Effect of High-Dose Intravenous Immunoglobulin Administration on the Levels of Interleukin-6 in Patients with Sepsis

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Abstract

Background: Intravenous immunoglobulin (IVIG) is administered to patients with sepsis to improve clinical outcomes. Here, we report the effectiveness of high-dose IVIG therapy in patients with sepsis admitted to a teaching hospital.

Methods: We analyzed 55 patients admitted to intensive care unit (ICU) due to sepsis. The patients were categorized into 2 groups depending on their IVIG dose: Patients administered high-dose (15 g/day for 3 days; total of 45 g) sulfonated human IVIG were designated the HD group, and those administered a standard divided dose (5 g/day for 3 days; total of 15 g) were designated the S group. The courses of interleukin (IL)-6 values were examined.

Results: The HD and S groups comprised 13 and 42 patients, respectively. The Log_{10} IL-6 values on Day 1 for HD and S groups were 3.3 ± 1.0 pg/mL and 3.4 ± 0.9 pg/mL (p=0.79). The repeated two-way ANOVA revealed no statistical inter-group difference for time course between 2 groups (p=0.42). The median Sequential Organ Failure Assessment (SOFA) scores on the day of ICU admission of the HD and S groups were 13.0 and 11.0, respectively (p=0.03). The most frequency of infection sources was abdomen in two groups, and there was no statistical difference for infection sources (p=0.18). The 28 day mortality rates for the HD and S groups were 30.8% and 14.3% (p=0.17), respectively.

Conclusion: This study showed that IVIG dose had no significant effect on IL-6 values despite of slightly lower course in high-dose IVIG group.

Keywords: Intravenous immunoglobulin; Sepsis; Septic shock

Background

Immunoglobulins counteract the effects of specific microorganisms and toxins by triggering various mechanisms, such as the opsonization process, complement system, antibody-dependent cell-mediated cytotoxicity, and increasing the susceptibility of bacterial cell walls to antimicrobial agents [1-3]. Due to these attributes, immunoglobulins are frequently used as adjuvant therapy for infections. Despite advances in infection treatments, sepsis and septic shock are still associated with high morbidity and mortality in intensive care patients [4].

Sepsis result to cytokine storm and one of the cytokines released during sepsis is interleukin (IL)-6 [5]. IL-6 was significant independent predictors of severe sepsis [6]. And, the previous study showed that IL-6 was useful marker for prognosis of sepsis [7]. Thus, IL-6 was remarkable cytokine for sepsis.

The judicious use of antibiotics and immunoglobulin has been previously shown to increase survival in patients with severe sepsis [8]. However, that study used an intravenous immunoglobulin (IVIG) dose of 7 mL/kg/day for 5 days, which

is substantially higher than the doses generally used in the Japanese clinical setting. As a result, little is known about the effects of high-dose IVIG therapy for the treatment of sepsis and septic shock in Japanese patients.

We have previously compared the use of single-dose and divided-dose IVIG therapy for sepsis and septic shock at a Japanese teaching hospital [9]. Building upon that analysis, this study additionally incorporates patients who received high-dose IVIG. The objective of this study was to investigate the association between IVIG administration of divided-dose IVIG therapy and IL-6 values in patients with sepsis.

Materials and Methods

Study design

This research was approved by the internal ethics review board of our institution. We performed a single-center before-after study. The sample comprised consecutive patients with severe sepsis and septic shock who were admitted to the intensive care unit (ICU) of Kansai Medical University Hospital between July 2009 and February 2016, and had agreed to participate in the study. These patients were categorized into 2 different groups based on IVIG dose and administration: Patients administered high-dose (15 g/day for 3 days; total of 45 g) sulfonated human IVIG were designated the HD group, and those administered a standard divided dose (5 g/day for 3 days; total of 15 g) were designated the S group. We aimed to compare the effectiveness of high-dose IVIG administration in the HD group with the S group. The data for analysis were obtained from clinical records and administrative claims data.

Definitions of sepsis and septic shock

This study used the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) definitions of severe sepsis and septic shock that were published in 1992 [10]. Severe sepsis defined as sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status. Septic shock defined as sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

Patient characteristics

Information on the following patient baseline characteristics was collected: age, sex, weight, infection source, and duration of mechanical ventilation in days. Designating the date of admission to the ICU as "Day 1", we assessed the interleukin (IL)-6 levels, SOFA score, and serum lactate levels on Days 1, 2, 4, and 8. IL-6 levels were Log_{10}-transformed prior to analysis.

A previous study reported that the administration of high-dose antithrombin III improved 90-day survival times in patients with

sepsis and septic shock complicated by disseminated intravascular coagulation [1]. And use of antithrombin III led to decrease of IL-6 levels [11]. Based on that finding, the use of antithrombin III was included as a study variable in our analysis. Because one of the definitions of severe sepsis proposed by Bone et al. stipulates a serum lactate level above 18 mg/dL [10], we also assessed the proportion of patients that fulfilled this criterion.

Statistical Analysis

Continuous variables were analyzed as means and standard deviations and categorical variables as percentages. Univariate analyses were initially performed using the Student t-test for continuous variables and the χ^2 tests or Fisher exact test for categorical variables, as appropriate; P values less than 0.05 were regarded as significant. The IL-6 levels, Sequential Organ Failure Assessment (SOFA) score, and serum lactate levels from Day 1, Day 2, Day 4 and Day 8 were compared using repeated two-way analysis of variance (ANOVA) due to revealing the inter-group differences. All analyses were performed using SPSS Version 24.0 (IBM Japan, Ltd., Tokyo, Japan).

Results

We identified 55 patients with severe sepsis or septic shock during the study period. Among these, 13 patients were categorized into the HD group and 42 patients into the S group. The patient characteristics and outcomes for the 2 groups are summarized in **Table 1**.

The univariate analyses indicated significant differences in patient age ($P<0.01$) and SOFA score on Day 1 ($P=0.03$). The mean ages of the HD group and S group were 74.9 ± 5.9 years and 66.7 ± 13.3 years, respectively; patients in the HD group were significantly older than those in the S group ($P<0.01$). Infections originating from the abdomen were the most common in all 2 groups. This was followed by infections originating in the respiratory tract in the HD group, and infections originating in the urinary tract in the S group. Antithrombin III was used in the majority of patients in all 2 groups, with no significant difference ($P=0.23$). Similarly, there were no significant differences ($P=0.44$) in the mean duration of mechanical ventilation, which exceeded 10 days in all 2 groups.

The Log_{10} IL-6 levels on Day 1 in the HD and S groups were 3.3 ± 1.0 pg/mL and 3.4 ± 0.9 pg/mL, respectively ($P=0.79$). The Log_{10} IL-6 levels trended to be slightly low from Day 2 to Day 8. The shifts, however, in the Log_{10} IL-6 levels for each group across Days 1, 2, 4, and 8 are no statistical difference **(Figure 1)**. The median SOFA scores on Day 1 of the HD group and S group were 13.0 and 11.0, respectively; patients in the HD group had significantly higher SOFA scores than those in the S group ($P=0.03$). The serum lactate levels on Day 1 for the HD group and S group were 32.9 ± 22.6 mg/dL and 41.9 ± 33.0 mg/dL, respectively ($P=0.36$). There were significant differences in the transitions of the SOFA score and serum lactate levels. Transitions in the SOFA scores and serum lactate levels are shown in **Figures 2 and 3**, respectively. There were significant differences in the transitions of these estimates among the groups ($P<0.02$ and $P<0.04$, respectively). The proportion of patients with serum lactate levels higher than 18

Table 1 Patient characteristics and outcomes.

	HD group (n=13)	S group (n=42)	*P* value
Patient characteristics			
Age (years)	74.9 ± 5.9	66.7 ± 13.3	<0.01
Sex (male %)	53.8	50.0	0.28
Weight (kg)	53.3 ± 11.1	54.5 ± 12.9	0.78
Infection source (%)			
Abdomen	61.5	54.8	
Respiratory tract	30.8	11.9	
Urinary tract	7.7	16.7	0.18
Other	0	16.7	
Duration of mechanical ventilation (days)	10.0 ± 7.9	12.9 ± 12.7	0.44
Use of antithrombin III	69.2	83.3	0.23
Log_{10} IL-6 (pg/ml)			
Day 1	3.3 ± 1.0	3.4 ± 0.9	
Day 2	2.5 ± 0.7	2.8 ± 0.7	
Day 4	1.8 ± 0.7	1.9 ± 0.6	0.42
Day 8	1.7 ± 0.5	1.7 ± 0.5	
SOFA score (IQR)			
Day 1	13.0(10.0-18.0)	11.0(8.0-13.0)	
Day 2	11.0(10.5-13.0)	10.5(8.8-13.0)	
Day 4	10.0(6.0-11.5)	9.0(6.8-11.3)	0.02
Day 8	8.5(3.3-9.0)	7.5(2.3-10.0)	
Serum lactate (mg/dL)			
Day 1	32.9 ± 22.6	41.9 ± 33.0	
Day 2	20.3 ± 12.0	32.6 ± 27.5	
Day 4	14.6 ± 6.9	16.9 ± 13.0	0.04
Day 8	12.8 ± 6.5	14.6 ± 8.1	
Serum lactate (>18 mg/dL) (%)	76.9	76.2	0.64
Outcome measures			
Duration of ICU stay (days)	12.0 ± 6.7	14.9 ± 11.3	0.39
28 day mortality (%)	30.8	14.3	0.17

Continuous variables: Mean ± SD; Categorical variables: Percentage

Abbreviations: ICU: Intensive Care Unit; IL: Interleukin; IQR: Interquartile Range; SOFA: Sequential Organ Failure Assessment

mg/dL exceeded 70% in all groups, but no significant differences were observed (*P*=0.64). The 28-day mortality rates for the HD group and S group were 30.8% and 14.3%, respectively. Two non-survival patients (15.4%) of 13 in the HD group diagnosed as Pneumocystis pneumonia.

Discussion

This single-center before-after study assessed the association between IVIG administration and IL-6 levels in patients with sepsis and septic shock. With the addition of patients who received high-dose IVIG to the sample from our previous analysis [9], the present study demonstrated a lack of a significant difference between high-dose IVIG and transitions of IL-6. The previous study on mice model demonstrated that suppression of IL-6 production following lipopolysaccharide stimulation led to improve survival rate [12]. In previous study on human model, IL-6 levels were strongly related to 28-day mortality and SOFA score [13]. In this study, higher SOFA score in HD group compared to S group were higher 28 day mortality, but IL-6 levels were similar between 2 groups. Kruger et al. [13] presented approximately 130 pg/ml in IL-6 levels and 8.0 in SOFA score. Compared to that study, our

study presented about 100 times in IL-6 levels and 2.5 times in SOFA score. Our study analyzed more severe patients than those of Kruger's study, and therefore IVIG itself might be preferable effect for rapid decrease on IL-6 level regardless of dose of IVIG administration.

A systematic review on IVIG for the treatment of sepsis and septic shock in critically ill adults reported that higher IVIG doses were associated with lower mortality rates [14]. As the doses reported in previous studies from other countries are higher than the standard doses used in Japan, we sought to evaluate the possible merits of a higher dose in the Japanese healthcare setting. But our results showed no significant clinical effect in short term prognosis. On the other hand, previous studies from overseas have used even higher doses [15-24] than that used in this study, and there may also be a need to conduct analyses in Japan using these higher doses on prognosis of severe sepsis and septic shock.

Although the mean SOFA scores in all our study groups were 11.0 or higher, the average of the 28-day mortality rate was 23%. A previous study on Japanese patients with sepsis reported
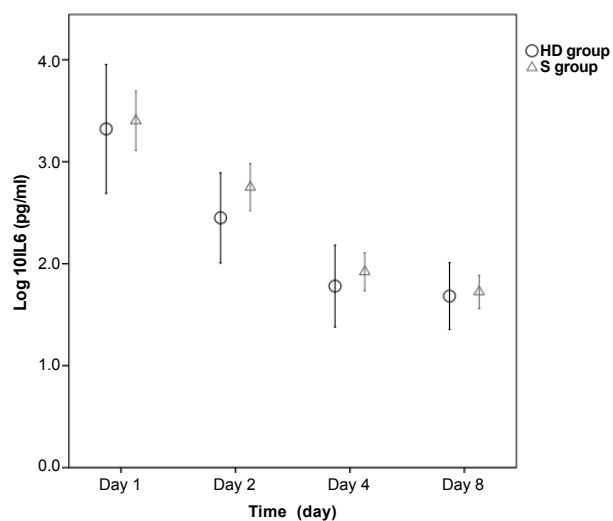
Figure 1 Results of the time-course analysis of Log_{10} IL-6 levels. The mean and 95% confidence intervals of each group are shown. The effect (between-subjects factor) in two-way repeated measures analysis of variance was P=0.42.
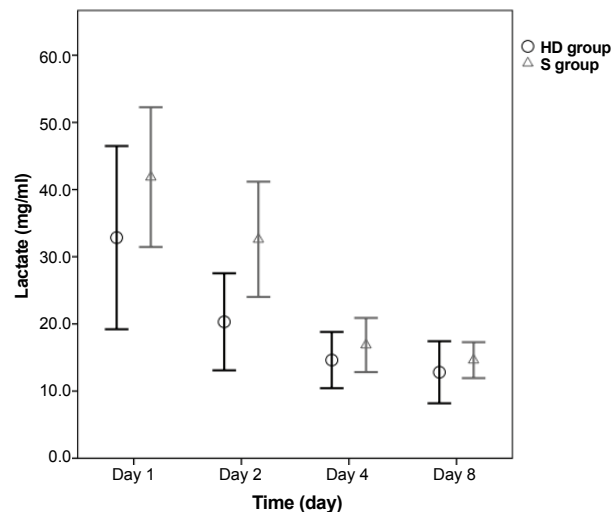
Figure 3 Results of the time-course analysis of serum lactate levels. The mean and 95% confidence intervals of each group are shown. The effect (between-subjects factor) in two-way repeated measures analysis of variance was P=0.04.
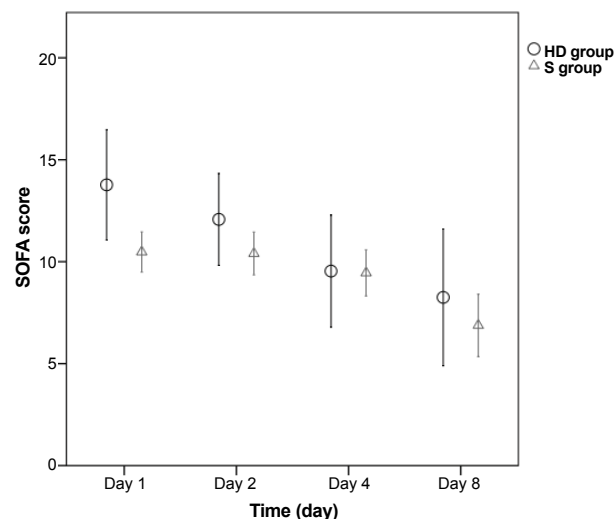
Figure 2 Results of the time-course analysis of SOFA scores. The mean and 95% confidence intervals of each group are shown. The effect (between-subjects factor) in two-way repeated measures analysis of variance was P=0.02.

that 28-day mortality in all patients (including those with organ dysfunction) was higher at 25.0% [25]. In comparison to that study, our sample had a generally low mortality rate regardless of whether the patients had one or more organ dysfunctions. A retrospective analysis on patients with sepsis conducted by Berlot et al. [26] found that a large proportion of survivors had received early IVIG therapy. As all the patients in our study had been administered IVIG on the first day of admission to the ICU, this early administration of IVIG may have contributed to the lower mortality rates. In addition, the mortality rates in our

sample are within the range of those reported (approximately 20-50%) in previous studies from other countries [26-31].

Based on transitions in IL-6 levels from our previous report, the single administration (15g for one day) of IVIG demonstrated faster post-therapy recovery than the S group [9]. However, our present study showed that there were no significant differences in the IL-6 levels between Day 1 and Day 2 despite of slight trend of rapid decrease on high-dose IVIG administration. It may be necessary to conduct further analyses on IL-6 level changes that focus not only on the dose and administration of IVIG, but also address the appropriateness of antibiotic therapy.

The main limitation of this study lies in its nonrandom design. As a result, we were unable to assess the patient characteristics that influence SOFA score. Therefore, the HD group had higher SOFA scores than the S groups and we were unable to make same severity of illness. The second limitation is that the HD group had a substantially smaller sample size than the S group in this study. Furthermore, two patients (15.4%) of 13 patients in HD group diagnosed as Pneumocystis pneumonia, which recognized as high mortality [32]. It may be beneficial to conduct further analyses using a longer study period to increase sample sizes. Finally, this study was a single-center analysis, which limits the generalizability of our findings. A multi-center collaborative study is therefore needed to further our understanding of the relationships assessed in this analysis.

Conclusion

This study showed that IVIG dose and administration had no significant effect on IL-6 values. Further research using a larger randomized controlled study is needed to obtain improved levels of evidence.

Acknowledgement

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki, and was approved by the internal ethics review board of our institution (Approval Number: 1404).

Consent for publication

Informed consent was obtained from the relatives or patients for all patients enrolled in the study.

Availability of data and material

The dataset supporting the conclusions of this article is available upon request. Please contact the corresponding author (Takeshi Umegaki).

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