Recombinant human soluble thrombomodulin and danaparoid combination anticoagulant therapy for disseminated intravascular coagulation in a child with streptococcal toxic shock syndrome: A case report

YUTAKA KATO[1,2], HIROSHI KAWAGUCHI[1], SHINICHIRO IWATAKI[2], HIROTAKA KIHARA[2,3] and SATOSHI OKADA[1]

[1]Department of Pediatrics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima 734-8551; [2]Department of Pediatrics, Japan Agricultural Cooperatives Onomichi General Hospital, Onomichi, Hiroshima 722-8508; [3]Department of Pediatrics, Hiroshima City Hiroshima Citizens Hospital, Hiroshima 730-8518, Japan

Received July 20, 2022; Accepted September 14, 2022

DOI: 10.3892/etm.2022.11650

Abstract. Disseminated intravascular coagulation (DIC) is a common and morbid complication of streptococcal toxic shock syndrome (STSS). Because DIC with STSS progresses rapidly, prompt and proper care is critical. The present report describes the case of a 10-year-old boy who survived STSS with DIC without sequelae after treatment with combination anticoagulant therapy of recombinant human soluble thrombomodulin (rhTM) and danaparoid. RhTM and antithrombin-III were administered on day 1. RhTM administration was continued. Despite this, on day 2, his general condition remained poor, his fever persisted and his DIC score increased from an initial 5 points upon admission to 9 points. Therefore, danaparoid was additionally administered from day 2 onwards. The patient recovered without serious complications. Combination anticoagulant therapy of rhTM and danaparoid for DIC in a child with STSS was effective and safe. Therefore, this combination therapy could be used as an option for managing high-risk, rapidly progressing disease states, which predispose to morbid sequelae and death, such as DIC with STSS. RhTM and danaparoid therapy may reduce the risk of serious complications, such as organ failure, and improve the prognosis not only in STSS but also in other conditions with infection and DIC concurrence, such as sepsis.

Correspondence to: Dr Hiroshi Kawaguchi, Department of Pediatrics, Hiroshima University Graduate School of Biomedical and Health Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
E-mail: hrkawa@hiroshima-u.ac.jp

Abbreviations: DIC, disseminated intravascular coagulation; ICU, intensive care unit; LRINEC, Laboratory Risk Indicator for Necrotizing Fasciitis; STSS, streptococcal toxic shock syndrome; rhTM, recombinant human soluble thrombomodulin

Key words: DIC, thrombomodulin, danaparoid, STSS, child

Introduction

Disseminated intravascular coagulation (DIC) is a common and morbid complication of streptococcal toxic shock syndrome (STSS). For instance, a retrospective study reported coagulation abnormalities in 71% of the patients (median age, 47 years) who had blood tests upon admission (1). Another children-centered study also reported that 78% of the patients developed coagulopathy (2). Accurate, quick administration of care is needed in DIC with STSS because patients tend to present with a rapidly developing clinical course. However, there is no standard anticoagulant therapy for managing DIC with STSS. Recombinant human soluble thrombomodulin (rhTM) and danaparoid are administered to patients with DIC. For example, in a retrospective study of 2663 patients with sepsis, 1247 received anticoagulants, out of which 717 received rhTM and 144 received either heparin or danaparoid (3). However, to the best of our knowledge, there have been no clinical studies regarding combination anticoagulant therapy of rhTM and danaparoid, nor are there reports regarding combination therapy for managing DIC with STSS. A concerningly high mortality rate as well as a prevalence of long-term sequelae due to STSS make exploring and suggesting new therapies necessary. A retrospective study reported a 58% mortality rate among 29 patients with STSS (1), while another study reported a 34.2% mortality rate; among those who survived, 26.8% suffered sequelae (2). Moreover, a third study reported a mortality rate of 30% among 20 patients with STSS (median age, 36) (4). Therefore, we present the case of a 10-year-old boy who survived without sequelae after treatment with combination anticoagulant therapy for managing DIC with STSS.

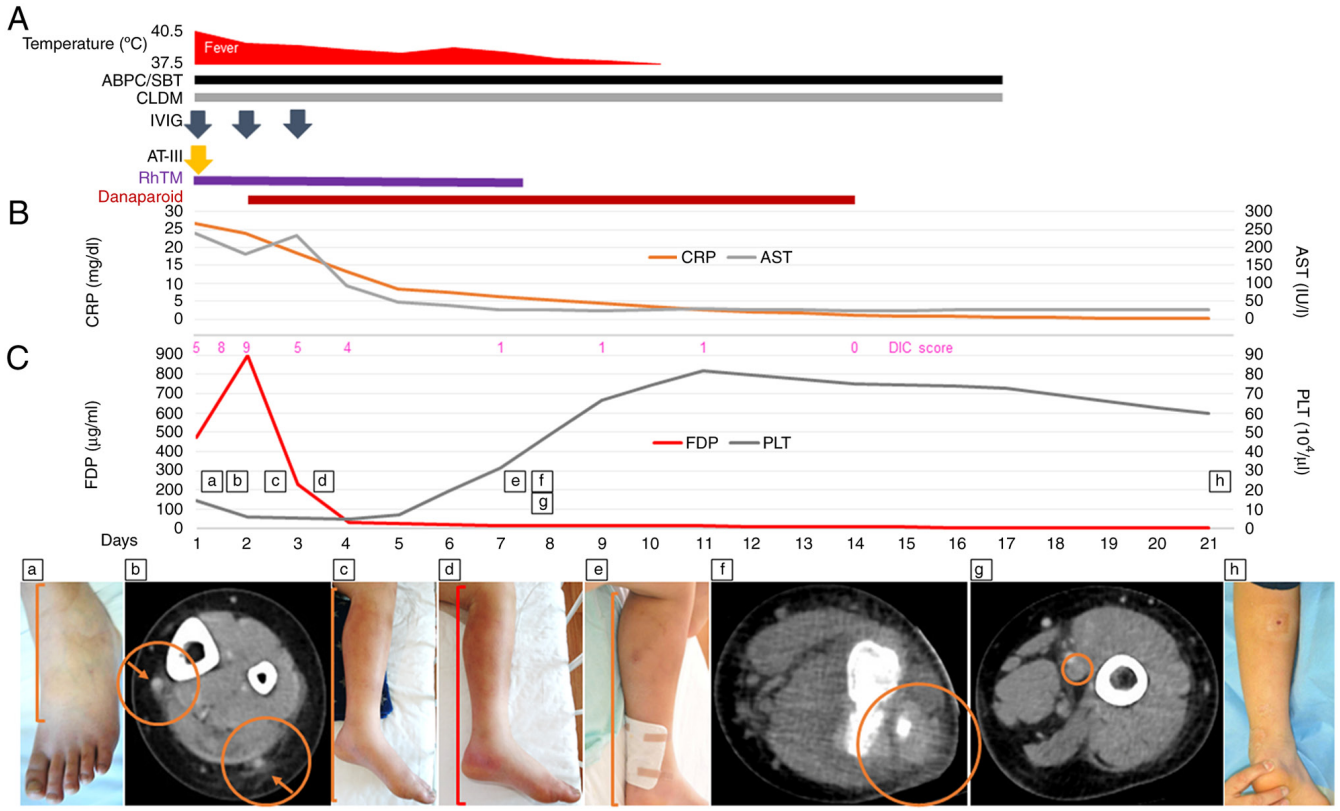

Figure 1. Clinical course of the patient with streptococcal toxic shock syndrome. (A) Time course of administered medications and the corresponding patient's temperature. (B) Time course of CRP and AST measurements. (C) Time course of FDP and PLT measurements with the corresponding DIC score and clinical findings. (a) Swelling and redness of the patient's left ankle joint upon admission. The line indicates swelling and redness. (b) Contrast-enhanced CT scan showing an increased fat concentration around the cutaneous veins of the patient's left lower leg upon admission. The right arrow indicates the cutaneous vein, and the right circle indicates the increased fat concentration around the vein. The left arrow indicates the cutaneous vein, and the left circle indicates the increased fat concentration around the vein. (c) Swelling and redness of the patient's left lower leg on day 2. The line indicates swelling and redness. (d) Swelling and redness of the patient's left lower leg on day 3. The line indicates swelling and redness. (e) Swelling and redness of the patient's left lower leg on day 7. The line indicates swelling and redness. (f) Contrast-enhanced CT scan showing a progressive increase in fat concentration of the patient's left lower leg on day 7. The circle indicates a progressive increase in fat concentration. (g) Contrast-enhanced CT scan showing a ring-shaped contrast enhancement of the popliteal vein of the patient's left lower leg on day 7. The circle indicates a ring-shaped contrast enhancement of the vein. (h) Almost no swelling and redness of the patient's left lower leg on day 21. ABPC/SBT, ampicillin/sulbactam; CLDM, clindamycin; IVIG, intravenous immunoglobulin; AT-III, antithrombin-III; RhTM, recombinant human soluble thrombomodulin; CRP, C-reactive protein; AST, aspartate aminotransferase; DIC, disseminated intravascular coagulation; FDP, fibrinogen and fibrin degradation products; PLT, platelet.

Case report

A 10-year-old boy presented to our hospital with a fever that had persisted for 7 days. He developed impetigo on the second day and diarrhea on the sixth day since fever onset. Medical history and family history were unremarkable.

On physical examination, the patient appeared acutely ill, uncomfortable, and irritable. He was unable to stand and converse normally. His vital signs were as follows: heart rate, 147 beats/min; blood pressure, 101/61 mmHg; temperature, 40.5˚C; respiratory rate, 42 breaths/min; and oxygen saturation, 100%. He presented with no nuchal rigidity, and lung fields were clear. Further examination revealed cheek and pharyngeal erythema, impetigo on the forehead and jaw, and abdominal tenderness. He had swelling, redness, and tenderness in his left elbow and left ankle joints (Fig. 1Ca).

Laboratory findings are shown in Table I. The rapid antigen detection test result for Group A *Streptococcus* pharyngitis was positive. The blood, throat, and impetigo pus cultures taken upon admission were positive for *Streptococcus pyogenes*, and the minimum inhibitory concentrations against the bacterium were as follows: ampicillin: ≤0.06 μg/ml; clindamycin: ≤0.12 μg/ml. A contrast-enhanced computed tomography (CT) scan revealed an increased fat concentration around the cutaneous veins of his left lower leg (Fig. 1Cb).

A diagnosis of STSS was made because this case met the criteria proposed by The Working Group on Severe Streptococcal Infections: coagulopathy, liver involvement, generalized erythematous macular rash, and isolation of Group A *Streptococcus* (5). Furthermore, he fulfilled the revised diagnostic criteria for DIC by the Japanese Society on Thrombosis and Hemostasis; his DIC score was 6 points, and since infectious-type DIC is diagnosed if the score is ≥5 points, a diagnosis of infectious-type DIC was made (6).

As the patient's state was worsening, he was immediately admitted to our intensive care unit (ICU). Since his blood pressure was within the normal range, aggressive intravenous rehydration was performed up to the maximum recommended maintenance limit (60 ml/kg/day) to avoid potential hypotension. Intravenous amoxicillin-sulbactam (180 mg/kg/day in 4 divided doses) and clindamycin (40 mg/kg/day in 4 divided doses) were administered to treat the invasive Group

Table I. Laboratory data on day 1.

Variable	Time after admission, h		
	0	8	16
White blood cell count, cells/μl	10,200	11,100	12,500
Neutrophils, %	92.0	97.0	94.3
Band forms, %	29.0	40.0	53.0
Platelet count, platelets/μl	145,000	67,000	63,000
International normalized ratio of prothrombin time	1.93	2.37	2.20
Activated partial-thromboplastin time, sec	49.1	61.4	59.0
Fibrinogen, mg/dl	487	257	267
Fibrin degradation products, μg/ml	471.1	801.8	896.1
D-dimer, μg/ml	183.0	290.3	≥300
Antithrombin-III, %	102	78	91
Thrombin-antithrombin-III complexes, ng/ml	ND	ND	85.1
Plasmin-α2-plasmin inhibitor complex, μg/ml	ND	ND	16.7
Total bilirubin, mg/dl	1.52	2.28	1.75
Aspartate aminotransferase, U/l	240	275	182
Alanine aminotransferase, U/l	109	102	93
Creatine kinase, U/l	143	153	ND
Creatinine, mg/dl	0.59	0.70	0.47
Ferritin, ng/ml	2,905.0	ND	ND
C-reactive protein, mg/dl	26.67	25.00	24.08
DIC score, points	5	8	9

ND, not done; DIC score, disseminated intravascular coagulation score.

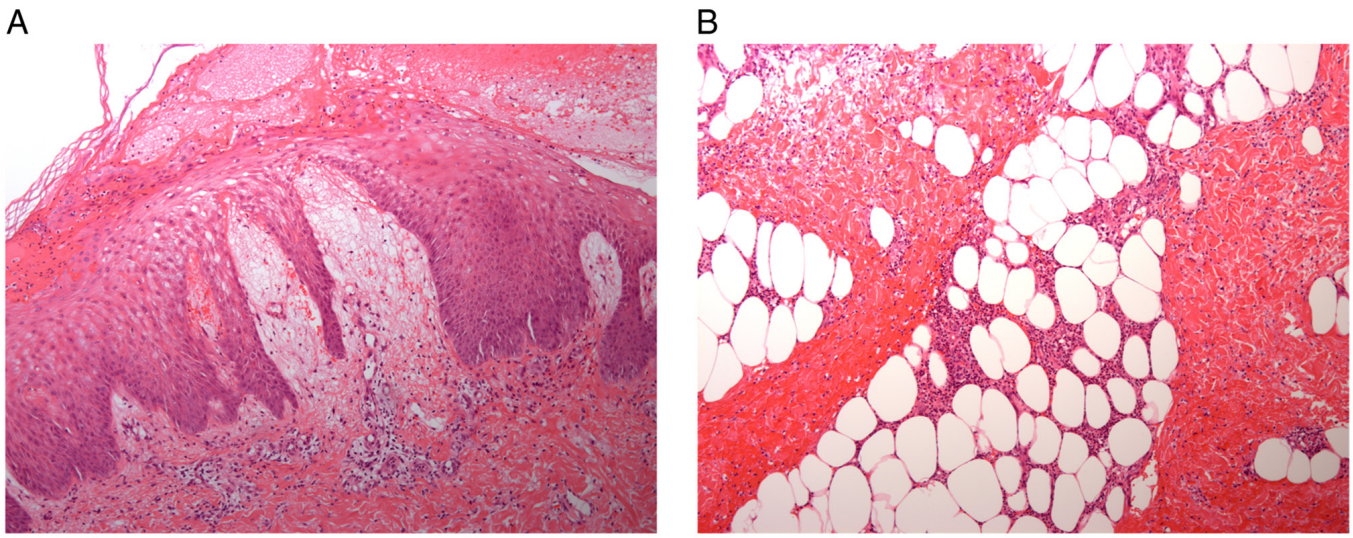

Figure 2. Histological images of a skin biopsy specimen (hematoxylin-eosin staining; magnification, x100). (A) Spongiotic dermatitis. (B) Suppurative panniculitis.

A *Streptococcus* infection. Intravenous immunoglobulins (150 mg/kg/day) were also administered. As a result, blood cultures were negative on the third day (day 3) of ICU admittance, whereas the fever thought to be caused by hypercytokinemia persisted until day 10 (Fig. 1A). RhTM (380 U/kg/day) and antithrombin-III (30 U/kg/day) were administered for managing DIC. Despite this, on day 2 after admission, the patient's general condition was poor, his fever persisted, and his DIC score was found to have increased from 5 points (PT/INR, 2; fibrinogen and fibrin degradation products, 3) upon admission to 9 points (platelet count, +3 points [≥30% decrease within 24 h]; thrombin-antithrombin-III

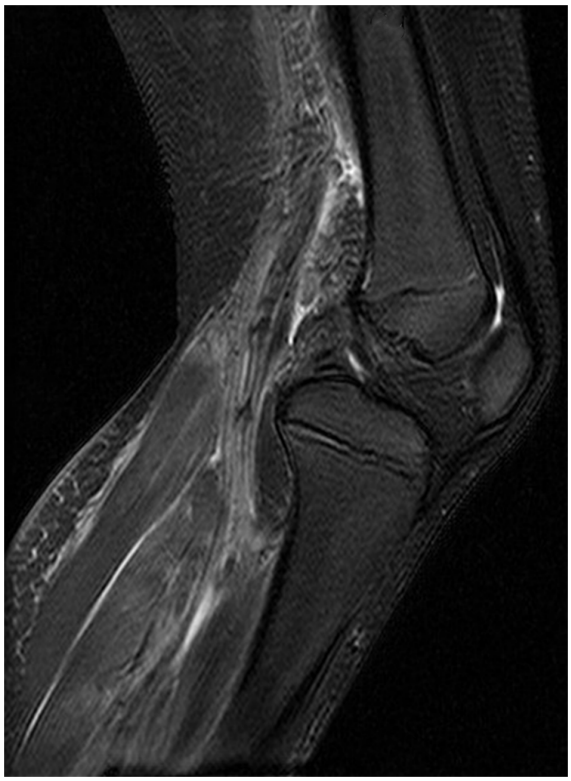

Figure 3. MRI of the left knee. MRI showing inflammatory findings in the regions of the left soleus, the left gastrocnemius and between the two muscles. No findings of arthritis or osteomyelitis.

complexes [TAT], +1 point). Thus, danaparoid (2,500 U/day in 2 divided doses), in addition to rhTM, was administered on the same day (day 2) after we obtained informed consent from his family. After danaparoid + rhTM administration, his general condition improved, and his laboratory findings became less alarming (Fig. 1B and C). From day 3 to day 4, the patient's DIC score decreased to 4 points from 5 points (fibrin degradation products, -1 point), indicating that the DIC was resolved.

Unfortunately, the redness, swelling, and pain in his left lower leg and elbow joint were gradually worsening (Fig. 1Cc-e); hence, a contrast-enhanced CT scan was performed on day 7. It revealed a progressive increase in fat concentration and ring-shaped contrast enhancement of his left popliteal vein, suggesting inflammation and coagulopathy (Fig. 1Cf and g). The patient's Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was 8. If the LRINEC score is ≥8, a strong possibility of necrotizing fasciitis is suggested (7). Skin biopsy was performed for differential diagnosis, and although a diagnosis of spongiotic dermatitis and suppurative panniculitis was made, his soft tissue did not progress to necrosis (Fig. 2A and B). Because the range of motion of the joint had not improved, magnetic resonance imaging (MRI) was performed on day 9. However, the MRI scan only showed inflammatory findings in the regions of the left soleus, left gastrocnemius, and between the two muscles; arthritis or osteomyelitis was not evident (Fig. 3). His condition improved gradually with sufficient recovery in his legs, enabling him to walk, and he was finally discharged on day 20 without sequelae (Fig. 1Ch). No medication-related adverse events were observed during or after treatment with the combination therapy. During four years of follow-up, he did not show any signs of disease, and his life seemed to have returned to its regular rhythm prior to hospital admission.

Discussion

This case presents two important clinical findings. First, the combination anticoagulant therapy of rhTM and danaparoid for managing DIC in a child with STSS was effective. Several reports have suggested that organ dysfunction, such as acute respiratory distress syndrome and acute renal failure, is a frequent complication in STSS (1,2,4). Coagulopathy, which is the cause of organ dysfunction, is found in approximately 70% of STSS cases (1,2). A previous case report has described anticoagulant therapy administered to a child for STSS. Intensive care was provided along with combined administration of rhTM and heparin for managing STSS in the 3-year-old boy, who, except for the amputation of his left distal metatarsal, survived with normal development and no sequelae (8). The mechanism of action of the anticoagulant therapy in this reported case is similar to that in ours (Fig. 4). The difference lies in the selection of heparin rather than danaparoid as the heparinoid. Unlike the anticoagulant profile of unfractionated heparin (1:1), that of danaparoid is characterized by a high ratio of anti-factor Xa to anti-factor IIa activity (≥20:1) (9); the clinical significance of this difference in anticoagulant effect is yet to be elucidated. Furthermore, the effective plasma concentration of rhTM estimated in phase II clinical trials was 500 ng/ml. It took 72 h after initial administration for this effective plasma concentration to persist and remain steady in patients with DIC under 65 years of age and patients with DIC with normal renal function (creatinine clearance ≥70 ml/min) (10). A prospective, clinical pharmacological study has reported the evolution of rhTM plasma concentrations over time in patients with DIC with acute renal dysfunction. Even when rhTM was administered to patients with acute renal dysfunction at a normal dosage (380 U/kg/day), it took 72 h after initial administration for this effective plasma concentration to persist (11). In our case, the progression of coagulation laboratory findings was observed on day 2, his fever had persisted as well, and his general condition was not improving. This was when additional danaparoid was administered. Because this combination therapy had a stronger anticoagulant effect than the single-agent therapy, he recovered without requiring mechanical ventilation or renal replacement therapy, which could have been necessary if he was not treated accordingly.

Second, the combination anticoagulant therapy of rhTM and danaparoid for managing DIC in a child with STSS was safe. Safety of rhTM for managing DIC in adults has been established (12). A retrospective cohort study has analyzed the efficacy and safety of rhTM for managing DIC in pediatric patients by comparing pediatric patients with DIC with adult patients with DIC, evaluating post-marketing surveillance study data. Newborn infants were excluded, after which data from 210 pediatric patients were analyzed and compared with data from 3786 adult patients. The results

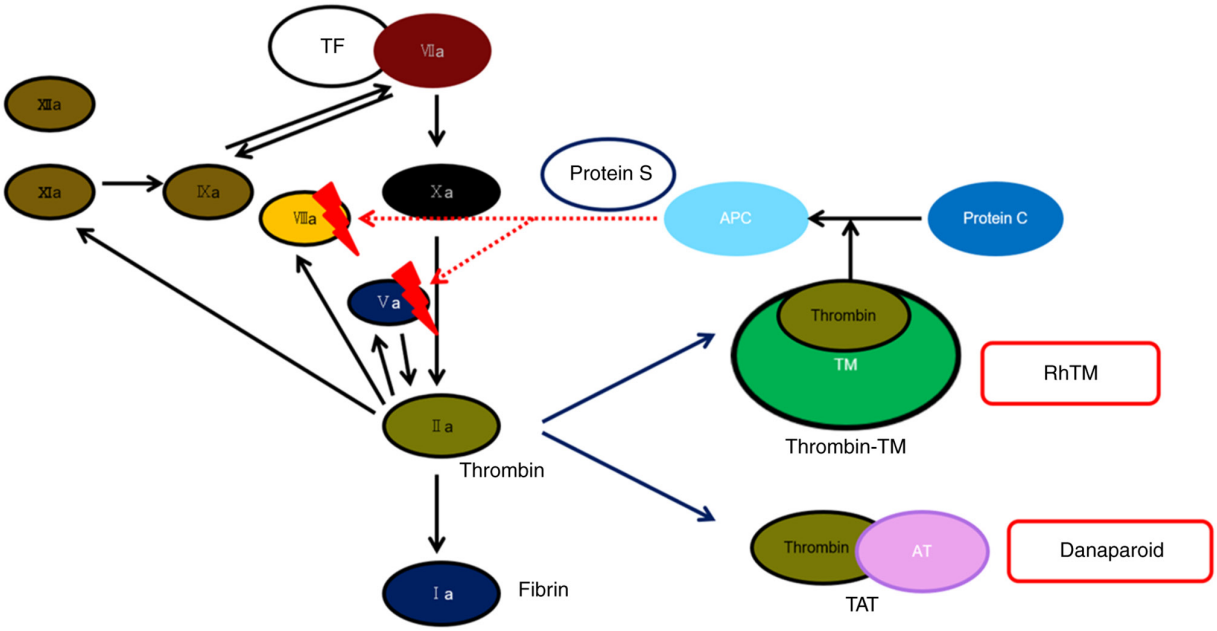

Figure 4. Conceptual diagram of the mechanism of action of anticoagulant therapy in this case. RhTM binds to thrombin and inhibits its functions. In addition, rhTM activates protein C, which degrades and inactivates Va and VIIIa. The arrow from rhTM indicates that protein C was activated and changed to APC. Danaparoid binds to AT and changes its structure, causing AT to bind coagulation factors, thrombin, VIIa, IXa, Xa, XIa, and XIIa, and inhibit their reaction. Darkening of VIIa, IXa, Xa, XIa and XIIa indicates their inactivation and the subsequent inhibition of their reactions. This figure was created with reference to several papers (17-20). RhTM, recombinant human soluble thrombomodulin; Ia, fibrin; IIa, thrombin; TF, tissue factor; Va, activated factor five; VIIa, activated factor seven; VIIIa, activated factor eight; AT, antithrombin; IXa, activated factor nine; Xa, activated factor ten; XIa, activated factor eleven; XIIa, activated factor twelve; TM, thrombomodulin; TAT, thrombin-antithrombin complex; APC, activated protein C.

of this study have suggested that the efficacy and safety of rhTM for managing DIC in pediatric patients were not significantly different from those in adults. In addition, 21.9% of pediatric patients with DIC who were administered rhTM were also administered unfractionated heparin (13). It can be assumed from these data that the safety of the combined administration of rhTM and heparin is not significantly low. In addition, safety can be enhanced by using danaparoid instead of unfractionated heparin, as demonstrated in this case. Danaparoid has a much higher anti-Xa/anti-IIa ratio and shows minimal effects on platelet function and thus has a relatively low risk of bleeding (9,14,15). Therefore, this combination therapy could be used as an option for disease states with rapid progression, concerning mortality rates, and a high risk for sequelae, as is the case in DIC with STSS.

A retrospective cohort study has reported the efficacy of anticoagulant therapies in sepsis. The results of this study have suggested that anticoagulant therapies are significantly associated with reduced mortality in subsets of patients diagnosed with DIC. In addition, anticoagulant therapies have been significantly associated with reduced mortality in the high-risk subset stratified according to the Sequential Organ Failure Assessment (SOFA) score: SOFA score 13-17 (3). Because organ failure and coagulopathy are common complications in STSS, anticoagulant therapies are an important avenue. Furthermore, this retrospective cohort study has reported the efficacy of rhTM in sepsis. As a result of this study, DIC scores were significantly decreased in the group in which rhTM was administered when compared with the scores from the no-rhTM control group on day 3 after the administration of rhTM. In addition, there was no difference in platelet counts between the two groups on day 3, and the recovery of platelet counts in the rhTM group was greater than that in the control group on day 7 (16). In this case, additional administration of danaparoid was started on day 2, and the DIC score was decreased to 5 points on day 3. In our case, it is possible that similar favorable outcomes could have been achieved by the single-agent therapy of rhTM for managing DIC. However, since several reports indicate high probabilities of mortality and sequelae with monotherapy (1,2,4,8), danaparoid addition to rhTM, and its potential improvement of clinical outcomes, cannot be dismissed. Taken together, it was quite possible that the combined administration of rhTM and danaparoid at an early stage, i.e., on day 2, led to positive outcomes in this case. However, future studies are required to further examine this possibility due to the current lack of research on the combination anticoagulant therapy of rhTM and danaparoid in sepsis-related DIC. Since fibrinolysis is suppressed in DIC with STSS or sepsis and the risk of coagulation-induced organ damage is higher than that of fibrinolysis-induced bleeding, this combination therapy may be considered in patients at high risk of sequelae or death.

In conclusion, combination anticoagulant therapy of rhTM and danaparoid for managing DIC in a child with STSS was effective and safe. This combination therapy could possibly be used as an option for rapidly progressive disease cases which present with high risks for sequelae and death, such as DIC with STSS. Furthermore, it is quite possible that this combination therapy reduces the risk of serious complications, such as organ failure, and improves prognosis, not only in children with STSS but also in cases of sepsis in general.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

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

Authors' contributions

YK was responsible for the patient's treatment as the attending physician, acquired, analyzed and interpreted the data and drafted the manuscript. HKa and SO analyzed and interpreted the data, critically revised the manuscript for intellectual content and are accountable for all aspects of the manuscript. SI and HKi contributed to the patient's treatment as medical managers and analyzed and interpreted the data. YK, SI and HKi confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Since rhTM and heparins are routinely used together and due to the urgency of this case, ethics approval was not required for this case study. Oral informed consent was obtained from the patient's parent.

Patient consent for publication

Oral informed consent was obtained from the patient's parent for the publication of the data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

References

1. Demers B, Simor AE, Vellend H, Schlievert PM, Byrne S, Jamieson F, Walmsley S and Low DE: Severe invasive group A streptococcal infections in Ontario, Canada: 1987-1991. Clin Infect Dis 16: 792-800; discussion 801-2, 1993.
2. Rodríguez-Nuñez A, Dosil-Gallardo S and Jordan I; ad hoc Streptococcal Toxic Shock Syndrome collaborative group of Spanish Society of Pediatric Intensive Care: Clinical characteristics of children with group A streptococcal toxic shock syndrome admitted to pediatric intensive care units. Eur J Pediatr 170: 639-644, 2011.
3. Yamakawa K, Umemura Y, Hayakawa M, Kudo D, Sanui M, Takahashi H, Yoshikawa Y, Hamasaki T and Fujimi S; Japan Septic Disseminated Intravascular Coagulation (J-Septic DIC) study group: Benefit profile of anticoagulant therapy in sepsis: A nationwide multicentre registry in Japan. Crit Care 20: 229, 2016.
4. Stevens DL, Tanner MH, Winship J, Swarts R, Ries KM, Schlievert PM and Kaplan E: Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. N Engl J Med 321: 1-7, 1989.
5. Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. The Working Group on Severe Streptococcal Infections. JAMA 269: 390-391, 1993.
6. Wada H, Takahashi H, Uchiyama T, Eguchi Y, Okamoto K, Kawasugi K, Madoiwa S and Asakura H; DIC subcommittee of the Japanese Society on Thrombosis and Hemostasis: The approval of revised diagnostic criteria for DIC from the Japanese Society on Thrombosis and Hemostasis. Thromb J 15: 17, 2017.
7. Wong CH, Khin LW, Heng KS, Tan KC and Low CO: The LRINEC (Laboratory Risk Indicator for Necrotizing fasciitis) score: A tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 32: 1535-1541, 2004.
8. Okuzono S, Ishimura M, Kanno S, Sonoda M, Kaku N, Motomura Y, Nishio H, Oba U, Hanada M, Fukushi JI, *et al*: *Streptococcus* pyogenes-purpura fulminans as an invasive form of group A streptococcal infection. Ann Clin Microbiol Antimicrob 17: 31, 2018.
9. Meuleman DG: Orgaran (Org 10172): Its pharmacological profile in experimental models. Haemostasis 22: 58-65, 1992.
10. Tsuruta K, Yamada Y, Serada M and Tanigawara Y: Model-based analysis of covariate effects on population pharmacokinetics of thrombomodulin alfa in patients with disseminated intravascular coagulation and normal subjects. J Clin Pharmacol 51: 1276-1285, 2011.
11. Hayakawa M, Kushimoto S, Watanabe E, Goto K, Suzuki Y, Kotani T, Kiguchi T, Yatabe T, Tagawa J, Komatsu F and Gando S: Pharmacokinetics of recombinant human soluble thrombomodulin in disseminated intravascular coagulation patients with acute renal dysfunction. Thromb Haemost 117: 851-859, 2017.
12. Saito H, Maruyama I, Shimazaki S, Yamamoto Y, Aikawa N, Ohno R, Hirayama A, Matsuda T, Asakura H, Nakashima M and Aoki N: Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: Results of a phase III, randomized, double-blind clinical trial. J Thromb Haemost 5: 31-41, 2007.
13. Shirahata A, Mimuro J, Takahashi H, Tsuji H, Kitajima I, Matsushita T, Eguchi Y, Kitamura N, Honda G and Sakata Y: Postmarketing surveillance of recombinant human soluble thrombomodulin (thrombomodulin α) in pediatric patients with disseminated intravascular coagulation. Clin Appl Thromb Hemost 20: 465-472, 2014.
14. Bradbrook ID, Magnani HN, Moelker HC, Morrison PJ, Robinson J, Rogers HJ, Spector RG, Van Dinther T and Wijnand H: ORG 10172: A low molecular weight heparinoid anticoagulant with a long half-life in man. Br J Clin Pharmacol 23: 667-675, 1987.
15. Hobbelen PM, Vogel GM and Meuleman DG: Time courses of the antithrombotic effects, bleeding enhancing effects and interactions with factors Xa and thrombin after administration of low molecular weight heparinoid Org 10172 or heparin to rats. Thromb Res 48: 549-558, 1987.
16. Yamakawa K, Ogura H, Fujimi S, Morikawa M, Ogawa Y, Mohri T, Nakamori Y, Inoue Y, Kuwagata Y, Tanaka H, *et al*: Recombinant human soluble thrombomodulin in sepsis-induced disseminated intravascular coagulation: A multicenter propensity score analysis. Intensive Care Med 39: 644-652, 2013.
17. Gando S, Levi M and Toh CH: Disseminated intravascular coagulation. Nat Rev Dis Primers 2: 16037, 2016.
18. Weitz JI and Bates SM: New anticoagulants. J Thromb Haemost 3: 1843-1853, 2005.
19. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, Granger C, Ohman EM and Dalen JE: Heparin and low-molecular-weight heparin: Mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 119 (Suppl): 64S-94S, 2001.
20. Wilde MI and Markham A: Danaparoid. A review of its pharmacology and clinical use in the management of heparin-induced thrombocytopenia. Drugs 54: 903-924, 1997.