Preoperative Clinical Application of Human Fibrinogen in Patients With Acute Stanford Type A Aortic Dissection: a Single-center Retrospective Study

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Abstract

Objective: To evaluate the perioperative clinical efficacy of preoperative human fibrinogen treatment in patients with acute Stanford type A aortic dissection (ATAAD).

Methods: Data of 159 patients with ATAAD who underwent emergency surgical treatment in our hospital from January 2019 to December 2020 were retrospectively analyzed. Patients were divided into two groups according to whether human fibrinogen was administered before surgery. The preoperative clinical data, surgical data, postoperative data, complications related to the coagulation function, and mortality of the two groups were compared and analyzed.

Results: The in-hospital mortality was similar in the two groups (2.9% versus 9.3%, P = 0.122). However, group A had a significantly shorter operation time (279.24±39.03 versus 298.24±45.90, P=0.008), lower intraoperative blood loss (240.48±96.75 versus 353.70±189.80, P□0.001), and reduced intraoperative transfusion requirement of red blood cells (2.61±1.18 versus 6.05±1.86, P□0.001). The postoperative suction drainage within 24 hours in group A was significantly decreased (243.24±201.52 versus 504.22±341.08□P=0.002). The incidence of postoperative acute kidney injury (AKI) in group A was lower than that in group B (3.8% versus 14.8%, P =0.023). Similarly, the incidence of postoperative hepatic insufficiency in group A was lower than that in group B (1.9% versus 9.3%, P =0.045). In group A, the mechanical ventilation time was shorter (47.68±28.61 versus 118.21±173.16, P=0.004) along with reduced ICU stay time (4.06±1.18 versus 8.09±9.42, P=0.003), and postoperative hospitalization days (19.20±14.60 versus 23.50±7.56, P=0.004).

Conclusion: Preoperative administration of human fibrinogen in patients undergoing ATAAD surgery can effectively reduce the intraoperative blood loss, blood transfusion amount, shorten the operation time, reduce postoperative complications, and improve the early prognosis of patients, in addition to being highly safe.

Introduction

Aortic dissection (AD) is a life-threatening condition, and acute Stanford type A aortic dissection (ATAAD) carries the highest mortality among all aortic dissection types. Studies have shown that mortality from AD is highest in the first 48 hours after the onset of symptoms, which can be more than 50%, and the highest mortality within 2 weeks can be more than 80%(1–3). Therefore, the primary management of ATAAD is emergency surgery, which is the only effective treatment(4, 5). Despite the continual improvement in surgical techniques, the rates of surgical complications, morbidity, and mortality remain high(6, 7).

Bleeding is one of the most common complications after ATAAD. Bleeding complications with ATAAD have not been adequately evaluated yet(8–11). Previous studies have shown that ATAAD can cause coagulation disorders(12, 13). Several studies have shown that patients with ATAAD have significant coagulation/fibrinolysis abnormalities before surgery(14). Preoperatively, when the blood flows through

the pseudolumen of non-endothelial tissue in patients with AD, it comes in contact with the damaged tissue, leading to turbulence. These factors can effectively activate the coagulation/fibrinolytic system and platelets, resulting in formation of thrombi and consumption of large amounts of clotting factors. Simultaneously, the inflammatory system is activated, and platelets are an important link to start the inflammatory response cascade. Many factors lead to the consumption of platelets in large quantities, thus reducing the number of platelets. Some researchers have shown that the degree of postoperative damage to coagulation factors and fibrinogen is greater than the degree of damage to platelet function(15). Therefore, fibrinogen plays an important role in the occurrence and development of AD. Cardiopulmonary bypass surgery further leads to dysfunction of the body's coagulation and fibrinolytic system, resulting in clotting-related complications(16). This can lead to increased postoperative blood loss, increased perioperative blood product infusion, increased incidence of vital organ complications, and death.

Therefore, in this study, patients with ATAAD who received fibrinogen as preoperative intravenous infusion were evaluated to explore the effect of fibrinogen on the prognosis of patients with intraoperative bleeding and postoperative bleeding-related complications, with the aim of providing a relevant theoretical basis for clinical treatment.

Methods

Patient population and data collection

A retrospective analysis was performed on 159 ATAAD patients admitted to the department of cardiac surgery, Union Hospital, Fujian Medical University from January 2019 to December 2020. Preoperative thoracic and abdominal aortic computed tomographic angiography (CTA) and cardiac echocardiography were performed in all patients to clarify the diagnosis and scope of the lesion. Preoperative basic information of the patients in group A and Group B is shown in Table 1. Intraoperative surgical methods are shown in Table 2. Inclusion criterion was within 2 weeks of onset. Exclusion criteria were as follows: 1) previous severe respiratory disease, nervous system disease, hematologic disease, severe pulmonary infection, thrombotic disease, abnormal liver and kidney function; 2) Patients with cardiac insufficiency, massive pericardial effusion, coronary heart disease, cerebrovascular accident, and obvious organ or limb malperfusion (including poor lower limb perfusion, brain perfusion, coronary artery perfusion, and visceral perfusion); 3) patients with ongoing anticoagulant and dual antiplatelet treatment.

Table 1
Preoperative data on the two patient groups.

Valuables	Group A(n=105)	Group B(n=54)	P value
Male, n (%)	78 (74.3%)	36 (66.7%)	0.312
Age (year)	52.6±11.3	50.1±13.5	0.214
Body mass index (Kg/Mˆ2)	25.5±3.5	24.8±3.4	0.247
Hypertension, n (%)	82 (78.1%)	40 (74.1%)	0.570
Diabetes, n (%)	3 (2.9%)	2 (3.7%)	0.849
Fibrinogen (ug/ml)	1.63±0.54	1.72±0.62	0.365
D-dimer (ug/mL)	12.65±7.40	10.71±7.34	0.119
Heamoglobin (g/L)	133.90±19.96	130.30±23.49	0.314
platelet count (10ˆ9/L)	186.77±58.67	188.22±66.77	0.888
Prothrombin time (sec)	14.14±1.72	14.46±1.73	0.271
K time (min)	2.42±1.30	2.21±0.56	0.157
Angle (deg)	57.55±10.98	59.27±8.89	0.319
Fibrinogen degradation products (ug/ml)	61.19±13.77	60.58±7.30	0.712
Serum creatinine (umol/L)	77.99±29.74	80.95±27.23	0.531
Lactic acid (mmol/L)	1.45±1.29	1.19±0.62	0.084
Albumin (g/L)	38.00±4.74	37.77±4.32	0.789
Alanine aminotransferase (IU/L)	51.72±107.43	41.61±62.69	0.456
Aspartate aminotransferase (IU/L)	59.37±157.16	41.17±40.46	0.404
LEEF (%)	62.21±9.00	63.96±7.12	0.217
Continuous normally distributed variables were expressed as mean±standard deviation(SD) and categorical data are given as the counts and percentage(n, %).			

Table 2
Surgical data on the two patient groups.

Valuables	Group A(n=105)	Group B(n=54)	P value
Surgical procedures			
Sun's procedure, n (%)	11 (10.5%)	6 (11.1%)	0.902
Ascending aorta replacement + Hemiarch Replacement + a triplebranched stent graft implantation, n (%)	34 (32.4%)	15 (27.8%)	0.552
Aortic valve-sparing + ascending aorta replacement + hemiarch replacement + a triple branched stent graft implantation, n (%)	45 (42.9%)	26 (48.1%)	0.525
Bentall+ascending aorta replacement + hemiarch replacement + a triple branched stent graft implantation, n (%)	15 (14.3%)	7 (13.0%)	0.819
Operative time (min)	279.24±39.03	298.24±45.90	0.008
CPB time (min)	133.92±39.39	131.74±30.37	0.722
Aortic clamp time (min)	43.27±12.06	43.76±21.05	0.874
SCP and low body arrest time (min)	11.77±3.06	12.89±4.54	0.067
Intraoperative blood loss (ml)	240.48±96.75	353.70±189.80	<0.001
Infusion of red blood cell (u)	2.61±1.18	6.05±1.86	<0.001
Infusion of fresh frozen plasma (ml)	41.43±96.69	54.61±100.13	0.422
Infusion of platelet (u)	0.13±0.31	0.12±0.32	0.832
Continuous normally distributed variables were expressed as mean±standard deviation(SD) and categorical data are given as the counts and percentage(n, %).			

Based on the preoperative use of Human Fibrinogen (Production enterprise: Green Cross [China] Biological Products Co., LTD.; Approval Number: S20003011 [2 g human fibrinogen intravenous drop]), patients were divided into two groups: Group A consisted of 105 patients who received intravenous human fibrinogen before the operation, while Group B consisted of 54 patients who did not receive human fibrinogen before the operation. There were no significant differences in sex, age, body weight, hypertension, preoperative fibrin level, and intraoperative operative procedures between the two groups, and the data of the two groups were comparable. This study was approved by the ethics committee of Union Hospital, Fujian Medical University and conformed to the Declaration of Helsinki. And this retrospective review of patient data did not require written informed consent from participants in accordance with national guidelines.

Preoperative baseline data of the two groups were retrospectively recorded and statistically analyzed. Intraoperative data related to the operation, including operation time, cardiopulmonary bypass (CPB) time, aortic clamp time, selective cerebral perfusion (SCP), low body arrest time, infusion of red blood cells, infusion of fresh frozen plasma, infusion of platelets, postoperative suction drainage within 24 hours, re-thoracotomy for hemostasis, mechanical ventilation time, intensive care unit (ICU) stay time, postoperative hospital stay, incidence of vital organ complications (including multiorgan dysfunction, acute kidney injury (AKI), hepatic insufficiency, gastrointestinal hemorrhage, cerebral infarction, cerebral hemorrhage), and thirty-day mortality rate were analyzed.

Statistical analysis

Analyses were conducted using SPSS® software (IBM® Corporation, Somers, NY, USA). Data are presented as mean ± standard deviation (SD), or median (25th, 75th quartiles). Fisher' s exact test was applied for categoric variables, and the Mann-Whitney U test or Kruskal-Wallis test was applied for continuous variables. Univariate analysis and multivariate analyses were used for the risk factors, categorical data are given as the counts and percentage(n, %). A minimum p-value of 0.05 was considered to be statistically significant.

Results

There was no significant difference in the preoperative baseline data between the two groups (P > 0.05), and the data of the two groups were comparable.

1. Group A had a significantly shorter operation time (279.24±39.03 versus 298.24±45.90, P=0.008), reduced intraoperative blood loss (240.48±96.75 versus 353.70±189.80, P<0.001), and reduced intraoperative transfusion of red blood cells (2.61±1.18 versus 6.05±1.86, P<0.001). There was no difference in the CPB time, aortic clamp time, SCP, and low body arrest time between the two groups (P>0.05).

2. The postoperative suction drainage within 24 hours in group A was significantly decreased (243.24±201.52 versus 504.22±341.08, P=0.002). The incidence of postoperative AKI in group A was lower than that in group B (3.8% versus 14.8%, P =0.023). Similarly, the incidence of postoperative hepatic insufficiency in group A was lower than that in group B (1.9% versus 9.3%, P =0.045). In group A, the mechanical ventilation time was shorter than in group B (47.68±28.61 versus 118.21±173.16, P=0.004), along with a shorter ICU stay time (4.06±1.18 versus 8.09±9.42, P=0.003)and fewer postoperative hospitalization days (19.20±14.60 versus 23.50±7.56, P=0.004).(Table 3)

3. The in-hospital mortality was similar in the two groups (5.7% versus 7.5%, P =0.122). (Table 3)

Table 3
Postoperative data on the two patient groups.

Valuables	Group A(n=105)	Group B(n=54)	P value
Suction drainage within 24 hours (ml)	243.24±201.52	504.22±341.08	0.002
Re-thoracotomy for hemostasis, n (%)	1 (1.0%)	1 (1.0%)	0.788
Mechanical ventilation time (h)	47.68±28.61	118.21±173.16	0.004
ICU stay time (d)	4.06±1.18	8.09±9.42	0.003
Postoperative hospital stay (d)	19.20±14.60	23.50±7.56	0.004
Thirty-day mortality, n (%)	3 (2.9%)	5 (9.3%)	0.122
Multiorgan dysfunction, n (%)	2 (1.9%)	5 (9.3%)	0.083
Single organ dysfunction			
AKI, n (%)	4 (3.8%)	8 (14.8%)	0.023
Hepatic insufficiency, n (%)	2 (1.9%)	5 (9.3%)	0.045
Gastrointestinal hemorrhage, n (%)	1 (1.0%)	3 (5.6%)	0.222
Cerebral infarction, n (%)	1 (1.0%)	1 (1.9%)	0.788
Cerebral hemorrhage, n (%)	0 (0.0%)	1 (1.9%)	N/A
Continuous normally distributed variables were expressed as mean±standard deviation(SD) and categorical data are given as the counts and percentage(n, %).			

Discussion

AAD is a rare and life-threatening condition in which the blood flows from a tear in the intima of the aorta into the middle layer of the aorta. Untreated patients have a mortality rate of 1–2% per hour after symptom onset. Prompt diagnosis and treatment can increase a patient's chances of survival and prevent serious complications(17–19). The survival rate of patients with acute AD is related to the timing of treatment, presence of end-organ dysperfusion, degree of aortic repair, and development of postoperative complications(20). ATAAD is a critical condition associated with high early surgical mortality rates, partly owing to bleeding complications(21). Previous studies on surgery for ATAAD have shown that there is an activation of the coagulation system along with consumption coagulopathy(22–24).

Prolongation of the prothrombin time occurs owing to a reduction in one or more coagulation factors and formation of fibrin and fibrinogen degradation products. Coagulopathy may result from the release of clotting substances from the aortic wall into the circulation, or from the accumulation of clotting factors at the site of the lesion, secondary to local exposure of the tissue factors in the torn arterial wall. Recent

studies by Straub and Kesslerhave have shown that local deposition of fibrinogen at the aneurysm site plays an important role in causing coagulation disorders(25). Baumgartner et al. reported that the aortic adventitia possesses a high fibrinolytic activator activity, whereas the aortic media and intima possess weak thromboplastic properties. Moreover, the exposure of subendothelial aortic tissues has been shown to lead to significant deposition of platelets(26). AD may be associated with a third pathway leading to coagulation abnormalities, which is activated by fibrinolytic activators present in the outer aortic membrane. Plasminase formation through this pathway leads to proteolysis of coagulation factors V, VIII, XII, and fibrinogen, resulting in the formation of fibrinogen and/or degradation products of fibrin.

During the development of AD, blood flows through the pseudolumen of non-endothelial tissue and comes in contact with the damaged tissue, thus leading to turbulence. These factors can effectively activate the coagulation system, fibrinolytic system, and platelets. The coagulation system is activated, resulting in a hypercoagulable state along with thrombin generation, thrombosis formation, and consumption of a large number of coagulation factors. Among them, fibrinogen is transformed into fibrin through the action of thrombin, which plays a role in hemostasis and the common coagulation pathway, and participates in a series of pathological and physiological processes in the body, such as inflammation and tissue damage and repair(27).

As a key component of blood clots, fibrinogen plays an important role in hemostasis and thrombosis(28). Some studies have shown that fibrinogen plays an important role in hemostasis and thrombosis in patients with cardiovascular disease(29, 30). Fibrinogen can be used as a prognostic indicator of ATAAD, and a low fibrinogen level at admission is an independent predictor of in-hospital mortality in patients with ATAAD(31). Other studies have shown that AAD activates the coagulation system before surgery, and the operation and intraoperative deep hypothermia can lead to a decrease in coagulation factors, platelet count and function, as well as the fibrinogen concentration and function(32–34). After hemostatic therapy, although the platelet count remains low, coagulation factors and platelet function return close to the preoperative level(23), however, the fibrinogen concentration and function remain significantly lower than that at the preoperative level. Fibrinogen level is also an important predictor of bleeding. For each 1g/L reduction in fibrinogen, the risk of bleeding increases 2.63 times(35).

The results of this study show that in patients with ATAAD with low fibrin level, preoperative human fibrinogen supplementation could significantly shorten the operation time, reduce the intraoperative blood loss and suction drainage within 24 hours, as well as decrease the incidence of postoperative AKI and hepatic insufficiency. It was found to not only significantly reduce the intraoperative and postoperative blood loss, but also play an important role in the patients' postoperative recovery. Furthermore, it can significantly reduce postoperative organ dysfunction, shorten the duration of ventilator use, ICU treatment, and postoperative hospital stay, but has little effect on the mortality at 30 days after surgery. Some researchers have shown that there is no correlation between a low fibrinogen level and in-hospital mortality, and that preoperative low fibrinogen level is the preferred indicator for predicting clinical complications in patients with ATAAD(31, 36).

It has been shown that coagulation factors and fibrinogen are significantly reduced in AAD. Studies using enzyme-linked immunosorbent assay and thromboelasmogram have also revealed a continuous activation of the coagulation system and depletion of coagulation factors, and that the degree of postoperative loss of coagulation factors and fibrinogen was greater than that of platelet function(23). The importance of fibrinogen in reducing blood loss and saving lives is being increasingly emphasized. Both cardiopulmonary bypass and hypothermia can reduce fibrinogen synthesis and affect platelet function. With the availability of fibrinogen concentrate, many European guidelines recommend early infusion of fibrinogen concentrate to correct coagulation disorders(37, 38). Therefore, we suggest that hemostatic therapy should focus on early, rapid, and adequate supplementation of coagulation factors and fibrinogen to improve the levels of consumable coagulation factors in patients with acute AD(26).

In conclusion, AD is characterized by a unique coagulation system change process, and a large number of studies have confirmed that there are pathological changes in the coagulation and fibrinolytic system functions after the onset of AD. Our study results suggest that preoperative preventive fibrinogen supplementation can significantly shorten the operation time, reduce intraoperative and postoperative blood loss, reduce the probability of postoperative organ dysfunction, and shorten the time of ventilator use, ICU treatment, and postoperative hospital stay in patients with AD. Therefore, its clinical guiding significance for postoperative treatment, outcome, and prognosis of AD cannot be ignored. At present, the mechanism of coagulation and fibrinolytic system changes in patients with AD is not clear. Further studies on the underlying molecular signaling mechanisms may provide a new theoretical basis for the occurrence and development of AD, and provide new targets for clinical treatment.

Limitations

This preliminary study has several limitations. One was the small sample that was retrospectively analyzed; however, it still has relevant statistical value. Based on the experience of the past two years and the results of this study, the author has designed a single center retrospective controlled trial to determine whether preoperative use of fibrinogen in patients with ATAAD has clinical application value. All patients were administered the same dose, but there may be bias between different patients, as there is no standard treatment regimen and individualized preoperative treatment was administered to different patients. We excluded patients with cardiac insufficiency, massive pericardial effusion, coronary atherosclerotic heart disease, cerebrovascular accident, and organ or limb malperfusion, which may have led to bias in the results. Therefore, further prospective randomized controlled studies are required.

Conclusions

Preoperative use of human fibrinogen can reduce intraoperative blood loss and red blood cell transfusion requirement in patients undergoing surgery for ATAAD, in addition to shortening the operation time, reducing postoperative complications, and improving the early prognosis of patients, and being highly safe.

Abbreviations

Aortic dissection(AD)

Acute aortic dissection(AAD)

Acute Stanford type A aortic dissection(ATAAD)

Computered tomograhy angiography(CTA)

Cardiopulmonary bypass(CPB)

Selective cerebral perfusion(SCP)

Acute kidney injury(AKI)

Left ventricular ejection fraction (LVEF)

Declarations

Ethics approval and consent to participate

The study's retrospective was approved by the ethics committee of Union Hospital of Fujian Medical University, and conformed to the Declaration of Helsinki. The requirement for informed consent was waived by Union Hospital of Fujian Medical University based on the study's retrospective analysis of patient data.

Consent for publication

Not Applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

Liangwan Chen designed the study and submitted the manuscript. Mirong Tang and Qingsong Wu prepared the first draft of the manuscript and made the literature review. And Jiahui Li and Qingsong Wu are contributed equally to this study and share first authorship. Mirong Tang and Yue Shen made substantial changes in the manuscript together. Zhihuang Qiu, Xiaodong Chen and Xingfeng Chen collected and analyzed data together. All authors read and approved the final manuscript.

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