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Intravenous immunoglobulin improves sepsis-induced coagulopathy: A retrospective, single-center observational study

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ABSTRACT

Introduction: Inflammation and coagulation are closely interrelated processes in the pathogenesis of sepsis. This study aimed to determine whether intravenous immunoglobulin (IVIg) could improve the hyperinflammatory state and coagulation/fibrinolysis abnormalities in patients with sepsis.
Methods: Forty-one patients with sepsis were included. Nineteen patients were treated with IVIg (IVIg group; 5.0 g daily for 3 days within 2 days after hospitalization), and 22 patients were not (non-IVIg group). Inflammatory and coagulation/fibrinolysis molecular markers, Japanese Association for Acute Medicine disseminated intravascular coagulation score, and the Sequential Organ Failure Assessment score were evaluated in each group.
Results: On admission, patients in the IVIg group had a significantly more severe condition. In the IVIg group, after treatment, C-reactive protein, procalcitonin, and interleukin-6 levels significantly decreased relative to values on admission. Also, compared with admission, the various coagulation/fibrinolysis molecular markers decreased after treatment. Moreover, the Japanese Association for Acute Medicine disseminated intravascular coagulation score and the Sequential Organ Failure Assessment score also significantly decreased after treatment. In contrast, in the non-IVIg group, only interleukin-6 level and thrombin-antithrombin complex levels significantly decreased. The 28-day mortality rate of the IVIg group was approximately one third of the value of the non-IVIg group (IVIg: 5.3% vs non-IVIg: 18.2%).
Conclusions: Intravenous immunoglobulin treatment significantly improved hemostatic abnormalities along with the hyperinflammatory state in patients with sepsis. Accordingly, IVIg treatment should be classified as an adjunctive therapy for patients complicated with sepsis-induced coagulopathy.

1. Introduction

Sepsis is diagnosed when patients meet the criteria for systemic inflammatory response syndrome as defined by the American College of Chest Physicians/Society of Critical Care Medicine guidelines [1], and an infectious source is documented or strongly suspected based on clinical presentation. Sepsis is a potentially lethal condition caused by a detrimental host response to an invading pathogen. In a global report on the mortality of 12 570 adult patients (from 37 countries) with severe sepsis in the intensive care unit (ICU) between December 2001 and December 2005, ICU mortality was 39.2% (ranging from 22.0% in Australia to 56.8% in Malaysia) [2]. Although the mortality rate of septic shock has tended to gradually decrease during the past decade because of significant technological advances in supportive therapies, it remains high, and effective specific treatments are still very limited [3].

Consensus on septic shock pathogenesis is that inflammation and coagulation are closely related and that deregulated interaction between inflammation and coagulation plays a pivotal role in the pathogenesis of sepsis. Evidence of extensive cross-talk between these 2 systems has been increasing [4], illustrating that inflammation leads to activation of coagulation, and coagulation considerably enhances inflammatory activity. Therefore, it is important to simultaneously control inflammation and coagulation to improve the condition of the patient.

In the last 3 decades, intravenous immunoglobulin (IVIg) has been increasingly used for the treatment of various autoimmune and systemic inflammatory diseases, and currently, the immune modulating indication is largely prevalent, mainly in off-label use. In a retrospective multicenter study in Japan of 624 patients with severe sepsis, 34.6% were treated with IVIg. The interventional rate for IVIg was the highest of any other adjunctive or supportive therapies (Fig. 1) [5]. Thus, IVIg treatment has been and continues to be one of the main and important treatments for sepsis in Japan. The established biological anti-inflammatory rationale for IVIg therapy in sepsis can be summarized into 4 main categories: (i) its role in pathogen recognition, clearance, and toxin scavenging; (ii) scavenging and inhibition of "upstream mediator" gene transcription; (iii) scavenging and inhibition of inflammatory "downstream mediator" gene transcription; and (iv) nonapoptotic and antiapoptotic immune cell effects [6].

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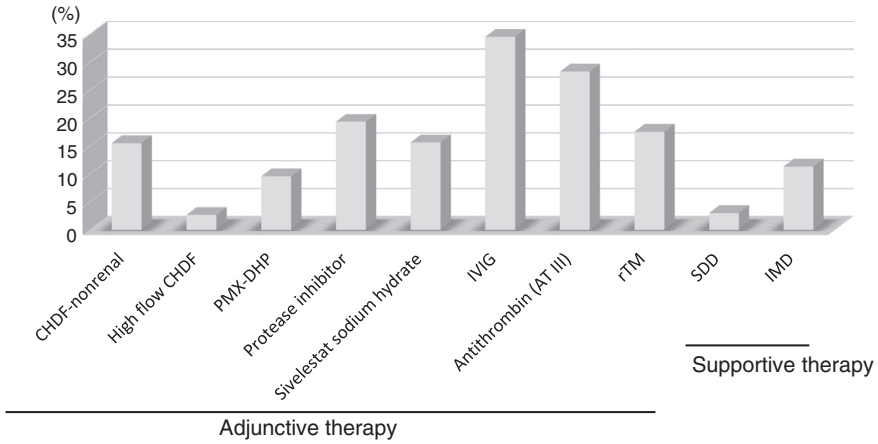

CHDF, continuous hemodiafiltration ; PMX-DHP, polymyxin -B immobilized column direct hemoperfusion ; IVIg , intravenous immunoglobulin ; rTM , recombinant thrombomodulin ; SDD, selective decontamination of the digestive tract ; IMD, immune -modulating diet .

Japanese Association for Acute Medicine Sepsis Registry (JAAM SR) Study Group.
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Fig. 1. Therapeutic interventions rate in severe sepsis and septic shock.

However, the relationship between IVIg and coagulation/fibrinolysis has never been investigated. The purpose of this study was to examine the effects of IVIg on coagulation/fibrinolysis as well as inflammation.

2. Materials and methods

2.1. Patient selection

This retrospective, single-center observational study was conducted at the Department of Emergency and Critical Care Medicine, Fukuoka University Hospital (a 915-bed referral, tertiary hospital), Fukuoka, Japan, between January and July 2013. Patients 18 years or older who had sepsis on admission were enrolled. Exclusion criteria included no sepsis, cardiopulmonary arrest on arrival, less than 7 days of ICU hospitalization, IVIg administration started more than 2 days from hospitalization, and/or missing data. Patients included were selected according to the 1992 diagnostic criteria for sepsis of the American Thoracic Society (American College of Chest Physicians/Society of Critical Care Medicine) [1].

2.2. Ethics statement

This study was approved by the ethics committee of our hospital. The need to obtain informed consent was waived because of its retrospective nature. In our hospital, every patient can provide a written refusal to use data at any time. Therefore, patients who refused the use of their record were excluded from the study.

2.3. Interventions

Commercially available human polyclonal IVIg was administered at 5.0 g (approximately 80-100 mg/kg) daily for 3 days within 2 days after hospitalization. This is the most common regimen for patients with sepsis in Japan. Whether IVIg would be administered was decided by the doctor in charge. All patients were principally treated according to the strategy of "Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012" [7].

2.4. Data collection

The following data were measured or calculated and obtained from electronic patient records: patient characteristics, therapeutic approach, inflammatory molecular markers (white blood cell count, C-reactive protein [CRP], interleukin [IL]-6, and procalcitonin [PCT]), coagulation and fibrinolysis molecular markers (platelet count, prothrombin time–international normalized ratio [PT-INR], activated partial thromboplastin time [APTT], fibrin/fibrinogen degradation product [FDP], D-dimer, thrombin-antithrombin complex [TAT], plasmin-α2 plasmin inhibitor complex, soluble fibrin [SF], and plasminogen activator inhibitor-1 [PAI-1]), Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, and Japanese Association for Acute Medicine (JAAM) disseminated intravascular coagulation (DIC) score on admission and at the end of IVIg administration. We regarded posttreatment as the period from days 1 to 3 after IVIg administration in the IVIg group. Generally, this was from days 4 to 7 if IVIg administration was started on the first day of admission and from days 5 to 8 if started on the second day. The most improved value during this period was adopted as the evaluation value. For the non-IVIg group, the most corrected value from days 4 to 7 was adopted as the posttreatment value. All patients were followed up for 28 days after admission, and 28-day all-cause mortality rate and amelioration of JAAM DIC in the posttreatment period were assessed.

2.5. Diagnosis of DIC

The scoring system of the JAAM was used for the diagnosis of DIC. This diagnostic algorithm for scoring DIC includes the following variables: platelet count, prothrombin time, FDP level, and systemic inflammatory response syndrome criteria. The details of the algorithm have been published elsewhere [8]. *Disseminated intravascular coagulation* was defined by a score of 4 or higher. The JAAM DIC scoring system is useful for identifying patients with sepsis at a stage of stressed but compensated DIC.

2.6. Statistical analysis

If not otherwise noted, data are reported as the mean ± SD. Comparisons between groups were performed using the χ^2 test or Fisher exact test for dichotomous variables, unpaired Student *t* test for continuous variables, and Mann-Whitney *U* test for median values, where appropriate. For all reported results, $P < .05$ was considered statistically significant. Statistical analysis was performed using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

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