomy cardiac failure (38.5%, n=5/13). In the transplantation group, 2 patients were post heart transplantation (15.4%), 2 patients (15.4%) received combined heart-lung transplantation and 3 patients (23.1%) after bilateral sequential lung transplantation. Majority of the patients were first time operated. Site of bleeding was mostly mediastinal (83.3%, n=10). Other sites for bleeding were lung (8.3%, n=1) and brain (8.3%, n=1). Thromboembolic events were seen in 4 (33.3%) patients, two patients developed pulmonary embolisms, one patient had thromboembolic occlusion of the femoral artery and one patient had a cerebral thromboembolic event. ECMO patients receiving rFVIIa did not develop significantly more thromboembolic events when compared to patients not on extracorporeal circulatory support. Further analysis showed that the patient with thromboembolic occlusion of the femoral artery was not on antegrade distal leg perfusion at time of thromboembolic occlusion. Postoperative dialysis was necessary in 8 patients (66.7%). All complications after rFVIIa administration are shown in Table 2. No ECMO systems were changed after administration of rFVIIa.

Blood transfusions and survival

Retrospective analysis of transfused blood products showed

Table 3: Need for blood product transfusion.

Blood Products	Prior to rFVIIa Administration	After rFVIIa Administration	P-value
Red Packed Cells	17.5± 15.0	5.7±3.5	**0.038***
Fresh Frozen Plasma	12.4± 6.9	4.7±3.1	**0.008***
Platelet Concentrate	6.6± 3.8	1.9± 1.5	**0.008***

Transfusion of blood products prior and in the first 24 hours after the introduction of rFVIIa in patients on ECMO. There was a significant reduction in the need for red packed cells, fresh frozen plasma and platelet concentrate after administration of rFVIIa. All values are mean ± SD. *Statistical significantly different (p <0.05).

that patients received 17.5 ± 15.0 units of Red Packed Cells (RPC), 12.4 ± 6.9 units of Fresh Frozen Plasma (FFP) and 6.6 ± 3.8 units of Platelet Concentrates (PC) transfused (all values mean ± SD) after the operation, but prior to administration of rFVIIa. After administration of rFVIIa, transfusion of blood products in the first 24 hours was significantly reduced to 5.7 ± 3.5 RPCs, 4.7 ± 3.1 FFPs and 1.9 ± 1.5 units of PCs transfused (all values mean ± SD) (Table 3). Overall mortality in the general population while on ECMO after cardiopulmonary bypass was 34%. In the rFVIIa treated ECMO population no significantly higher mortality was seen when compared to patients treated with rFVIIa without ECMO therapy (Figure 1). In patients receiving rFVIIa during ongoing ECMO therapy, weaning from ECMO was successful in 5 patients (41.7%). Thirty-day mortality was 75%, overall survival during total follow up was 25%.

Discussion

In this paper, we present a highly complicated and delicate patient population. Patients in need of ECMO therapy are mostly in respiratory, cardiac or combined failure. Cessation of the acute bleeding in the postoperative patient is of pivotal role for survival. In the acute setting, surgical management of the bleeding focus, optimization of the coagulation cascade and substitution of thrombocytes and bringing the patient to normal body temperature are first measurements against uncontrollable postoperative bleeding. However, there still remains a population where these measurements do not suffice in maintaining control of the situation. In this population, administration of recombinant FVIIa has been proposed as a last resort for uncontrollable bleeding [12]. In this paper, we describe the safety and efficacy of recombinant FVIIa in bleeding patients on ECMO therapy. Our research showed a series of 74 patients receiving rFVIIa due to uncontrolled bleeding after cardiac surgery in the period of 2005-2020. Of these patients, 12 were on ECMO at the time of rFVIIa administration. Use of rFVIIa in refractory bleeding when on ECMO has shown to be effective in blood loss. Our results showed a significant reduction in the need for blood product transfusion after administration of rFVIIa. This may support the hypothesis that application of rFVIIa may be effective in the reduction of bleeding in postcardiotomy ECMO patients. Similar results have previously been reported by others [12]. After administration of rFVIIa, our data showed stable ongoing ECMO therapy, no patients needed ECMO system change due to clotting or decreased oxygenator function. Currently, no data on system malfunction after rFVIIa in the adult population is available. However, in the pediatric population, one case of oxygenator malfunction after rFVIIa administration has been reported [13]. As ECMO system change can be achieved relatively simple and quick, we state that this should not be a reason for withdrawal of rFVIIa in refractory

bleeding. Three patients developed thromboembolic events, with one leading to massive cerebral infarction and brain death. Although these adverse effects were diagnosed after administration of rFVIIa, we could not determine a direct causality with the application of rFVIIa. Literature showed similar results in other research groups [14]. Other complications were renal insufficiency with the need for dialysis, one case of lung bleeding and one patient developed cerebral hemorrhage. One patient developed distal femoral artery thrombosis, which had to be treated surgically. This patient, however, was not treated with distal femoral perfusion at the time of ECMO. Previous work showed the absence of distal limb to be an independent risk factor for critical distal limb ischemia during VA-ECMO and thus may not be accounted to the application of rFVIIa [15]. Although we saw high overall mortality (75%), more than 40% of our population could be successfully weaned from ECMO. This supports the save application of rFVIIa in bleeding patients. Furthermore, the major cause of death was multi-organ failure or graft failure after transplantation, suggesting no rFVIIa associated mortality.

Conclusion

In conclusion, we report on a series of highly complex patients with complex hemostatic problems. Our data suggest the possibility of safe application of rFVIIa in ECMO patients with refractory bleeding. Although we could not establish direct causality between clot formation and application of rFVIIa, we propose its use as a last resort. Further study needs to be done in randomized clinical trials to establish its role in hemostatic management during bleeding while on ECMO.

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