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Original Research Article

Effect of the intraoperative infusion of recombinant activated coagulation factor VII on short-term prognosis and thoracic complications after acute aortic coarctation

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Abstract

Purpose: *To investigate the impact of intraoperative infusion of recombinant human-activated coagulation factor VII (rFVIIa) on postoperative outcomes in patients with acute aortic dissection (AAD).*
Methods: *This study involved 120 individuals who underwent aortic coarctation surgery between January 1, 2020, and December 31, 2022 in the First Affiliated Hospital of Xinjiang Medical University, Xinjiang, China. The participants were divided into control (receiving only conventional treatment) and study (receiving rFVIIa infusion in addition to conventional treatment) groups. Various parameters, including patient status, postoperative measures, and complications were evaluated.*
Results: *There was no significant difference in age, gender distribution, duration of myocardial block, onset time, or surgery duration ($p > 0.05$) between both groups. However, the study group exhibited longer extracorporeal circulation duration ($p < 0.05$). The study group also demonstrated lower levels of chest drainage compared to the control group 12 and 24 h after surgery ($p < 0.05$). Moreover, fewer concentrated red blood cells and fresh frozen plasma transfusions were administered to study group ($p < 0.05$). Despite having longer stays in the ICU ($p < 0.05$), the study group required less postoperative mechanical ventilation ($p < 0.05$). There was a significant difference in the incidence of postoperative thrombosis cases, positive gram-negative bacilli sputum culture results, and deaths within the study group ($p < 0.05$).*
Conclusion: *Intraoperative rFVIIa infusion in AAD patients enhances short-term prognosis, with elevated risk of chest complications. However, further studies with larger sample sizes is essential to comprehensively assess clinical advantages and drawbacks.*

Keywords: *Recombinant activated coagulation factor VII, Acute aortic coarctation, Prognosis, Lung infection, Mechanical ventilation, Thrombosis*

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INTRODUCTION

Acute aortic dissection (AAD) is a life-threatening disease. Acute aortic dissection presents with rapid onset and progression, exhibiting an aggressive nature. Typical symptoms include severe chest pain, lower back pain, abdominal pain, hypotension, or syncope [1,2]. Among these symptoms, acute aortic dissection (AAD) is the most serious and life-threatening aortic

disease [3], necessitating urgent surgical intervention to prevent cardiac compression or sudden death. Hemorrhage is a common and significant complication during perioperative period. It occurs when blood flow enters the middle layer of the aortic wall through endothelial ruptures, resulting in the development of pseudo-tumors which forms a parallel and retrograde strip along the communication to the aortic lumen through one or more ruptures. This process leads to consumptive coagulation disorder [4]. It has been reported that 20 % of in-hospital deaths during perioperative period of aortic coarctation are attributed to coagulation dysfunction, while patients with acute type A aortic dissection (ATAAD) undergoing extracorporeal circulation, hypothermia, and blood loss during treatment may further exacerbate this condition [5,6]. Consequently, there is a significant increase in perioperative blood loss which poses a life-threatening risk. Initially indicated for hemophilia or acquired coagulation factor VII deficiency, recombinant human coagulation factor VIIa (rFVIIa) has shown promising results in reducing postoperative bleeding and drainage after cardiac surgery [7]. However, its effectiveness specifically in ATAAD surgery has only been reported on an individual case basis. The purpose of this study was to investigate the correlation between short-term prognosis and chest complications in ATAAD patients after intraoperative infusion of rFVIIa.

METHODS

General patient information

The study included a total of 120 patients who underwent aortic coarctation surgery in the First Affiliated Hospital of Xinjiang Medical University, Xinjiang, China between January 1, 2020, and December 31, 2022. Based on the different postoperative treatment modalities, patients were divided into control and study groups comprising of 60 cases each. This study complied with the relevant regulations of medical ethics and was approved by the Medical Ethics Committee of First Affiliated Hospital of Xinjiang Medical University (approval no. 20190225-114). Patients and/or their families provided informed consent and the sudy followed the guidelines of the Declarations of Helsinki [8].

Inclusion criteria

Diagnosis of ATAAD confirmed by imaging, with an onset time < 12 h, < 65 years old, no malignant tumor, hematological system diseases, liver function abnormalities, etc resulting in coagulation disorders and diffuse intravascular coagulation tendency. Also, patients treated with emergency open-heart aortic surgical hand surgery under hypothermic extracorporeal circulation, severe uncontrollable postoperative bleeding after cessation of extracorporeal circulation.

Exclusion criteria

Severe preoperative coagulation abnormalities, continuous preoperative application of anticoagulant or antiplatelet drugs such as warfarin, aspirin, heparin, clopidogrel, etc. History of combined forms of cardiac surgery or postoperative bleeding due to other surgical factors.

Treatments

Patients in both groups underwent aortic surgery and developed severe uncontrollable postoperative bleeding after cessation of extracorporeal circulation. Based on the clinical situation, including the assessment of contraindications to rFVIIa, a joint decision was made on whether to transfuse rFVIIa intraoperatively.

Control patients who were not suitable for rFVIIa transfusion received only conventional treatment, including component blood transfusion therapy, maintenance of normal acid-base balance, appropriate calcium supplementation, restoration of body temperature, and administration of drugs such as tranexamic acid injection, sodium carnosulfate injection, and hemagglutinin hemostatic treatment. Study group received both conventional treatment and rFVIIa transfusion therapy. The rFVIIa was used when there was severe intraoperative uncontrollable bleeding at 100 µg/kg administered in 2 intravenous infusions.

Evaluation of parameters/indices

General condition of patients

General condition of patients including age, female percentage, duration of myocardial block, onset, duration of extracorporeal circulation, and duration of surgery were determined and recorded.

Postoperative chest drainage and transfusion volume

The 12-h and 24-h postoperative chest drainage, postoperative transfusion volume including the volume of red blood cell concentrate transfused

Table 1: Baseline characteristics of patients (mean ± SD, n = 60)

Group	Age (years)	Female n (%)	Duration of myocardial blockade (min)	Onset time (h)	Duration of extracorporeal circulation (min)	Duration of surgery (min)
Control	49.87±11.75	24	92.32±21.56	4.31±1.76	190.98±20.56	7.95±1.45
Study	48.98±10.89	20	93.13±22.34	4.29±1.97	198.42±19.19	8.01±1.20
t/χ2		0.449	0.202	0.059	2.049	0.247
P-value		0.574	0.840	0.953	0.043	0.805

and the volume of fresh frozen plasma transfused, were determined by routine measurements.

Length of ICU stay

Duration of postoperative mechanical ventilation, postoperative thrombosis and length of ICU stay were determined for the two groups and compared.

Chest complications

Chest complications were determined by monitoring the results of sputum culture for *Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *Acinetobacter baumannii.* These organisms are used to broadly reflect the complications of pulmonary infections, and the number of deaths were recorded.

Statistical analysis

Statistical Package for Social Science (SPSS) 21.0 software (IBM, Armonk, NY, USA) was utilized for data analysis. Measurement data were presented as mean ± standard deviation (SD) and non-conformity was assessed using the rank sum test. Comparisons between groups were conducted using t-tests or ANOVA while count data were expressed as frequencies and percentages (%) and compared using the chi-square (χ^2) test. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of patients

There was no significant difference in age, proportion of females, duration of myocardial block, onset time, and duration of surgery between in control and study groups ($p > 0.05$). However, length of extracorporeal circulation was significantly longer in study group compared to control group ($p < 0.05$; Table 1).

Chest drainage after surgery

There was a significant reduction in mediastinal chest tube drainage 12 and 24 h after surgery in study group compared to control group ($p < 0.05$; Table 2).

Table 2: Postoperative chest drainage (mean ± SD, n = 60)

Group	Chest drainage (mL)	
	12 h postoperative	***24 h postoperative***
Study	247.56±89.78	410.34±150.35
Control	280.45±90.67	467.89±167.32
T-value	1.997	1.982
P-value	0.048	0.050

Volume of blood transfusion

Quantity of concentrated red blood cells and fresh frozen plasma transfused was significantly lower in study group compared to the ($p < 0.05$; Table 3).

Table 3: Postoperative blood transfusion (mean ± SD, n = 60)

Group	Infusion of concentrated red blood cell volume (U)	Volume of fresh frozen plasma transfused (mL)
Study	3.52±1.72	367.85±108.53
Control	4.21±2.02	412.65±132.45
T-value	2.014	2.026
P-value	0.046	0.045

Length of stay in ICU and postoperative mechanical ventilation

Study group exhibited significantly longer length of stay in postoperative ICU, while also demonstrating a significantly lower incidence of postoperative mechanical ventilation compared to control group ($p < 0.05$; Table 4).

Postoperative thrombosis, number of deaths, and chest complications

Study group exhibited significantly higher incidence of postoperative thrombosis, positive

sputum culture for gram-negative bacilli, and mortality compared to control group ($p < 0.05$; Table 5).

Table 4: Length of stay in ICU and postoperative mechanical ventilation (N = 60 in each group)

Group	Length of stay in ICU (h)	Duration of postoperative mechanical ventilation (h)
Study	220.89±108.34	90.56±25.80
Control	176.76±127.28	101.23±30.21
T-value	2.045	2.080
P-value	0.043	0.040

Table 5: Postoperative thrombosis, number of deaths, and chest complications

Group	Number of patients with postoperative thrombosis (n)	Positive sputum culture for gram-negative bacilli (n)	Death toll (n)
Study	13	30	7
Control	2	19	1
$\chi 2$	4.033	4.174	4.821
P-value	0.045	0.041	0.028

DISCUSSION

Incidence of aortic coarctation, a severe and life-threatening cardiovascular disease characterized by critical and dangerous conditions, rapid onset, rapid progression, and high mortality rate [9], is gradually increasing, with an annual incidence ranging from 4 to 7 in 100,000 cases. Moreover, age of onset is progressively decreasing. According to the International Registry of Aortic Coarctation, incidence of aortic coarctation is 23.9 in 100,000 cases globally. However, there is no available epidemiological data for China [10-12]. According to statistics, the morbidity and mortality rate of patients with acute aortic dissection (AAD) gradually increases with duration of hospitalization. Mortality increases 1 % per hour within 48 h and reaches up to 74 % within one week. Specifically, individuals with type A AAD (ATAAD) face a higher risk of rupture due to involvement of the ascending aorta root [13,14]. This region experiences elevated pressure levels, resulting in significant augmentation of impact and sheer force exerted on the vessel wall by blood flow. Consequently, it becomes more susceptible to rupture [15].

The problem of persistent perioperative bleeding, despite significant advancements in the surgical approach to ATAAD, has not been adequately addressed, and remains the most severe or even life-threatening complication of ATAAD surgery. This significantly impacts short- and long-term quality of survival for patients [16]. The pathogenesis of intractable bleeding due to ATAAD is multifaceted and diverse. Firstly, the inherent pathological characteristics of aortic coarctation causes dysfunction within the body's coagulation system. Secondly, the intricate surgical procedure involving aortic anastomosis and prolonged extracorporeal circulation disrupts normal coagulation processes by inducing platelet and coagulation factor dysfunction, activating the fibrinolytic system, and causing metabolic acidosis within the body [17], particularly during deep hypothermic arrest cycle when aortic arch replacement is performed [18]. Residual heparin also leads to increased post-extracorporeal circulation bleeding in patients [19]. Moreover, intraoperative blood loss results in significant platelet and coagulation factor depletion, further contributing to prolonged bleeding [20].

In summary, aortic coarctation has the potential to trigger coagulation disorders, while surgical interventions also exacerbate coagulation abnormalities. These mechanisms interact with each other and collectively contribute to the development of refractory bleeding during perioperative period. Primary mechanism through which rFVIIa plays a crucial role in the coagulation process is by binding to exposed tissue factor (TF) on damaged vessel wall, forming a complex that activates platelets and generates thrombin. This activation occurs via the activation of cell surface FX [21].

The presence of these thrombin enzymes, along with activated platelets and factor V at the injury site, leads to fibrinogen conversion into fibrin and subsequent thrombus formation, resulting in localized episodes of blood clotting [22,23]. Although it has been suggested that rFVIIa should only be used as a last resort when all other clinical attempts to control bleeding, and coagulation disorders have failed [24]. Management of surgical bleeding often necessitates administration of allogeneic red blood cells and other blood components, thereby posing a risk factor for reoperation [25]. Allogeneic blood transfusions are associated with an 8-fold increased risk of death and reduced long-term survival [7]. Therefore, early application of rFVIIa may reduce overall use of blood products and associated morbidity and mortality [8].

In this study, the application of rFVIIa significantly reduced postoperative thoracic drainage at 12 and 24 h. The amount of concentrated red blood cells and fresh frozen plasma transfused were also significantly

reduced after surgery. Incidence of acute lung injury resulting from massive blood transfusion was significantly reduced, leading to a significant reduction in the duration of mechanical ventilation. However, study group exhibited significantly longer total length of stay in the ICU compared to control group, due to increased occurrence of postoperative thrombosis and pulmonary infection-related chest complications. In terms of in-hospital mortality, number of deaths was also higher in study group compared to control group after rFVIIa treatment. It is possible that certain patients may have presented with concomitant serious complications prior to surgery, characterized by a significantly compromised baseline condition and unstable vital signs. However, it remains unclear whether the cause of death was due to intraoperative infusion of rFVIIa.

The present study also examined the impact of rFVIIa on chest complications, revealing a significantly higher incidence of positive sputum culture results in study group compared to control group. This disparity may be attributed to the considerably compromised baseline health status and potential preoperative respiratory comorbidities among patients receiving rFVIIa treatment in this study. Also, extracorporeal circulation time was significantly prolonged in study group, which consequently elevated the risk of pulmonary infection. Therefore, it is imperative to regularly monitor relevant sputum culture indices when employing rFVIIa clinically and adjust antibacterial medications as necessary to mitigate lung infections and improve longevity. Early removal of tracheal intubation shortens duration of ICU stay, but patients with poor autonomy in ICU and tracheal intubation are prone to formation of venous thrombosis by bed braking.

Limitations of this study

This study is limited by the small number of cases enrolled, and a relatively short-term follow-up. As a result, the safety of rFVIIa in ATAAD patients may not have been fully investigated.

CONCLUSION

Intraoperative administration of rFVIIa in acute aortic coarctation enhances short-term patient prognosis, albeit with an augmented risk of thoracic complications. Therefore, further clinical investigations encompassing larger sample sizes, and a multicenter approach featuring long-term follow up are imperative to comprehensively investigate the merits and drawbacks of this intervention.

DECLARATIONS

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Ethical approval

This study was approved by the Medical Ethics Committee of First Affiliated Hospital of Xinjiang Medical University (approval no. 20190225-114).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Yilihamujiang Keyoumu and Pazelaiti Mohemaiti contributed equally to this work.

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