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A retrospective study on safety and efficacy of recombinant human soluble thrombomodulin to acute aortic dissection with disseminated intravascular coagulation

Tsukasa Ikeda[1,2], Masateru Uchiyama[1*], Naomi Ozawa[1], Tomohiro Imazuru[1] and Tomoki Shimokawa[1]

Abstract

Objectives Recombinant human soluble thrombomodulin (rTM) has recently been used as a promising therapeutic natural anti-coagulant drug for disseminated intravascular coagulation (DIC). Here we investigated the safety and efficacy of rTM after aortic surgery in patients with acute aortic dissection (AAD).

Methods A total of 316 patients diagnosed with AAD underwent emergent ascending aortic replacement or total arch replacement between 2010 and 2019. We retrospectively analyzed the clinical information of 62 patients with the Japanese Association for Acute Medicine's acute-stage DIC diagnostic criteria (JAAM criteria) with a score of ≥ 4. We assigned 62 patients to two groups, either non-rTM group (n = 29) or rTM group (n = 33). Patient characteristics, surgical procedures, and postoperative outcome data including coagulation function and the JAAM DIC score in both groups were collected.

Results The decrease in the number of platelets was clearly suppressed on days 1–3 in the rTM group. On days 1–4, fibrin degradation product levels were upregulated in the non-rTM group but significantly downregulated in the rTM group. Five operative deaths occurred within 30 days postoperative (two [6.9%] in the non-rTM group vs. three [9.1%] in the rTM group). The JAAM DIC score showed a gradually improving trend from postoperative day 1 in the rTM group.

Conclusions Postoperative rTM administration for AAD may be a safe and promising novel treatment strategy for improving the JAAM DIC score.

Keywords Thrombomodulin, Acute aortic dissection, Disseminated intravascular coagulation

Introduction

Disseminated intravascular coagulation (DIC) associated with acute aortic dissection (AAD) often occurs. However, its detailed mechanism of action has not yet been elucidated [1]. The diagnosis of DIC is generally based on dysfunction of the vascular endothelium triggered by systemic inflammation due to malignant tumors, trauma, or sepsis and DIC can be fatal if the initial treatment is delayed. Some patients diagnosed with AAD develop DIC during the acute phase of aortic surgery.

*Correspondence:
Masateru Uchiyama
mautiya@yahoo.co.jp
[1] Department of Cardiovascular Surgery, Teikyo University Hospital, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan
[2] Department of Cardiovascular Surgery, Kawakita General Hospital, Tokyo, Japan

When vascular structures and tissue factors damaged by AAD are exposed to the false lumen, there is a high probability that DIC was developed by disruption of the coagulation-fibrinolytic system [2, 3]. Thrombomodulin (TM) was used as a promising therapeutic natural anticoagulant drug in clinical trials of managing acute DIC [4–6]. Once the anticoagulatory mechanisms of TM were gradually elucidated, the use of recombinant human soluble TM (rTM) for treating DIC and severe infections was approved in Japan in 2008, leading to many mega-studies on TM. For example, in Japan, in 2007, a randomized, double-blind clinical phase III trial of the effects of rTM and low-dose heparin on DIC associated with hematologic malignancy or infection demonstrated that rTM could improve the DIC resolution rate (rate of recovery from DIC) and clinical course of bleeding symptoms [5]. Shortly thereafter, rTM was classified as an anticoagulant and could induce potential bleeding complications. However, motivated by favorable outcomes in clinical trials and its promising efficacy for managing coagulation under severe systemic conditions [5–7], we hypothesized that rTM administration may carry a lower risk of bleeding complications. Therefore, here we investigated the safety and efficacy of rTM after aortic surgery in patients with AAD.

Methods

Study design

A total of 316 patients diagnosed with DeBakey type I AAD underwent emergent ascending aortic or total arch replacement at our institution between February 2010 and December 2019. Of them, 62 were diagnosed with the Japanese Association for Acute Medicine's acute-stage DIC diagnostic criteria (JAAM criteria) with a score of ≥ 4 (Table 1) [8], and we retrospectively reviewed and analyzed their clinical characteristics. The decision to use rTM was made by each surgeon. Based on the medical records, we assigned the 62 patients to no treatment with rTM (non-rTM group; n = 29) or treatment with rTM (rTM group; n = 33). This study excluded patients with preoperative cardiac arrest, cardiogenic shock, the need for postoperative percutaneous cardiopulmonary support, concomitant cardiac surgery such as coronary artery bypass grafting and valve surgery, current use of anti-platelet or anti-coagulant drugs, and a history of hematologic diseases and severe liver disorders.

In the rTM group, a dose of 380 U/kg of rTM was administered as a 30-min infusion immediately after cardiac surgery. In patients with renal impairment (creatinine clearance rate < 10 mL/min) or those undergoing dialysis, 130 U/kg of rTM was administered. rTM was administered over 1 h once daily. When the duration of rTM administration exceeded 6 days or the JAAM DIC score became ≤ 3, the administration was ended.

Table 1 Scoring system for disseminated intravascular coagulation

Factors	Score
Systemic inflammatory response syndrome criteria	
≧ 3	1
0–2	0
Platelet count ($\times 10^4$/μL)	
< 8 or ≧ 50% decrease within 24 h	3
≧ 8 and < 12 or ≧ 30% decrease within 24 h	1
≧ 12	0
Prothrombin time (value of patient/normal value)	
≧ 1.2	1
< 1.2	0
Fibrin/Fibrinogen degradation products (μg/mL)	
≧ 25	3
≧ 10 and < 25	1
< 10	0

Systemic inflammatory response syndrome is defined by the satisfaction of any of the criteria below: (1) Body temperature over 38 or under 36 degrees Celsius, (2) Heart rate greater than 90 beats/minute, (3) Respiratory rate greater than 20 breaths/minute or partial pressure of CO_2 less than 32 mmHg, (4) Leukocyte count greater than 12,000 or less than 4000/microliters or over 10% immature forms or bands

Study variables and operative outcomes

The patients' characteristics, surgical procedures, and postoperative outcomes were recorded for each group. Follow-up data were obtained from clinical records at our institution. All data and variables were compared, including perioperative bleeding, blood transfusion, re-exploration for bleeding, intensive care unit (ICU) length of stay, hospitalization length of stay, and 30-day mortality. Additionally, postoperative coagulation function (platelet count, prothrombin time [PT], activated partial thromboplastin time [APTT], and fibrinogen/fibrin degradation products [FDP]) and the JAAM DIC score were evaluated in a time series. False lumen thrombosis was assessed using contrast-enhanced computed tomography on postoperative day (POD) 7 and classified into three categories: no thrombosis of the entire false lumen; thrombosis of the thoracic aorta and no thrombosis of the abdominal aorta; and thrombosis of the entire false lumen.

Statistical analysis

Continuous data are presented as mean ± standard deviation, while categorical variables are given as the number and percentage of patients. Continuous variables were compared using unpaired t-test. A *P* value of less than 0.05 was regarded as significant.

Ethical approval

All subjects enrolled in this research gave their informed consent, which alongside the study design, has been approved by the institutional committee on human research (22–191).

Table 2 Patient characteristics

	non-rTM group (n = 29)	rTM group (n = 33)	*P* value
Age, years	64 ± 12	71 ± 12	0.018
Female gender	10 (34.5%)	18 (54.5%)	ns
Coexisting condition			
Hypertension	23 (79.3%)	25 (75.8%)	ns
Diabetes mellitus	0 (0%)	1 (3.0%)	ns
Hyperlipidemia	3 (10.3%)	3 (9.1%)	ns
Coronary artery disease	1 (3,4%)	1 (3.0%)	ns
Peripheral artery disease	0 (0%)	0 (0%)	ns
Chronic pulmonary disease	0 (0%)	0 (0%)	ns
Atrial fibrillation	7 (24.1%)	10 (30.3%)	ns
Renal insufficiency	15 (51.7%)	16 (48.5%)	ns
Hepatic insufficiency	1 (3.5%)	1 (3.0%)	ns

* Data are mean ± SD or n (%) unless noted otherwise

ns no significant difference, *rTM* recombinant human soluble thrombomodulin, *SD* standard deviation

Results

Patients and intra-/post-operative outcomes

Table 2 summarizes the patients' baseline characteristics by group. There were no significant intergroup differences in sex, coexisting conditions, or surgical procedures. The average age of the rTM group was significantly higher than that of the non-rTM group (71 ± 12 years vs. 64 ± 12 years, respectively; Table 2). As shown in Table 3, the operative characteristics, including the average operative time, cardiopulmonary bypass time, and circulatory arrest time, tended to be shorter in the rTM group, but the differences were not statistically significant. Conversely, the ICU and hospitalization lengths of stay tended to be mildly prolonged, but the differences were not statistically significant. The mean duration of rTM administration was 5 ± 1 days.

Safety and adverse events

There was no significant difference in mean perioperative bleeding volume (Table 3) or blood transfusion requirement (Table 3). Regarding early mortality, five deaths occurred within POD 30 (two [6.9%] in the non-rTM group vs. three [9.1%] in the rTM group; Table 3). In the non-rTM group, one patient died of severe cerebral infarction on POD 8, while the other died of myocardial ischemia on POD 4. In the rTM group, one patient died of aortic root rupture on POD 25, the second patient died

Table 3 Operative and postoperative characteristics

	non-rTM group (n = 29)	rTM group (n = 33)	*P* value
Aortic replacement			
AAR	17 (58.6%)	23 (69.7%)	ns
TAR	12 (41.4%)	10 (30.3%)	ns
Operation time, min	321.0 ± 99.7	294.2 ± 100.2	ns
Cardiopulmonary bypass time, min	173.9 ± 68.4	159.1 ± 72.5	ns
Circulatory arrest time, min	40.0 ± 18.3	36.9 ± 25.6	ns
Perioperative bleeding, mL	1286.4 ± 960.4	1345.2 ± 862.2	ns
Postoperative blood transfusion			
Red cell concentrate, mL	685.5 ± 671.8	823.0 ± 696.3	ns
Fresh frozen plasma, mL	587.6 ± 523.4	472.7 ± 446.9	ns
Platelet concentrate, mL	75.9 ± 155.0	133.3 ± 178.0	ns
Term of rTM administration, day	–	5.0 ± 1.0	–
ICU length of stay, day	7.2 ± 10.6	8.1 ± 10.3	ns
Hospitalization, day	22.8 ± 18.3	24.4 ± 16.7	ns
Heparin	2 (6.9%)	8 (24.2%)	ns
Tranexamic acid	14 (48.3%)	22 (66.7%)	ns
Early mortality	2 (6.9%)	3 (9.1%)	ns
Re-exploration for bleeding	1 (3.4%)	2 (6.1%)	ns

* Data are mean ± SD or n (%) unless noted otherwise

AAR ascending aortic replacement, *ICU* intensive care unit, *ns* no significant difference, *rTM* recombinant human soluble thrombomodulin, *SD* standard deviation, *TAR* total arch replacement

of acute renal failure on POD 11, and the third patient died of sepsis on POD 18. The operative complications, including re-exploration for bleeding, did not differ significantly between groups (one case [3.4%] in the non-rTM group vs. two cases [6.1%] in the rTM group).

Effects on rTM

The decrease in the number of platelets was clearly suppressed on days 1–3 in the rTM group versus the non-rTM group (Fig. 1A). Moreover, FDP levels were upregulated on days 1–4 in the non-rTM group but significantly downregulated in the rTM group (Fig. 1B). Time-course data for APTT were similar between the groups (Fig. 1C). Although the mean PT-International Normalized Ratio (PT-INR) differed significantly between groups on days 1 and 5 (Fig. 1D), the difference did not appear to be clinically significant. The JAAM DIC score showed a gradually improving trend from POD 1 in the rTM group (Fig. 2). Additionally, as shown in Table 4, the postoperative evaluation of false lumen thrombosis revealed no significant differences in any section.

Discussion

DIC resulting from AAD accounts for 2–4% of all cases, and the mechanisms of AAD-induced DIC are considered to differ from those induced by sepsis [9]. One possible mechanism of AAD-induced DIC involves the activation of intrinsic and extrinsic clotting factors by the impairment of vascular endothelial cells due to AAD and the subsequent enhancement of the fibrinolysis system by various cytokines released by inflammatory cells [9]. In these conditions, despite intensive treatment, including a massive blood transfusion, postoperative bleeding management may be difficult because the only treatment involves surgical removal of the impaired vascular intima to stabilize the vascular endothelial cells and surrounding tissues. Indeed, many cardiovascular surgeons may have difficulty with postoperative management, including treatment for DIC, because the bleeding points of bleeding re-exploration are unclear. Regarding the postoperative management of bleeding, safely controlling DIC and reducing the number of blood transfusions are important. rTM is thought to form a complex with thrombin, which activates protein C and inactivates factors Va and VIIIa to regulate subsequent thrombin formation. Additionally, rTM is used as a therapeutic drug to regulate excessive fibrinolysis by activating thrombin-activated fibrinolysis inhibitors. This is the first study in Japan to show that rTM can be used after AAD surgery without increasing bleeding, re-exploration for bleeding, and mortality and that rTM can improve postoperative coagulation fibrinolytic abnormalities.

Regarding safety, the most remarkable finding of this study was that the postoperative administration of rTM did not result in an increased risk of blood transfusion, re-exploration for bleeding, or 30-day mortality. The

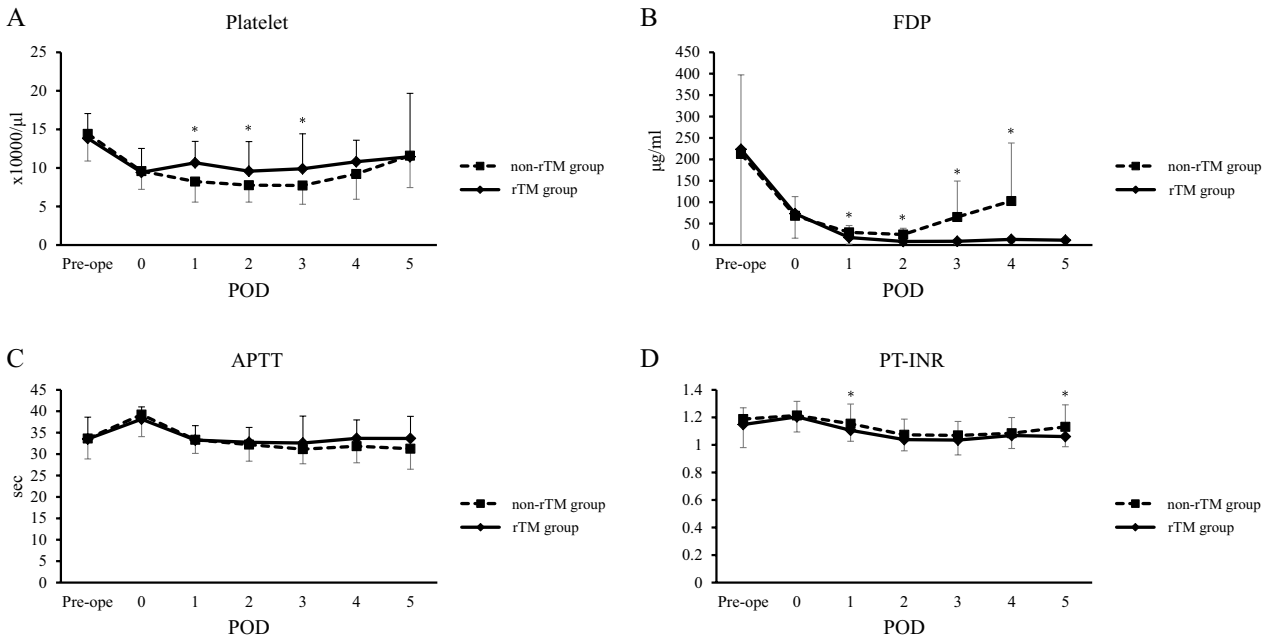

Fig. 1 Postoperative time-series evaluation of coagulation and fibrinolysis system **A** Platelet, **B** Fibrinogen/fibrin degradation products (FDP), (**C**) Activated partial thromboplastin time (APTT), (**D**) PT-International Normalized Ratio (PT-INR). *$P < 0.05$ compared with the non-rTM group. *POD* postoperative day, *rTM* recombinant human soluble TM

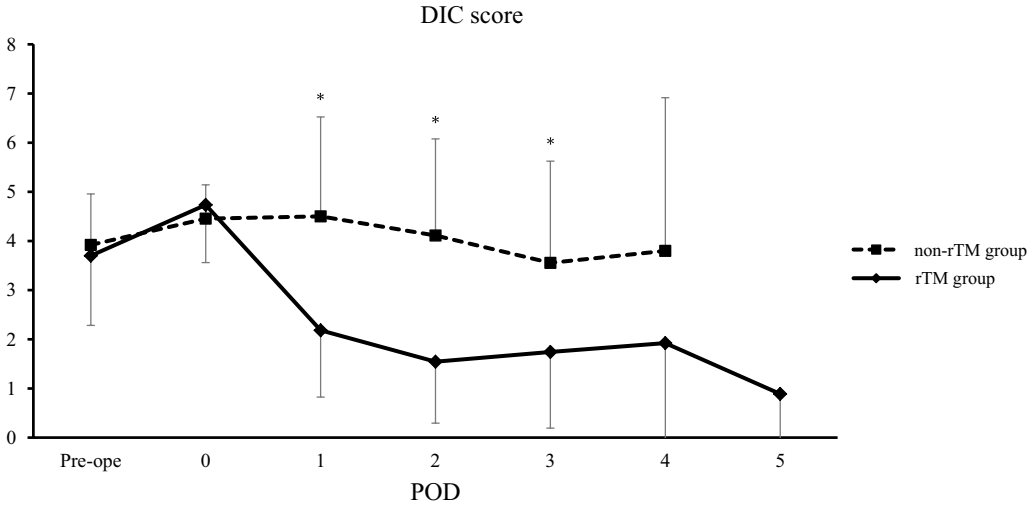

Fig. 2 Postoperative time-series evaluation of DIC score *$P < 0.05$ compared with the non-rTM group. *POD* postoperative day, *rTM* recombinant human soluble TM

Table 4 Postoperative evaluation for false lumen thrombosis

	non-rTM group (n = 29)	rTM group (n = 33)	*P* value
No thrombosis of the entire false lumen	21 (72.4%)	22 (66.7%)	ns
Thrombosis of the thoracic aorta and no thrombosis of the abdominal aorta	4 (13.8%)	6 (18.2%)	ns
Thrombosis of the entire false lumen	4 (13.8%)	5 (15.2%)	ns

* Data are n (%) unless noted otherwise

ns no significant difference, *rTM* recombinant human soluble thrombomodulin

average perioperative bleeding volume and blood transfusion tended to increase slightly in the rTM group; however, there was no statistically significant difference between the non-rTM and rTM groups (Table 3). Re-exploration for bleeding was required in one patient in the non-rTM group versus two patients in the rTM group, but there was no statistically significant difference in the incidence. No clear bleeding points were detected in any cases. Although a direct comparison cannot be made, our data are consistent with those of a previous multicenter, double-blind, randomized, parallel-group trial showing that rTM showed more marked improvement in the clinical course of bleeding symptoms than heparin [5]. Additionally, 30-day mortality was observed in two patients (6.9%) in the non-rTM group and three patients (9.1%) in the rTM group, but there was no statistically significant difference in the incidence. Compared with the 10% 28-day mortality rate after rTM administration in patients undergoing cardiovascular surgery complicated by DIC reported in Japan [10], our data showed favorable early outcomes. Nevertheless, our findings suggested a few concerns that rTM administration could result in slightly increased mortality despite the tendency of favorable intraoperative outcomes, including shorter operation time and cardiopulmonary bypass time as well as no significant differences in the amount of perioperative bleeding and blood transfusion. One potential factor is that the average age was significantly higher for the rTM group. Advanced age is generally considered a main causative factor of high mortality when a highly invasive operation is performed [11]. In one study addressing this issue, early mortality in patients aged > 70 years was reportedly greater than that in patients aged < 70 years (21% vs. 13%) [12]. Consistent with this previous study, a slightly increased mortality rate in our study may have resulted from the fact of aging around 7 years old in the rTM group. In this regard, further investigations are required; however, this may be improved by detailed data accumulation and analysis of limited diseases in this field. Collectively, the use of rTM was not significantly associated with increased perioperative complications including perioperative bleeding and exploration, suggesting that rTM may be a safe option in the acute phase after surgery.

In addition to the safety of rTM, this study found significant gradual improvement in the postoperative JAAM

DIC score after surgery for AAD in the rTM group (Fig. 2). Although a direct comparison between previous studies and ours is difficult, our results are consistent with the improvement in the JAAM DIC score following rTM administration after cardiovascular surgery as shown in a previous trial in Japan in 2013 [10]. Our study demonstrated that rTM administration could suppress the decrease in platelet count without clinically detrimental changes in coagulation factors such as APTT and PT-INR (Fig. 1A, 1C, and 1D), suggesting that it might manage excessive coagulation pathway activity. Judging from the transition in FDP levels in the rTM group (Fig. 1B), the anti-coagulatory effects of rTM could alleviate DIC induced by AAD. Moreover, there was no significant intergroup difference in the postoperative evaluation of false lumen thrombosis, which indicates that rTM may hinder excessive thrombosis through controlling coagulation and the fibrinolysis system, stabilizing formed thrombi, or other unknown mechanisms. Several studies have addressed an intriguing issue in which the *N*-terminal lectin-like domain D1 of TM shows anti-inflammatory effects [13] and graft protective effects [14, 15], suggesting that these mechanisms may stabilize vascular endothelial cells and the surrounding tissues. Considering these findings, although further evidence of the correlation between DIC score improvements and improved prognosis [16–18], it appears possible that rTM administration improves the JAAM DIC score by managing postoperative excessive consumption of platelets, the coagulation and fibrinolysis system, and domain-dependent angioprotective effects.

Study limitations

The present study had some limitations. First, this report consists of a non-randomized and retrospective analysis of existing data with significant differences in preoperative characteristics such as age. Second, the difference in data collection timing between the non-rTM and rTM groups was carefully considered depending on the specificities and maturity of our facility. Many patients in the non-rTM group were enrolled in the first half of the investigation when the DIC evaluation had not yet been established within the facility. Conversely, the other patients in the rTM group were enrolled in the second half of the investigation period, and there was a tendency toward active cardiac surgery, even if the patients were older or had severe conditions. Third, there are no appropriate diagnostic criteria for DIC following cardiovascular surgery. Finally, the thrombin-antithrombin complex, soluble fibrin monomer, and alpha2-plasmin inhibitor-plasmin complex, rather than platelets and FDP, are likely to be more appropriate indicators of coagulation and fibrinolysis activity. Resolving the issue of many facilities taking several days to obtain the results for these indicators will allow for further investigations.

Conclusion

Our findings demonstrate that rTM administration after surgery for AAD may be a safe and promising treatment strategy for improving the JAAM DIC score.

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Author contributions
Tsukasa Ikeda—designing the study, collecting the data, analyzing data and images, writing article, reviewing patient notes, and approving final submission. Masateru Uchiyama—corresponding author; collecting the data, analyzing data and images, writing article, reviewing patient notes, and approving final submission. Naomi Ozawa—collecting the data, analyzing data and images, reviewing patient notes, and approving final submission. Tomohiro Imazuru—collecting the data, analyzing data and images, reviewing patient notes, and approving final submission. Tomoki Shimokawa—designing the study, reviewing patient notes, analyzing data and images, and approving final submission.

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Availability of data and materials
The datasets used are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
All patients provided informed consent, and the study protocol was approved by the Ethics Committee of Teikyo University.

Consent for publication
Written consent was obtained from all patients for writing this study and accompanying data. Identifying details have been omitted.

Competing interests
The authors declare no competing interests.

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