Recombinant human soluble thrombomodulin and short-term mortality of infection patients with disseminated intravascular coagulation: 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.

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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.
about the meta-analysis training held by the Chinese Medical Doctor Association, an authoritative medical organization in China. Infectious disease and DIC were the key exposure variables at baseline. Most subjects in our reviews had serious infections or sepsis, and a small population had mild infections. We extracted information from the selected studies, including author names, year of publication, inclusion and exclusion criteria, patient population, dose and duration of rhTM, all-cause mortality at 28 or 30 days, and duration of follow-up. The primary end point was 28- or 30-day mortality. In addition, bleeding events were also evaluated in our research.

2.4. Statistical analysis

Review Manager 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for this meta-analysis. Both the fixed-effects model and the random-effects model were considered according to heterogeneity. The latter model is usually applied when heterogeneity exists. Compared with the fixed-effects model, random model can improve the accuracy of the CI and enhance the test power. We assessed the between-study heterogeneity using the I² statistics, which assessed the appropriateness of pooling the individual study results. In the 5.0 version of the Cochrane Handbook for Systematic Reviews of Interventions, heterogeneity is sorted by 4 degrees according to the value of I²: 0-40%, slight; 40%-60%, moderate; 50%-90%, large; and 75%-100%, great [16]. In Cochrane systematic review, heterogeneity could be accepted when the value of I² was equal to or less than 50% [16]. We found the clinical and statistical heterogeneity among these studies by estimating the search method, population, criterion, and the value of I². Then, we selected the Mantel-Haenszel and random-effects model. The RR and the 95% CI were used as common measures of the association between mortality and rhTM.

Potential publication bias was assessed by visual inspection of the funnel plots. The Newcastle-Ottawa Scale (NOS), which is usually applied for case-control and cohort studies, was used to assess the risk of bias of the observational studies. Selection, comparability, and exposure were adopted in the star system to evaluate the evidence quality. A study with 6 or more stars was considered a high-quality study. Quality assessments in our study were first independently conducted by 2 reviewers and then checked by the first author of this article. Moreover, the risks of bias in the 2 RCTs were assessed according to the criteria established by the Cochrane Collaboration that included random sequence generation and concealment of allocation, blinding of participants and personnel, blind assessment of outcomes, incomplete outcomes data, and selective outcome reporting and other bias [16].

3. Results

3.1. Literature search

According to our search strategy, we obtained 1351 articles after the initial search. Then, we removed case reports, reviews, correspondence, and irrelevant articles. There were 213 articles left for the further evaluation. Finally, we excluded duplicate studies, native language studies, and studies that reported outcomes without 28- or 30-day mortality. A total of 12 studies were used for our final analysis. A flowchart of the study selection process is shown in Fig. 1.

3.2. Study characteristics

The selected 12 studies included 18,288 patients. There were 821 patients in RCTs and 17,467 in observational studies. The basic characteristics of these researches are shown in Tables 1 and 2. All of these studies were conducted in Japan, except the RCT performed by Vincent et al [17], which was a multicenter study. The Japanese Association for Acute Medicine (JAAM), International Society on Thrombosis and Haemostasis (ISTH), or Japanese Ministry of Health and Welfare (JMHW) definitions of DIC were adopted in these selected studies. Most patients were given rhTM at a dose of 0.06 mg kg⁻¹ d⁻¹ or 380 U kg⁻¹ d⁻¹. The infection sites of patients included respiratory, digestive, urinary system, and others. The infection sites are listed in Tables 1 and 2. The detailed interventions of the studies by Murata et al [18] and Hayakawa et al [19] were not mentioned. In the control groups, antithrombin III, gabexate mesilate, or unfractionated heparin were used for the treatment of DIC. Conventional medical therapy was given in all studies. All populations were followed up for at least 28 days.

3.3. 28-day or 30-day mortality

Two RCTs were included in our research. Fig. 2 showed the results from the random-effects models combining the RR for all-cause 28- or 30-day mortality. A total of 821 patients were included, and no significant difference existed between the 2 groups (RR, 0.81; 95% CI, 0.61-1.06; P = .12). However, the mortality of patients in the rhTM group decreased approximately 20% compared with the control group. We also found that there was no heterogeneity between the 2 RCTs (I² = 0%).

The results of the other 10 observational studies, including 17,467 patients, are presented in Fig. 3. Among the 10 studies, 7 showed a tendency of reduced mortality after rhTM therapy. However, the RRs for the association varied from 0.24 to 1.08 across the studies. Overall, there was no statistically significant reduction in mortality in the rhTM group (RR, 0.96; 95% CI, 0.92-1.01; P = .15). Slight heterogeneity was observed (P = .05, I² = 48%). Fig. 4 shows the publication bias of the 10 studies.

3.4. Bleeding events

Serious bleeding is the most concerning complication; among all the included studies, Yamato et al [20] reported that only one serious bleeding event was found in the rhTM group rather than in the control group. The authors did not identify the relationship between rhTM and the bleeding event. The 2 RCT trials showed no significant bleeding risk associated with using rhTM compared with the control group. One of the RCT studies conducted by Saito et al [21] reported that the occurrence rate of serious bleeding was lower in the rhTM group compared with

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Population</th>
<th>Mean ages (y)</th>
<th>Infection site</th>
<th>No. of patients</th>
<th>Intervention</th>
<th>Follow-up (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aikawa et al [22]</td>
<td>Japan</td>
<td>RCT</td>
<td>JMHW DIC</td>
<td>NA</td>
<td>Respiratory system; digestive system; nervous system; other</td>
<td>80</td>
<td>0.06 mg kg⁻¹ d⁻¹</td>
<td>6 d</td>
</tr>
<tr>
<td>Vincent et al [17]</td>
<td>Multinational</td>
<td>RCT</td>
<td>ISTH DIC</td>
<td>57</td>
<td>Respiratory system; digestive system; urinary system; other</td>
<td>741</td>
<td>0.06 mg kg⁻¹ d⁻¹</td>
<td>6 d</td>
</tr>
</tbody>
</table>

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the heparin group. Most of these observational studies demonstrated that rhTM therapy did not increase the bleeding risk.

3.5. Assessment of quality and bias risk

As mentioned previously, the 10 observational studies were evaluated by the researchers by using the NOS, and 8 observational studies earned 6 or more stars, whereas 2 studies earned 5 stars (Tables 3 and 4). In addition, we used the Cochrane Collaboration’s tool to assess the risk bias of the 2 RCTs. Fig. 5 shows the detailed outcomes. The double-blind method was not mentioned, but it did not affect our primary result (mortality). Therefore, we defined the blind item as low risk. Both Aikawa et al [22] and Vincent et al [17] were judged as studies with a low risk of bias.

4. Discussion

According to our analysis results, based on current published studies, the use of rhTM could not decrease short-term mortality of infection patients with DIC. Both the 2 RCTs and the 10 observational studies showed a declining tendency of 28- or 30-day mortality. However, no statistically significant benefit was found in these studies. In addition, 3 retrospective cohort studies [23-25] presented adverse tendency compared with other studies.

Thrombomodulin presents initially as an endothelial anticoagulant factor that promotes the thrombin-mediated activation of protein C [26]. Three domains, including the N-terminal lectin-like domain, epidermal growth factor-like domain, and O-glycosylation–rich domain, make up the extracellular portion of rhTM [1]. The N-terminal lectin-like domain plays a role in the inflammatory response. This advantage might rely on the neutralizing lipopolysaccharide [27] and degrading HMGB1 [28]. In addition, epidermal growth factor–like domain and O-glycosylation–rich domain are important for the activities of the anticoagulant factor, including inhibiting of thrombin and activating of protein C [1].

The close relationship between the inflammatory response and coagulation has raised increasing concern recently. Hence, thrombomodulin, a new drug with both anti-inflammatory and anticoagulation effects, has become an important topic worldwide. Some animal studies have illustrated a reduction in mortality with rhTM treatment in a sepsis model [29]. In the phase 1 study by Moll et al [30], tolerance and long-half life in clinical therapy were demonstrated. Saito et al [21]

### Table 2
The main characteristics of observational studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Population</th>
<th>Mean ages (y)</th>
<th>Infection site</th>
<th>No. of patients</th>
<th>Intervention</th>
<th>Follow-up (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ogawa et al [33]</td>
<td>Japan</td>
<td>HC</td>
<td>JAAM DIC</td>
<td>69.5</td>
<td>Respiratory system; digestive system; urinary system; other</td>
<td>86</td>
<td>41/45</td>
<td>0.06 mg kg⁻¹ d⁻¹ 6 d</td>
</tr>
<tr>
<td>Kato et al [32]</td>
<td>Japan</td>
<td>RC</td>
<td>JAAM DIC</td>
<td>67</td>
<td>Respiratory system; digestive system; urinary system; other</td>
<td>35</td>
<td>12/23</td>
<td>0.06 mg kg⁻¹ d⁻¹ 3-7 d</td>
</tr>
<tr>
<td>Yamato et al [20]</td>
<td>Japan</td>
<td>HC</td>
<td>JAAM DIC</td>
<td>NA</td>
<td>Respiratory system; digestive system; urinary system; other</td>
<td>22</td>
<td>14/8</td>
<td>0.06 mg kg⁻¹ d⁻¹ NA</td>
</tr>
<tr>
<td>Yamakawa et al [29]</td>
<td>Japan</td>
<td>RC</td>
<td>JAAM DIC</td>
<td>66</td>
<td>Respiratory system; digestive system; urinary system; other</td>
<td>162</td>
<td>68/94</td>
<td>0.06 mg kg⁻¹ d⁻¹ 6 d</td>
</tr>
<tr>
<td>Murata et al [18]</td>
<td>Japan</td>
<td>RC</td>
<td>JMHW DIC</td>
<td>73.3</td>
<td>Respiratory system; digestive system; urinary system; other</td>
<td>7535</td>
<td>3934/3601</td>
<td>Dose unknown</td>
</tr>
<tr>
<td>Takazono et al [25]</td>
<td>Japan</td>
<td>RC</td>
<td>JAAM DIC</td>
<td>79.8</td>
<td>Respiratory system; digestive system; urinary system; other</td>
<td>23</td>
<td>13/10</td>
<td>130-360 U kg⁻¹ d⁻¹ 6-0.6 d</td>
</tr>
<tr>
<td>Hashimoto et al [34]</td>
<td>Japan</td>
<td>RC</td>
<td>JAAM DIC</td>
<td>75.7</td>
<td>Digestive system</td>
<td>156</td>
<td>107/49</td>
<td>0.06 mg kg⁻¹ d⁻¹ 3-14 d</td>
</tr>
<tr>
<td>Tagami et al [23]</td>
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<td>RC</td>
<td>JAAM DIC</td>
<td>NA</td>
<td>Digestive system; respiratory system</td>
<td>2202</td>
<td>726/1476</td>
<td>380 U kg⁻¹ d⁻¹ 14 d</td>
</tr>
<tr>
<td>Tagami et al [24]</td>
<td>Japan</td>
<td>RC</td>
<td>JAAM DIC</td>
<td>74.6</td>
<td>Respiratory system</td>
<td>6342</td>
<td>1280/5062</td>
<td>380 U kg⁻¹ d⁻¹ NA</td>
</tr>
<tr>
<td>Hayakawa et al [19]</td>
<td>Japan</td>
<td>RC</td>
<td>JAAM DIC</td>
<td>NA</td>
<td>Circulatory system; nervous system; digestive system; urinary system; other</td>
<td>904</td>
<td>452/452</td>
<td>Dose unknown</td>
</tr>
</tbody>
</table>

Abbreviations: AT-III, antithrombin III; GM, gabexate mesilate; HC, historical control study; NA, not available; RC, retrospective cohort study; w/o, without.

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performed a multicenter, randomized, double-blind clinical trial that seemed to show that the DIC resolution rate improves dramatically in the rhTM group compared with heparin, and the rhTM group had a lower incidence of bleeding-related adverse events. However, the effects of rhTM on mortality were not clarified in that trial.

In the previous meta-analysis [14], the included observational studies showed a significant reduction in short-term mortality with rhTM, and the 2 included RCT studies showed different findings. Several reasons might explain this difference. First, only 571 patients, which is a relatively small sample size, were included in the observational studies and 838 patients were included in the RCT studies. Furthermore, a subgroup analysis made by Yoshimura et al [31] indicated that higher risk of death in patients with sepsis-induced DIC may obtain more advantage. An observational study by Yamakawa et al [29] included 162 patients and hold high weight value in the previous analysis. Nevertheless, the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) score is higher in patients and hold high weight value in the previous analysis. Neverthe-

In our study, 3 studies [18,23,24] with a total of 16,079 patients were included; this sample size was much larger than the size in the previous meta-analysis, which makes our analysis more statistically powerful. From a mechanism viewpoint, thrombomodulin might bring a benefit to patients with infection-induced DIC. However, neither the 2 RCTs nor the 10 observational studies in our meta-analysis found a notable reduction of mortality using rhTM. The cases in these 2 RCTs were insufficient, and more RCTs need to be performed in the future. We do not deny that using rhTM might reduce the length of stay [18] and DIC resolution rate [32], as found in previous studies.

At present, 3 criteria, including the ISTH, JAAM, and JMHW, are popular for use worldwide. Patients with DIC identified by different criteria might have different severities and characteristics [13]. The JAAM scoring system seems to be more appropriate for diagnosing patients with infection-associated organ failure–type DIC. Because the different criteria might affect the judgment of patients and even the research outcomes, we performed a subanalysis and excluded the study by Murata et al [18], which used the JMHW DIC standard. However, the result did not change. The detailed data are shown in Fig S1 in the online version at http://dx.doi.org/10.1016/j.ajem.2016.06.001.

The main concern regarding the use of rhTM is the possibility of bleeding. In our included studies, using rhTM did not raise the bleeding risk, which is consistent with the findings of the multicenter randomized and double-blind clinical trial performed by Saito et al [21]. It seemed that the incidence of bleeding-related adverse events was lower in the rhTM group compared with the heparin group. This finding might be supported by the fact that the anticoagulative effect of rhTM depends on the available thrombin. That is to say, it prefers in when and where thrombin exists without having an effect on the generation of thrombin [30]. From the drug safety perspective, rhTM is a good choice in clinical therapy. However, we select a treatment measure mostly on the basis of its efficacy, not its safety.

5. Limitations

There were several limitations of our study. First, only 2 RCT studies met the inclusion criteria, and we excluded some Japanese RCT studies because of the language problem. Second, differences in the basic characteristics of the included subjects and research methods might be a reason that resulted in the heterogeneity of our analysis. A retrospective cohort study performed by Kato et al [32] indicated that the JAAM criteria have an advantage of diagnosis of the early phase of DIC.
compared with the ISTH criteria. In our included studies, both the ISTH and JAAM criteria were used to diagnose DIC. The subanalysis maintained the same result, but the 2 RCTs using the JMHW DIC and ISTH DIC standards might have a major effect on the statistical outcomes. Therefore, the RCTs performed in the future are expected to use the JAAM scoring system. In addition, the nonuniform interventions in control groups might influence the results. Third, our study population was infection-DIC and mainly comprised patients with severe infections. Compared with the study by Yamakawa et al. [14], this method expanded the research range and increased the sample size as well as added the research perspective from Japan. In our included studies, both the ISTH and JMHW DIC criteria were used to diagnose DIC. Compared with the JMHW DIC criteria, the JMHW DIC criteria showed a lower sensitivity and a higher specificity when compared with the ISTH criteria.

6. Conclusions

This analysis demonstrated that using rhTM could not decrease the short-term mortality of infection patients with DIC based on the current published studies. More RCTs are needed to evaluate the effect of using rhTM for these patients. In addition, using rhTM did not increase the bleeding risk of the patients, which meant that it is a relative safe therapy for DIC patients at least. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ajem.2016.06.001.

References


