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Recombinant soluble thrombomodulin for postoperative disseminated intravascular coagulation

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ARTICLE INFO

Article history:
Received 22 October 2014
Received in revised form
10 March 2015
Accepted 14 April 2015
Available online 18 April 2015

Keywords:
Disseminated intravascular coagulation
Thrombomodulin
Gastroenterological operation
Complication

ABSTRACT

Background: Thrombomodulin is a thrombin receptor on the endothelial cell surface that plays an important role in the regulation of intravascular coagulation. The purpose of this study was to evaluate the efficacy and safety of treatment with recombinant human soluble thrombomodulin (rhTM) for patients with septic-disseminated intravascular coagulation (DIC) associated with gastroenterological surgery.

Materials and methods: From April 2011–September 2013, 201 patients with DIC associated with gastroenterological surgery were treated in 16 institutions in Kumamoto, Japan. The patients were diagnosed according to the Japanese Association for Acute Medicine DIC scoring system. The clinical course, mortality rate at 28 d, and adverse events were evaluated retrospectively.

Results: Forty-five patients were excluded because they did not meet the Japanese Association for Acute Medicine DIC criteria or had an insufficient duration of drug administration. Thus, 156 patients were analyzed. Of these patients, 107 received rhTM at the discretion of the attending surgeon and 49 did not. The most common reason for surgery in both groups was peritonitis due to perforation of the colon. Within 7 d, the platelet count, prothrombin time–international normalized ratio, DIC score, neutrophil count, and C-reactive protein level significantly improved in the rhTM group compared with those in the control. Treatment with rhTM was significantly associated with reduced inhospital mortality at 28 d. The incidence of adverse events did not differ between the two groups.

Conclusions: Therapy with rhTM may be associated with reduced inhospital mortality in patients with septic DIC associated with gastroenterological surgery without increasing adverse events.

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http://dx.doi.org/10.1016/j.jss.2015.04.048

1. Introduction

Disseminated intravascular coagulation (DIC) frequently complicates hematologic malignancies and infections such as sepsis [1,2]. Sepsis-induced DIC is a life-threatening condition characterized by systemic activation of blood coagulation, which generates intravascular fibrin and leads to multiple organ dysfunction syndrome or even death [3,4].

Emergency gastroenterological surgery for conditions such as perforation of diverticulitis, ulceration, or tumors is associated with high morbidity and mortality rates, and postoperative sepsis and DIC often develop in such patients [5,6]. Although these operations are necessary to improve the condition of the patient, such emergency procedures are very invasive. Additionally, after the performance of elective gastroenterological operations, severe postoperative complications such as intra-abdominal abscess formation, anastomotic leakage, pneumonia, and acute respiratory distress syndrome may occur, and each of these conditions may be associated with the development of DIC [7,8]. Furthermore, these gastroenterological operations frequently lead to systemic inflammation such as that seen in systemic inflammatory response syndrome. Thus, the patient's response to treatment for surgery-related DIC may differ from that for DIC unrelated to a prior operation.

Guidelines for the diagnosis and treatment of DIC were recently published in Britain [9], Japan [10], and Italy [11]. Treatment for surgery-related DIC is complicated for a surgeon; however, it has been not discussed enough in these guidelines. In addition, some differences in the recommendations for various anticoagulant therapies exist among these guidelines. Recombinant human soluble thrombomodulin (rhTM) is a novel biological agent [12,13]. Two randomized clinical trials involving patients with DIC due to hematologic malignancy or infection showed that rhTM therapy more effectively improves DIC and alleviates bleeding symptoms than does heparin therapy [14,15]. Similarly, another retrospective cohort study indicated that rhTM therapy may be associated with reduced inhospital mortality in mechanically ventilated adults with sepsis-induced DIC [16]. However, the effects of rhTM on DIC associated with gastroenterological surgery have not been thoroughly evaluated, whereas these patients' condition and effect of treatment may differ from patients with DIC, which is not associated with operation. Additionally, the potentially increased risk of bleeding as an adverse event of rhTM has never been discussed in the treatment for DIC, which has developed after gastroenterological surgery.

Thus, it may be necessary to distinguish the optimal therapeutic strategies between DIC that is and is not associated with gastroenterological surgery. To support our hypothesis that rhTM is effective for DIC after elective or emergency gastroenterological surgery without increasing adverse events such as bleeding, we conducted this retrospective multicenter study.

2. Material and methods

2.1. Patients

This investigation was a retrospective study of patients who were admitted to 16 tertiary referral hospitals in Japan after developing septic DIC associated with gastroenterological surgery. All patients who were included in this study were Japanese. These patients were treated with or without rhTM from April 2010–July 2013. Patients who fulfilled the criteria of the Japanese Association for Acute Medicine (JAAM) DIC scoring system [17] (DIC score of $\geq$4) were included in the investigation, and those who did not fulfill these criteria (DIC score of $\leq$3) were excluded (Fig. 1). No predefined protocol regarding the definite indications for rhTM treatment was used in this retrospective study. For patients with severe sepsis with DIC, rhTM was used at the clinical decision of the attending surgeon. rhTM was principally administered intravenously at a dose of 0.06 mg/kg per day and continued as necessary. In previous prospective studies, rhTM was continued for 6 d [14,15]. Because this is a retrospective study, the duration of rhTM therapy was determined by the attending surgeon. To make clear the therapeutic effect of rhTM on DIC, patients who received rhTM for $\leq$2 d were excluded from the investigation because this duration was possibly too short to evaluate (Fig. 1). Finally, the patients were assigned to one of two groups: those treated with rhTM (rhTM group) and those treated without rhTM (control group; Fig. 1). The patients' characteristics, comorbidities, coexisting complications, clinical course, and mortality rate at 28-d from all causes and adverse events were evaluated. Administration of antithrombin concentrate or heparin and/or low-molecular weight heparin (LMWH) was not routinely performed, but these agents were administered to some patients at the discretion of the attending surgeon, based on the individual patient's condition. Any treatment for DIC, including rhTM, antithrombin concentrate, and heparin and/or LMWH, was not added to the study population before the determination by the JAAM criteria. The study protocol was approved by the Institutional Review Board of Kumamoto University Hospital.

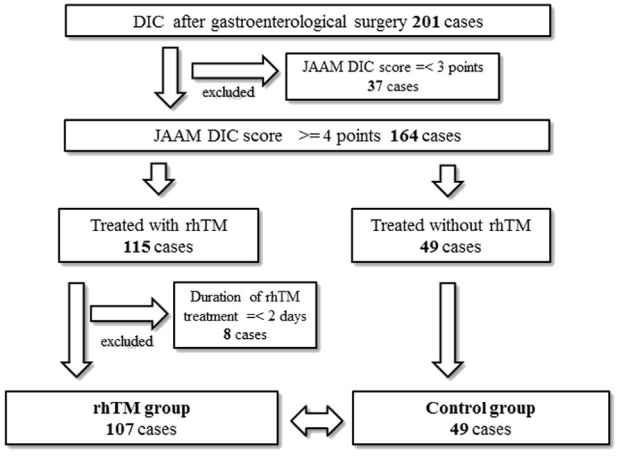

Fig. 1 – Patient flow diagram DIC = disseminated intravascular coagulation.