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Full Length Article

The anticoagulant treatment for sepsis induced disseminated intravascular coagulation; network meta-analysis

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ABSTRACT

Introduction: The benefits and harm caused by anticoagulant treatments for sepsis induced disseminated intravascular coagulation (DIC) remain unclear. Therefore, we performed a network meta-analysis to assess the effect of available anticoagulant treatments on patient mortality, DIC resolution and the incidence of bleeding complication in patients with septic DIC.

Materials and methods: We considered all studies from four recent systematic reviews and searched the PubMed, MEDLINE, and Cochrane databases for other studies that investigated anticoagulant treatment for septic DIC using antithrombin, thrombomodulin, heparin, or protease inhibitors in adult critically ill patients. These four anticoagulants and placebo were compared. The primary outcome in this study was patient mortality, and the secondary outcomes were the DIC resolution rate and incidence of bleeding complications.

Results: The network meta-analysis included 1340 patients from nine studies. There were no significant differences in the risks of mortality and bleeding complications among all direct comparisons and the network meta-analysis. Using a placebo was associated with a significantly lower rate of DIC resolution, compared to antithrombin in the direct comparison (odds ratio [OR]: 0.20, 95% credible interval [95% CrI]: 0.046–0.81) and in the network meta-analysis (OR: 0.20, 95% CrI: 0.043–0.84).

Conclusions: Our study revealed no significant differences in the risks for mortality and bleeding complications when a placebo and all four anticoagulants were compared in septic DIC patients. The results also indicated that antithrombin was associated with a five-fold higher likelihood of DIC resolution, compared to placebo.

1. Introduction

In septic patients, disseminated intravascular coagulation (DIC) is common and can worsen patient outcomes [1]. There are number of anticoagulants proposed as possible treatments to resolve DIC and improve outcomes in patients with septic DIC [2]. However, their benefit on the outcomes is still unclear [3,4]. For example, administration of an anticoagulant in one study had the potential to increase the risk of bleeding and worsen patient outcomes [5]. To determine the benefit and harm caused by anticoagulant treatments in this cohort,

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several meta-analyses were conducted [6–9]. Although available randomized controlled trials (RCTs) exploring this topic had assessed the effect of various anticoagulants such as antithrombin, thrombomodulin, and heparin, traditional meta-analyses can compare only 2 interventions. Thus, it was difficult to evaluate and make conclusions regarding the effect of individual anticoagulation treatments, especially to rank each treatment and placebo in accordance with the effect.

Network meta-analyses allow for comparisons of multiple treatments, by summarizing a comprehensive and coherent set of comparisons [10,11]. This approach allows for direct comparisons of interventions within RCTs, as well as indirect comparisons across trials based upon a common comparator (e.g., placebo or a standard treatment) [12]. Accordingly, we performed a network meta-analysis to assess the effect of each anticoagulant treatment on mortality, DIC resolution, and the incidence of bleeding complications in patients with septic DIC.

2. Methods

For the current study, we performed a network meta-analysis using randomized controlled trials to assess the effect of anticoagulant treatments in adult critically ill patients with septic DIC. This study was conducted according to the recommendations and checklist from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for network meta-analysis [10]. We developed a review protocol before starting the review process.

2.1. Eligible inclusion

Studies were considered eligible if they fulfilled the following criteria: (1) studies that were RCTs; (2) studies with full-text publication in English; (3) studies that included adult critically ill patients with sepsis induced DIC; (4) studies that aimed to assess the effect of anticoagulant treatment on mortality, DIC resolution rate, and the incidence of bleeding complications.

Although there are various definitions of DIC, we included all definitions of DIC mentioned in the studies. These definitions were based on the International Society on Thrombosis and Haemostasis (ISTH) overt DIC criteria, ISTH non-overt DIC criteria [13], the Japanese Association for Acute Medicine (JAAM) DIC criteria [14], or the authors' original criteria. The primary outcome in this study was short term mortality. The secondary outcomes were the DIC resolution rate and incidence of bleeding complications. DIC resolution was defined as a score of less than the thresholds of DIC criteria in each study.

2.2. Search strategy

For the network meta-analysis, we searched the PubMed, MEDLINE, and Cochrane databases to June 18, 2017 using the following search terms: (“disseminated intravascular coagulation”) AND (“randomized” or “randomized”). In addition, we considered all studies from four recent systematic reviews [6–9]. We also evaluated the reference lists of the relevant clinical trials to identify additional studies.

2.3. Study selection

All authors participated in the review process. Two reviewers independently screened titles and abstracts to determine potential eligibility. These reviewers also independently assessed the eligibility of each full-text paper. If the opinion of two reviewers conflicted in the process, another reviewer also independently evaluated the studies. We then finalized the decisions through group discussion.

2.4. Data collection

We created the abstracted data, which included the first author's name, year of publication, number of study sites, number of patients, cause of DIC, age, sex, diagnostic criteria for DIC, dose and duration of intervention drug and control treatment. We also collected the information for outcomes including mortality, definition of mortality, DIC resolution rate, and incidence of bleeding complications. Methodological quality was evaluated using the Cochrane risk of bias assessment tool, which evaluates randomization, allocation concealment, blinding of the study participants and personnel, blinding of the outcome assessments, incomplete outcome data, selective outcome reporting, and other potential sources of bias [15].

2.5. Statistical analysis

The network meta-analysis was performed within a Bayesian framework using JAGS software (version 4.1.0), R software (version 3.1.1), and the rjags and gemtc packages [16,17]. Comparative odds ratios (OR) were reported with their 95% credible intervals (CrI), and a random effects model was selected. Furthermore, a Bayesian framework meta-analysis provided a rank probability for each of the anticoagulant treatments and placebo and outcome. Inconsistencies were assessed using Bayesian *P*-values based on a node splitting analysis from the rjags and gemtc packages. Substantial heterogeneity was defined as an I^2 value of $\geq 50\%$ [18,19].

Our primary analysis was attempted in all studies including those with a post-hoc subgroup analysis. We then further performed the same analysis excluding these studies.

3. Results

3.1. Study selection

Fig. 1 shows the flowchart indicating the steps of the study selection. In our literature search, we identified 254 publications through the PubMed search, 244 publications through the MEDLINE search, and 115 publications through the Cochrane search. In addition, we found 49 studies that were included in the four previous systematic reviews [6–9]. After screening the titles and abstracts of all searched articles, we selected 26 studies. After the full-text screening, we excluded 17 studies (Supplementary appendix 1). Accordingly, our analysis included 1340 patients from nine studies [20–28]. Two studies were subgroup analyses of main RCTs [21,26].

Table 1 shows the detailed information for each study. Among nine studies, five were multicenter studies [20,21,23,24,26]. The number of included patients was a median of 60 patients (IQR; 36–161). The mean age of the patients varied from 49 to 76 years.

A total of four studies assessed antithrombin III; three of these studies compared antithrombin III with a placebo [20–22] and one compared antithrombin III with gabexate mesilate [23]. There were three studies that assessed thrombomodulin; two of these studies compared thrombomodulin with a placebo [24,25], and one compared thrombomodulin with heparin. There was one study that assessed gabexate mesilate and one study that assessed heparin, and both studies compared each drug with a placebo.

In regard to the definition of DIC, three studies used the JAAM criteria for diagnosing DIC [20,23,24], two studies used the ISTH criteria [21,24], another two studies used the Japanese Ministry of Health and Welfare criteria [26,27] and the last two studies used the authors' original criteria [22,28]. The risks of bias for each study are shown in Fig. 2.

3.2. Mortality

The network of eligible comparisons for the meta-analysis for mortality (nine RCTs) is shown in Fig. 3A. The forest plot for mortality is shown in Fig. 3B. There were no significant differences in these outcomes for all direct comparisons and the network meta-analysis. The