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Review

Recombinant human soluble thrombomodulin and short-term mortality of infection patients with DIC: a meta-analysis☆,☆☆

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ABSTRACT

Objective: Several studies have demonstrated that recombinant human soluble thrombomodulin (rhTM) has potential advantages for the treatment for patients with infection complicated by disseminated intravascular coagulation (DIC). However, whether injection of rhTM can affect the mortality of those patients in clinical treatment remains controversial. Therefore, we conducted a meta-analysis to evaluate the clinical efficacy for patients with infection complicated by DIC.
Methods: The PubMed, Web of Science, Embase, and Cochrane Library databases were searched for relevant articles that met the inclusion criteria through April 2016. Reference lists of the retrieved articles were also reviewed. The 28- or 30-day mortality and bleeding risk after using rhTM were evaluated.
Results: Ten observational studies and 2 randomized controlled trials (RCTs) involving 18 288 patients were included in this meta-analysis. The risk ratio for the 28- or 30-day mortality was 0.81 (95% confidence interval, 0.61-1.06) in RCT studies and 0.96 (95% confidence interval, 0.92-1.01) in observational studies. There were no significant differences in the bleeding risk between the rhTM group and the control group.
Conclusion: Based on the current studies, using rhTM for the treatment for infection patients complicated with DIC does not decrease the short-term mortality of those patients. More high-quality RCT studies need to be performed to confirm this finding.

1. Introduction

Disseminated intravascular coagulation (DIC), a kind of coagulation disorder that produces thrombotic occlusion in microvessels for widespread and excessive activation of coagulation within blood vessels, results in thrombotic occlusion of microvessels [1]. It usually occurs in association with other severe clinical conditions, including severe infection, malignancy, obstetrical complications, and trauma, especially infection [1,2]. The study of Wada et al [3] suggested that early treatment for DIC patients could improve the outcomes of these patients. A randomized controlled trial (RCT) performed by Gando et al [4] indicated that a moderate dose of antithrombin improved DIC scores and increased the recovery rate in patients with sepsis. In addition, heparins are often used for the treatment of severe sepsis with DIC, although the study by Zarychanski et al [5] found that the effect of heparin in sepsis, septic shock, and infection with DIC was uncertain. Until 2011, recombinant activated protein C had been the only internationally approved anticoagulant for the treatment of severe sepsis with DIC [6,7]. However, after the PROWESS-SHOCK, an RCT, was performed, the recombinant activated protein C was no longer available because of its higher risk of bleeding and indistinctive reduction in mortality compared with placebo [8]. At present, different committees have published several guidelines for the diagnosis and treatment for DIC patients, although no consistent treatment standards in the clinic exist [9].

Thrombomodulin, an endothelium-associated glycoprotein that converts thrombin from a procoagulant protease to an anticoagulant, was first extracted from rats by Esmon et al in 1981 [1,8]. Recombinant human soluble thrombomodulin (rhTM) has been applied in many diseases, such as aortic aneurysm, hematologic disease, acute respiratory distress syndrome, and DIC [1,10,11]. Increasing numbers of studies are focused on rhTM in patients with infection-induced DIC. On one hand, thrombomodulin played a role as an anticoagulant factor by promoting the thrombin-mediated activation of protein C [8]. On the other hand, it participated in anti-inflammatory responses via the sequestration and degradation of high-mobility group box 1 protein (HMGB1), which is an important inflammatory mediator [1]. These mechanisms showed that rhTM could be a potential effective treatment target for patients with infection complicated by DIC.

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An epidemiologic study by Murata et al [12] reported that the use of rhTM for DIC has dramatically increased since 2008, and it was considered as a potentially recommended drug by guidelines for DIC in Japan [13]. Many observational or RCT studies have proved that injection of rhTM might be an effective treatment method for patients with infection plus DIC because it had been approved in Japan in 2008. A systemic review and meta-analysis performed by Yamakawa et al [14] showed that there was no statistical reduction of short-term mortality after using rhTM (risk ratio [RR], 0.81; 95% confidence interval [CI], 0.62-1.06) in 3 RCT studies, although an obvious decline was shown in the other observational studies included in their analysis (RR, 0.59; 95% CI, 0.45-0.77). To date, there is still no confirmed conclusion about the advantage of rhTM in reducing the mortality of infection patients with DIC.

Recently, there were newly reported studies with large sample size examining the effect of rhTM on infection patients with DIC. Considering the small sample size of the meta-analysis of Yamakawa et al, we performed a new, comprehensive meta-analysis of all published eligible studies to evaluate the effectiveness and safety of using rhTM in infection patients with DIC.

2. Methods

We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines [15].

2.1. Search strategy

We searched the PubMed, Web of Science, Embase, and Cochrane Library databases through April 2016. Articles that included the following terms were used for our analysis: (1) ART-123 (a code name for rhTM), recomodulin (brand name of rhTM), or thrombomodulin, and (2) systemic inflammatory response syndrome, DIC, sepsis, or infection. We also searched the reference lists of recent articles.

2.2. Study selection

Before the full-text review, we performed an initial screening of titles or abstracts to exclude irrelevant studies. Then, the articles that met these criteria were considered eligible studies for our further analysis: (1) RCT or observational studies; (2) adult patients with infectious disease or severe sepsis plus DIC (noninfectious diseases such as hematologic trauma, solid trauma, and obstetrical complications were excluded); (3) patients have been given rhTM at any dose through the vein (control patients were given placebo or other therapy other than rhTM); and (4) studies reported 28- or 30-day mortality.

2.3. Data extraction

Two researchers abstracted the data independently and resolved any disagreement by discussion. All of them have attended classes

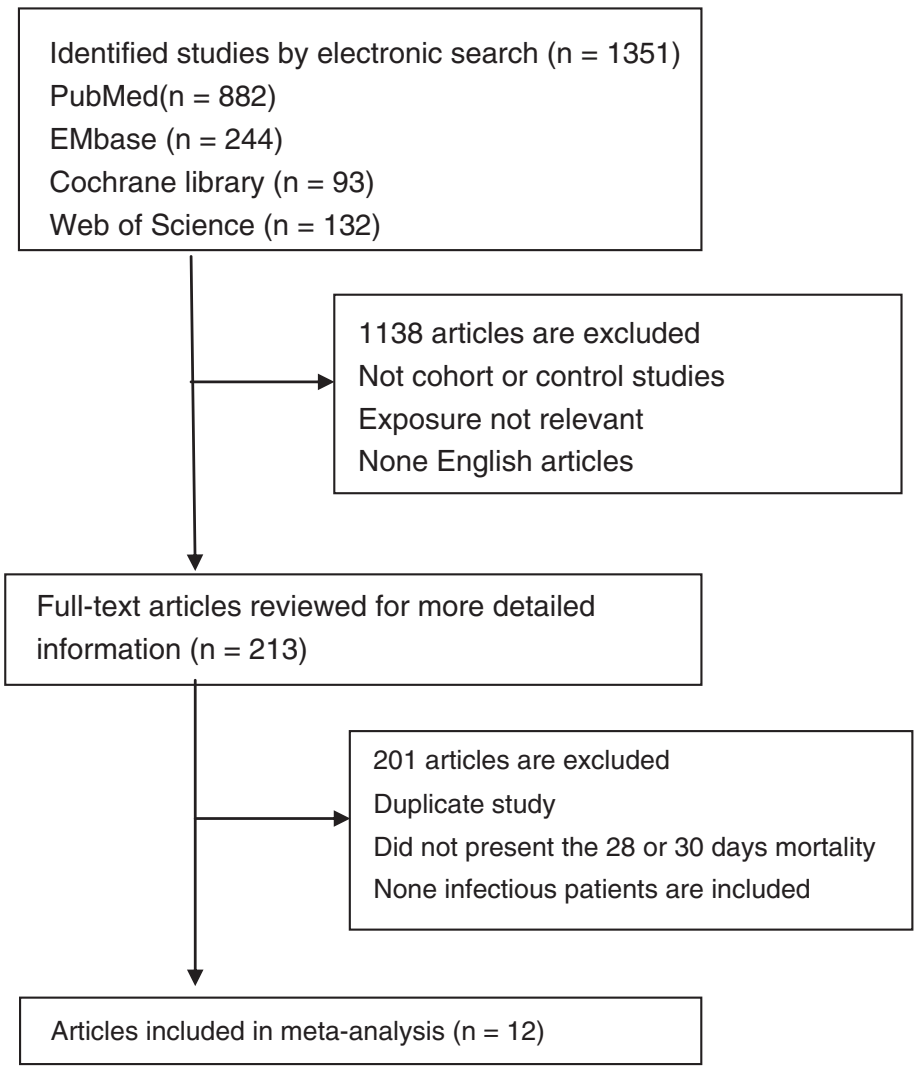

Fig. 1. Flowchart depicting the selection process of studies included in the meta-analysis.