Thrombosis Research 163 (2018) 22–29

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Impact of non-anticoagulant therapy on patients with sepsis-induced disseminated intravascular coagulation: A multicenter, case-control study

Daisuke Kudo[a,*], Mineji Hayakawa[b], Kota Ono[c], Kazuma Yamakawa[d]

[a] Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan
[b] Emergency and Critical Care Center, Hokkaido University Hospital, 5 Kita8jonishi, Kita-ku, Sapporo 060-0808, Japan
[c] Clinical Research and Medical Innovation Center, Hokkaido University Hospital, 5 Kita8jonishi, Kita-ku, Sapporo 060-0808, Japan
[d] Division of Trauma and Surgical Critical Care, Osaka General Medical Center, 3-1-56 Bandaihigashi, Sumiyoshi-ku, Osaka 558-0056, Japan

ARTICLE INFO

Keywords:
Anticoagulants
Antithrombin
Disseminated intravascular coagulation
Sepsis
Thrombomodulin

ABSTRACT

Introduction: Anticoagulant therapy for patients with sepsis is not recommended in the latest Surviving Sepsis Campaign guidelines, and non-anticoagulant therapy is the global standard treatment approach at present. We aimed at elucidating the effect of non-anticoagulant therapy on patients with sepsis-induced disseminated intravascular coagulation (DIC), as evidence on this topic has remained inconclusive.

Materials and methods: Data from 3195 consecutive adult patients admitted to 42 intensive care units for the treatment of severe sepsis were retrospectively analyzed via propensity score analyses with and without multiple imputation. The primary outcome was in-hospital all-cause mortality.

Results: Among 1784 patients with sepsis-induced DIC, 745 (41.8%) were not treated with anticoagulants. The inverse probability of treatment-weighted (with and without multiple imputation) and quintile-stratified propensity score analyses (without multiple imputation) indicated a significant association between non-anticoagulant therapy and higher in-hospital all-cause mortality (odds ratio [95% confidence interval]: 1.59 [1.19–2.12], 1.32 [1.02–1.81], and 1.32 [1.03–1.69], respectively). However, quintile-stratified propensity score analyses with multiple imputation and propensity score matching analysis with and without multiple imputation did not show this association. Survival duration was not significantly different between patients in the propensity score-matched non-anticoagulant therapy group and those in the anticoagulant therapy group (Cox regression analysis with and without multiple imputation: hazard ratio [95% confidence interval]: 1.26 [1.00–1.60] and 1.22 [0.93–1.59], respectively).

Conclusions: It remains controversial if non-anticoagulant therapy is harmful, equivalent, or beneficial compared with anticoagulant therapy in the treatment of patients with sepsis-induced DIC.

1. Introduction

Disseminated intravascular coagulation (DIC) occurs in 30–50% of sepsis patients [1–5]. The pathophysiology of sepsis involves pathogen-associated molecular patterns, such as lipopolysaccharide (LPS) from Gram-negative bacteria and lipoteichoic acid from Gram-positive bacteria, as well as alarmins, cytokines, and other mediators of endothelial damage and coagulopathy [6–8]. Coagulopathy can causes multiple organ dysfunction, and the mortality rate of sepsis-induced DIC is high (35–40%) [1–5]. However, the effect of anticoagulant therapy on patients with sepsis-induced DIC remains controversial [9,10].

Retrospective studies showed that antithrombin and recombinant human thrombomodulin (rhTM) were associated with a reduction in 28-day or in-hospital mortality in patients with sepsis-induced DIC [11–13]. One randomized controlled trial (RCT) showed that recombinant human activated protein C (rhAPC) was associated with a reduced in 28-day mortality in patients with severe sepsis [14]. A meta-analysis showed that rhTM correlated with a reduction in 28–30-day mortality and anticoagulant therapies showed a reduction in all-cause mortality in patients with sepsis-induced DIC [15,16]. In contrast, three major randomized controlled trials (RCTs) of anticoagulants that included sepsis patients with and without DIC failed to confirm any survival benefits of antithrombin, rhAPC, and rhTM [17–19].

In the latest Surviving Sepsis Campaign guidelines 2016, no recommendations on the use of rhTM, heparins, and protease inhibitors were made; the use of antithrombin was not considered suitable [20]. The PROWESS-SHOCK study, an RCT on rhAPC, also did not report a survival benefit of the anticoagulant in patients with septic shock,

* Corresponding author.
E-mail addresses: kudodaisuke@med.tohoku.ac.jp (D. Kudo), mineji@dream.com (M. Hayakawa), kota.ono@huhp.hokudai.ac.jp (K. Ono).

https://doi.org/10.1016/j.thromres.2017.12.022
Received 25 July 2017; Received in revised form 12 December 2017; Accepted 29 December 2017
Available online 03 January 2018

including those with and without DIC patients; subsequently, rhAPC was withdrawn from the global market [17].

Non-anticoagulant therapy is the current standard global treatment approach for patients with sepsis. However, a recent meta-analysis of RCTs revealed that anticoagulant therapies had beneficial effects in patients with sepsis-induced DIC only (but not in the whole population of sepsis patients with or without DIC) [15]. It remains unclear whether non-anticoagulant therapy has superior, equivalent, or inferior effects in the treatment of patients with sepsis-induced DIC compared with anticoagulant therapy. Therefore, the aim of the present study was to elucidate the effect of non-anticoagulant therapy on patients with sepsis-induced DIC.

2. Materials and methods

This case-control study was conducted as part of the Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) study (UMIN000012543 [University Hospital Medical Information Network Clinical Trials Registry]), which was implemented in 42 intensive care units (ICUs) in 40 institutions throughout Japan [2] and approved by the Institutional Review Board of each institution. All boards waived the need for informed consent owing to the retrospective nature of the study, in accordance with Japanese guidelines [21].

2.1. Patient selection and data collection

The JSEPTIC DIC study retrospectively collected the data of consecutive patients who were admitted to the ICU owing to severe sepsis/septic shock between January 2011 and December 2013. Severe sepsis and septic shock were defined according to the Surviving Sepsis Campaign guidelines 2008 [22]. Patients aged < 16 years and those who developed severe sepsis/septic shock after admission to the ICU were excluded.

The following data were collected: age, sex, admission route to the ICU, pre-existing organ dysfunction, pre-existing hemostatic disorders, Acute Physiology and Chronic Health Evaluation (APACHE) II score [23], Sequential Organ Failure Assessment (SOFA) score [24] on admission, primary site of infection, blood culture findings, causative pathogen, daily laboratory test results during the first week after ICU admission, lactate levels, medications (including anticoagulants for DIC, other anticoagulants not for DIC, immunoglobulins, and low-dose steroids) during the first week after ICU admission, number of transfusions and bleeding complications during the first week after ICU admission, therapeutic interventions (including surgical interventions at the site of infection), renal replacement therapy (RRT), RRT for non-renal indications, polymyxin B-immobilized fiber column direct hemoperfusion during the first week after ICU admission, durations of ICU and hospital stays, and in-ICU as well as in-hospital outcomes. The severity of DIC was assessed using the scoring algorithm of the Japanese Association for Acute Medicine (JAAM) DIC criteria [25]. Missing values were scored as zero in the analyses without multiple imputation.

2.2. Definitions and outcome measures

Patients with DIC were defined as being free of pre-existing hemostatic disorders and had DIC scores ≥ 4 within one week after ICU admission (DIC scores were obtained on days 1, 3, or 7). They were divided into two groups according to whether they were treated with anticoagulants or not. The attending physicians decided on the use of anticoagulants, and there was no predefined protocol for DIC treatment.

The anticoagulants comprised antithrombin, rhTM, protease inhibitors, and heparins, which are frequently administered to patients with sepsis-induced DIC in Japan [26]. rhAPC was not available on the market in Japan. The anticoagulants were administered according to the guidelines of medical insurance in Japan. Physicians chose which anticoagulants to administer with consideration of institutional guidelines. For rhTM, 380 U/kg were administered to patients without severe renal dysfunction for 6 days, whereas 130 U/kg/day were administered to patients with severe renal dysfunction for 6 days. For antithrombin, 1500 IU were administered for 3 days to patients with antithrombin levels < 70%. For the protease inhibitor component, 20–39 mg/kg of gabexate mesylate or 0.06–0.20 mg/kg of nafamostat mesylate was administered until the DIC was resolved. Finally, 10,000–20,000 units of heparin were administered until the DIC was resolved. Heparins are often administered for venous thromboembolisms, atrial fibrillation, and extracorporeal circulation in ICUs. As the JSEPTIC database included the aim of the anticoagulant therapies, we excluded patients who received heparins for reasons other than the treatment of DIC.

The main outcome of this study was in-hospital all-cause mortality; secondary outcomes were 28-day mortality, duration of the ICU stay, and ventilator support-, RRT-, and vasopressor-free days. The incidence of bleeding complications was used as a secondary outcome. The number of event-free days (events were defined as ICU stay, RRT, mechanical ventilator use, and vasopressor administration) within a 28-day period was calculated by subtracting the duration of the event(s) from 28 days. If a patient was dead before 28 days after ICU admission, the number of event-free days was calculated by subtracting the duration of the event(s) from the duration of the ICU stay; i.e., the number of ICU-free days was considered zero if a patient was dead before discharge from the ICU.

2.3. Statistical analysis

Categorical and continuous variables are expressed as numbers (%), means ± standard deviations, or medians (interquartile ranges), as appropriate. Missing values for white blood cell counts, prothrombin time-international normalized ratio (PT-INR), fibrin/fibrinogen degradation products (FDP), and D-dimer levels, which are included in the JAAM DIC criteria, were scored as zero. To account for the significant proportions of missing values for FDP (27.4%) and D-dimer (21.1%) levels in patients with sepsis-induced DIC, we also conducted our analyses with multiple imputation. Multiple imputation through chained equations with predictive mean matching was employed to impute all missing values for the variables in the whole dataset of the JSEPTIC DIC study. Multiple imputation generated 20 data sets with 20 iterations [27,28]. In the multiple imputations, patients with DIC were extracted as subjects from each generated dataset that included all patients with severe sepsis.

To estimate the propensity scores, a logistic regression model for anticoagulant therapy as a function of the variables related to patient characteristics, therapeutic interventions, and ICU characteristics was fitted. This resulted in models based on: age; sex; body weight; admission route to the ICU; pre-existing organ dysfunction; pre-existing hemostatic disorder; APACHE II score; SOFA score for each organ (except coagulation) on day 1 (i.e. day of ICU admission); systemic inflammatory response syndrome score on day 1; DIC score on day 1; primary site of infection; blood culture results; causative pathogen; laboratory tests (including white blood cell count, platelet count, hemoglobin level, and PT-INR) on day 1; use of other anticoagulants, immunoglobulins, or steroids; surgical interventions at the infection site; RRT; RRT for non-renal indications; polymyxin B-immobilized fiber column direct hemoperfusion; extracorporeal membrane oxygenation; intra-aortic balloon pumping; ICU characteristics; ICU policy; and number of beds in the ICU. Some laboratory tests (fibrinogen, FDP, D-dimer, antithrombin, and lactate) were not used to estimate the propensity score because the proportion of missing data exceeded 10% in the analyses without multiple imputation. In the present analysis, various therapeutic interventions were used to estimate the propensity score because they were usually performed simultaneously with anticoagulant therapy. In multiple imputation, all the variables stated above were applied to estimate the propensity scores for each generated dataset.