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Intravenous Immunoglobulin G Modulates the Expression of Sepsis-Induced Coagulopathy Factors and Increases Serum IgM Levels: A Prospective, Single-Center Intervention Study

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Key words: Sepsis, Septic Shock, Immunoglobulin G, Immunoglobulin M, Coagulopathy

ABSTRACT

Sepsis and sepsis-related multiple organ failure are major causes of mortality in intensive care unit (ICU) settings. This study aimed to determine the effect of intravenous immunoglobulin G (IVIgG) on different types of immunoglobulin and anti-coagulant factor types in sepsis patients. A single-center observational study of patients with sepsis, severe sepsis, or septic shock was conducted from August 2008 to March 2013. Patients were divided into the IVIgG (immunoglobulin G [IgG] <870 mg/dL; lower normal range) and non-IVIgG (IgG ≥870 mg/dL) groups. The IVIgG group received IVIgG for three days, and other standard medications. Serial measurements were taken of serum IgG, immunoglobulin A (IgA), immunoglobulin M (IgM), total plasminogen activator inhibitor 1 (tPAI-1), and protein C. Patients in the IVIgG treatment group had significantly higher serum IgM level on Days 4 and 7 than on Day 1, but no significant changes in IgM levels were observed in patients in the non-IVIgG group. Patients in the IVIgG treatment had lower tPAI-1 levels on Days 4 and 7 than on Day 1 and increased protein C levels on Day 7 compared to those on Days 1 and 4. There were no significant differences in tPAI-1 levels or protein C levels in the non-IVIgG group, although a similar trend was observed. IVIgG administration increased patients' serum IgM and protein C levels and decreased their serum tPAI-1 levels. IVIgG has potential application for preventing sepsis-induced coagulopathy and disseminated intravascular coagulation.

INTRODUCTION

Sepsis and sepsis-related multiple organ failure are major causes of mortality in intensive care unit (ICU) settings worldwide, affecting more than 19 million people each year. Sepsis initiates a complex immunologic response that varies over time, with an alternating predominance of both pro-inflammatory and anti-inflammatory mechanisms (1-4).

To decrease the high mortality associated with sepsis (5), various adjunctive therapies have been proposed. Low-dose intravenous immunoglobulin G (IVIgG) administration (5 g/day for three days, total 15 g) is widely used as an adjunctive therapy for patients with sepsis in Japan. It was approved for clinical use based on the positive results of a randomized controlled trial by Masaoka et al. (6). In the trial, the administration of IVIgG, even at a low dose, was associated with an earlier improvement in the clinical signs and symptoms of sepsis.

IVIgG use has several theoretical advantages in sepsis treatment, and is thought to activate the human immune system and alleviate the symptoms of infection. The mechanisms behind the effectiveness of IVIgG are antitoxic effects such as pathogen recognition, clearance and toxin scavenging via the Fab region, and immunomodulation effects such as antiinflammation, neutrophil death induction, neutrophil adhesion and macrophage activation suppression, B cell apoptosis induction, and B cell proliferation suppression via the Fc region (7,8). IVIgG preparations may have beneficial effects on the host response to infection (9,10). Recently, several studies have reported on the efficacy of IgM-enriched IVIgG in sepsis patients (11-14). However, no reports to date have focused on the effect of IVIgG for other types of immunoglobulin (IgA and IgM), or its anti-coagulant effect, especially tPAI-1 and protein C as common anti-coagulant factors. The purpose of the present study was to determine the effect of IVIgG on different types of immunoglobulin and anti-coagulant factors in sepsis patients.

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MATERIALS AND METHODS

This prospective interventional study, was conducted from August 2008 to March 2013. The study was approved by the ethics board of the Kobe University Hospital in Japan (IRB no. 190024). Patients with sepsis, severe sepsis or septic shock were prospectively included. Those who had severe sepsis and had been admitted to either the emergency department or ICU were enrolled in the study after obtaining written informed consent from the patients or their next of kin. In this study, we used previously reported definitions of sepsis, severe sepsis, and septic shock (15). Exclusion criteria included age less than 18 years, history of allergy to IVIgG and/or antibiotics, hepatopathy (aspartate aminotransferase or alanine aminotransferase level ≥100 U/L) because of the possibility of coagulopathy, nephropathy (serum blood urea nitrogen level ≥25 mg/dL or serum creatinine level ≥2.0 mg/dL), acute myocardial infarction or chronic heart failure in the previous six weeks, postoperative infection associated with solid cancer, immunosuppressor use, and hypogranulocytosis.

On admission to the hospital, patients diagnosed with sepsis and who met the inclusion criteria, were enrolled in the study and divided into two groups: an IVIgG group with IgG level <870 mg/dL (lower normal range) and a non-IVIgG group with IgG level ≥870 mg/dL. Patients' demographic and laboratory data were collected and included: (i) age, sex, initial vital signs, type of sepsis (sepsis, severe sepsis, septic shock) (16,17), and source of infection; (ii) duration of catecholamine administration (days), ventilator use, fever (body temperature >38°C, days) and length of ICU stay (days); (iii) Systemic Inflammatory Response Syndrome (SIRS) score, disseminated intravascular coagulation (DIC) score, and Sequential Organ Failure Assessment score; (iv) serum concentrations of IgG, IgA, IgM, total plasminogen activator inhibitor 1 (tPAI-1) and protein C; and (v) multiple organ dysfunction syndrome (18), and survival. The DIC score was based on the Japanese Association for Acute Medicine criteria. The IVIgG group was administered IVIgG for three days (Day 1: 5 g, Day 2: 2.5 g, Day 3: 2.5 g) in addition to the standard medications.

Statistical analysis

SPSS16.0.2 Japanese for Windows was used for all statistical analyses. $P<0.05$ was considered statistically significant. Results are presented as the mean ± standard deviation. Patients' baseline characteristics were compared using the Mann-Whitney U test. Categorical variables were compared using Fisher's exact test. The percentages of outcomes were compared using the χ^2 test. Two-way repeated analysis of variance (ANOVA) was performed to determine the main effects of IVIgG and time (Days 1, 4, and 7), and the interaction between these two factors. In the IVIgG group, we also performed subgroup analyses on patients with serum IgG levels <650 mg/dL or ≥650 mg/dL. Univariate logistic regression analyses were conducted to determine which factors were associated with the outcomes.

RESULTS

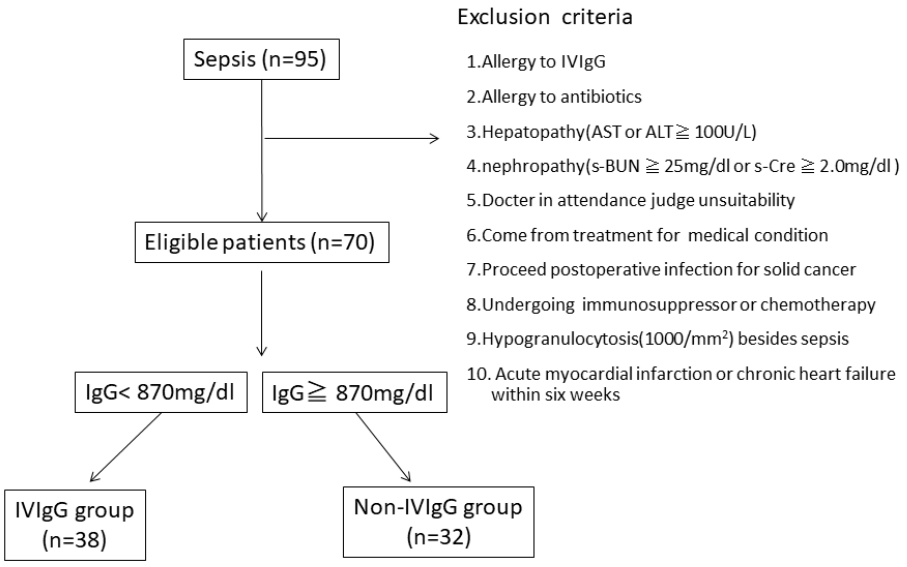


Figure 1: Flow chart of participant enrolment

A total of 70 patients was enrolled in the study. Participant characteristics are shown in Table I. There were 38 patients (20 males and 18 females) in the IVIgG group, with a mean age of 68.2±16.3 years, and 32 patients (21 males and 11 females) in the non-IVIgG group. with a mean age of 72.9±16.1 years.

Table I. Participant Characteristics

Variables	IVIG group (n=38)	Non-IVIG group (n=32)	P-value
Age (yr)	68.2±16.3	72.9±16.1	NS
Male (%)	20 (52.6)	21 (65.6)	NS
Infection source (%)			
Intra-abdominal infection	22 (57.9)	6 (18.8)	<0.001
Respiratory infection	11(28.9)	14 (43.8)	NS
Skin and soft tissue infection	2 (5.3)	4 (12.5)	NS
Central nervous system infection	2 (5.3)	2 (6.3)	NS
Urinary tract infection	1 (2.6)	6 (18.8)	NS
Types of sepsis (%)			
Sepsis	8 (21.2)	15 (46.9)	<0.005
severe sepsis	10 (26.3)	9 (28.1)	NS
septic shock	20 (52.6)	8 (25.0)	<0.05
Serum concentration on admission			
IgG (mg/dL)	628±160	1192±369	<0.001
IgA (mg/dL)	163±82	279±114	<0.001
IgM (mg/dL)	47±30	61±28	<0.05
Total protein (g/dL)	4.5±0.9	5.7±0.9	<0.001
Albumin (g/dL)	2.6±0.5	2.7±0.6	NS
TAT (ng/mL)	12.3±17.1	9.5±10.7	NS
Total PAI-1 (ng/mL)	76.9±75	33.7±35.9	<0.01
Protein C (μg/mL)	49.7±22.3	60.8±29.9	NS
CRP (mg/dl)	15.4±10.9	14.2±8.2	NS
HMGB1 (ng/mL)	9.6±10.5	8.3±5.1	NS
PCT (ng/mL)	38.3±64.9	15.2±37	NS
Severity			
SIRS score	2.9±0.9	2.7±1.0	NS
DIC score	3.0±2.4	2.2±2.2	NS
SOFA score	6.9±4.5	5.7±3.8	NS
Duration of fever (days)	8.3±8.5	7.4±9.6	NS
Duration of ventilation (days)	6.0±5.9	5.1±7.8	NS
Duration of catecholamine administration (days)	2.9±3.5	2.6±5.0	NS
ICU stay (days)	8.3±6.8	7.1±6.9	NS
MODS (%)	22 (57.9)	17 (53.1)	NS
Decrease of DIC score (from Day1 to Day7)	1.4±2.4	0.9±2.0	NS
Death (%)	3 (7.9)	2 (6.3)	NS

TAT: thrombin/antithrombin; PAI: plasminogen activator inhibitor; CRP: C-reactive protein; HMGB1: high mobility group box 1; PCT: procalcitonin; SIRS: systemic inflammatory response syndrome; DIC: disseminated intravascular coagulation; SOFA: sequential organ failure assessment; ICU: intensive care unit; MODS: multiple organ dysfunction syndrome; NS: not significant

Effect of IVIgG treatment on serum IgM levels

Patients in IVIgG treatment group had higher serum IgM level on Days 4 and 7 than on Day 1, but there was no significant change in the serum IgM levels in the non-IVIgG group (Fig. 2).

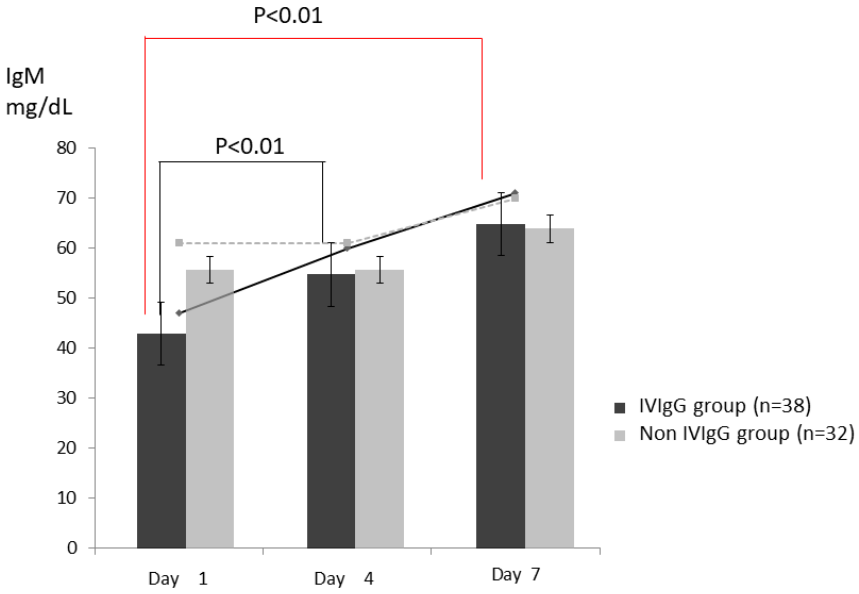


Figure 2. Effect of IVIgG treatment on serum IgM levels. Patients in the IVIgG treatment group had higher serum IgM levels on Day 4 than on Day 1, but no difference in the serum IgM level was observed between Days 1 and 4 in the non-IVIgG group. IVIgG, intravenous immunoglobulin G; IgM, immunoglobulin M

Effect of IVIgG treatment on serum tPAI-1 and protein C levels

Patients in the IVIgG treatment group had lower tPAI-1 levels on Days 4 and 7 than on Day 1 (Fig. 3A), and higher protein C level on Day 7 than on Days 1 and 4, but there were no significant changes in the tPAI-1 or protein C levels in the non-IVIgG group (Fig. 3B).

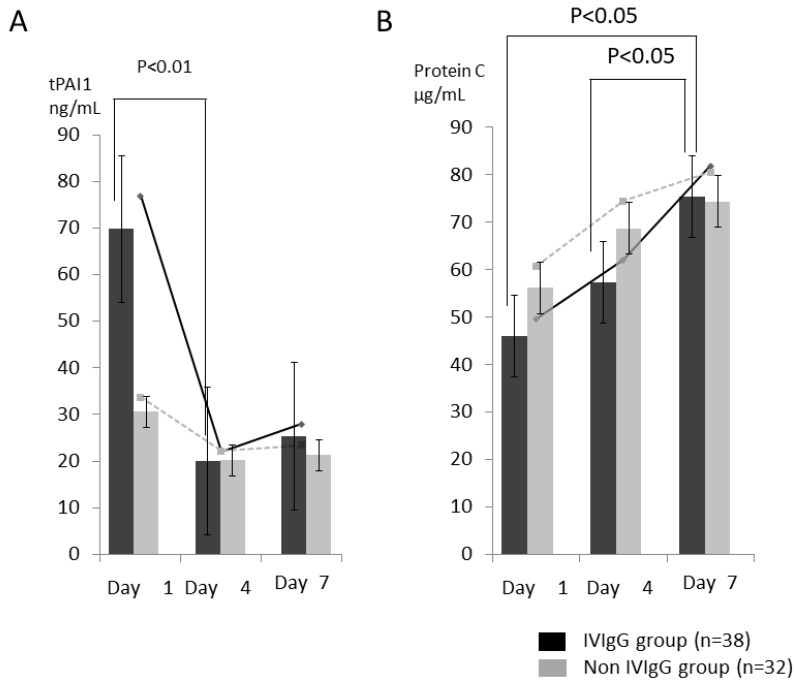


Figure 3. Effect of IVIgG treatment on the serum tPAI-1 and protein C levels.
3A: IVIgG treatment decreased the tPAI-1 level on Day 4 compared to that on Day 1. 3B: IVIgG treatment increased the protein C level on Day 7 compared to that on Day 4, but no difference was observed between Days 1 and 4 in the non-IVIgG group. IVIgG, intravenous immunoglobulin G; tPAI-1, total plasminogen activator inhibitor 1

Effect of IVIgG treatment on serum IgA and IgG levels

Two-way ANOVA showed that the serum IgG and IgA levels in patients in the IVIgG group were consistently significantly lower than those in the non-IVIgG group (Additional Figs. 1 and 2). The serum IgG and IgA levels in both groups increased between Day 1 and Day 7.

DISCUSSION

This study showed that, in sepsis patients, IVIgG administration can increase serum IgM and protein C concentrations and decrease serum tPAI-1 level demonstrating the potential of this therapy in the prevention of sepsis-induced coagulopathy and DIC. It is the first study to show that IVIgG administration can increase serum IgM levels and decrease the levels of serum tPAI-1 and protein C in sepsis patients. Although IVIgG therapy did not reduce the patient death rate, the results suggest that IVIgG has the potential, not only to increase the levels of several types of immunoglobulins, but also to prevent sepsis-induced coagulopathy and DIC development in sepsis patients.

Although the current consensus does not favor the use of IVIgG (19), this therapy has several functions in infection treatment through the attack on pathogens, such as the: (i) opsonization effect; (ii) bacteriolysis function of complement activation; (iii) toxin and virus neutralization function; (iv) antibody-dependent cell medicated cytotoxicity function; (v) antibacterial drug sensitivity (20); and (vi) anti-cytokine function (21). Since sepsis is commonly observed in older people and compromises the host with an immunosuppressed state, characterized by exhausted T cells (15,22) and a decreased degree of B cell function (23), immunomodulation for sepsis patients is an important strategy to decrease bacterial load. Therefore, notwithstanding the present study results, IVIgG still has potential as an immunomodulator for improved survival in sepsis patients.

In this study, IVIgG treatment decreased the serum level of tPAI-1 and increased the level of protein C. Protein C levels are decreased in sepsis patients, and our investigation showed that IVIgG medication use improved this condition. It is known that tPAI-1 is an inhibition factor in the fibrinolytic system; tPAI-1 is increased by endotoxin and inflammatory cytokine expression, and tPAI-1 creates blood thrombin in microcirculation, to hold pathogenic organisms, pathogen-activated molecular patterns, damaged-associated molecular patterns, and thrombin in the local area (24). DIC with sepsis and SIRS-related organ failure tend to occur in combination owing to increased PAI-1 values and delayed thrombin melting. In our study, IVIgG administration decreased tPAI-1, suggesting that IVIgG prevents DIC. Recently, Ishikura et al. (25) reported that IVIgG treatment significantly reduced the degree of hemostatic abnormalities that accompany the hyperinflammatory state in patients with sepsis. Accordingly, IVIgG treatment should be classified as an adjunctive therapy for patients with sepsis-induced coagulopathy-related complications.

Serum IgG levels are basically low in sepsis patients owing to the consumption and leaking of IgG from vessels (26-28). Among sepsis patients, the serum IgG levels of survivors have been shown to be significantly higher following IVIgG administration than those of non-survivors (26). In this study, IVIgG treatment for sepsis increased the serum level of IgM, even though the amount of IgM in IVIgG products is small (2.5 ± 1.7 mg/dL). Although the detailed mechanism whereby IVIgG administration increases serum IgM levels remains unclear, we speculate that IVIgG treatment improves the consumption of antigen-antibody interaction and reduces the leaking of IgG by increasing the degree of peripheral vascular resistance, and may improve the state of the immune system, leading to an increased production of IgM and IgA.

The combined presence of low levels of endogenous immunoglobulins IgG1, IgM, and IgA in plasma is associated with reduced survival in patients with severe sepsis or septic shock (29). IgM is a prognostic factor for improved survival in septic shock (30). IgM-enriched polyclonal immunoglobulins reduce short-term mortality in extremely low birth weight infants with sepsis (31). The protective role of IgM in sepsis models is reportedly critical for the circulation of lipopolysaccharide clearance (32,33), and IgM administration has been suggested as a strategy for sepsis management as well as a prophylaxis for patients at a high risk of acquiring nosocomial gram-negative infections (33). Accordingly, using a peritonitis sepsis model, reconstituting IgM secretion-defective mice with IgM purified from wild-type mice, Boes et al. (32) demonstrated that natural IgM is required for survival. Since IgM is a potent activator of the complement cascade, it may function by opsonizing enteric bacteria to trigger complement-dependent pathogen clearance (34).

Several reports have focused on the effectiveness of IVIgG administration in sepsis. One systematic review including a total of 21 trials showed immunoglobulin treatment was associated with a reduced mortality (35); however, in a subgroup analysis that included only high-quality trials the results did not show a statistically significant difference. Similarly, Laupland et al. (36) found a significant reduction in mortality with the use of IVIgG treatment, but, when only high-quality studies were pooled, the results were no longer statistically significant. Most IVIgG-related studies conducted to date have been small, and some showed a high risk of bias; the only large study ($n = 624$) on the topic showed no effect (37). The Surviving Sepsis Guideline 2016 recommends against the use of IVIgG (19). Large multicenter studies are needed to further evaluate the effectiveness of other intravenous polyclonal immunoglobulin preparations in patients with sepsis.

This study has several limitations. It had a small sample size and was conducted at a single center. IVIgG was administered to patients with low serum IgG levels. Proportion of patients with septic shock is higher compared with non-IVIG group. Although univariate logistic regression analyses were conducted to explore factors associated with outcomes, no significant factor was observed in our study. While the detailed mechanism

of how IVIgG administration increases serum IgM levels remains unclear, we speculate that IVIgG treatment improves the consumption of antigen-antibody interaction and reduces leaking of IgG by increasing the degree of peripheral vascular resistance. Further study is needed to clarify the effectiveness of IVIgG in sepsis patients.

Conclusions

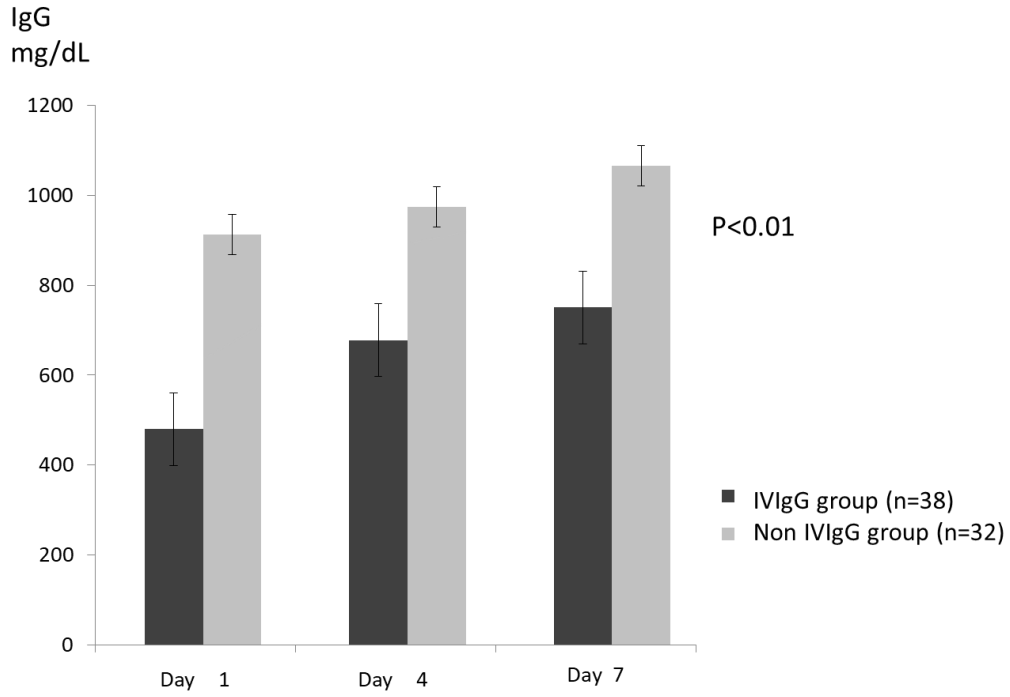
In sepsis patients, IVIgG administration may increase serum IgM and protein C concentrations and decrease the concentration of serum tPAI-1. IVIgG has the potential, not only to increase the levels of several types of immunoglobulins, but also to prevent sepsis-induced coagulopathy and DIC in sepsis patients.

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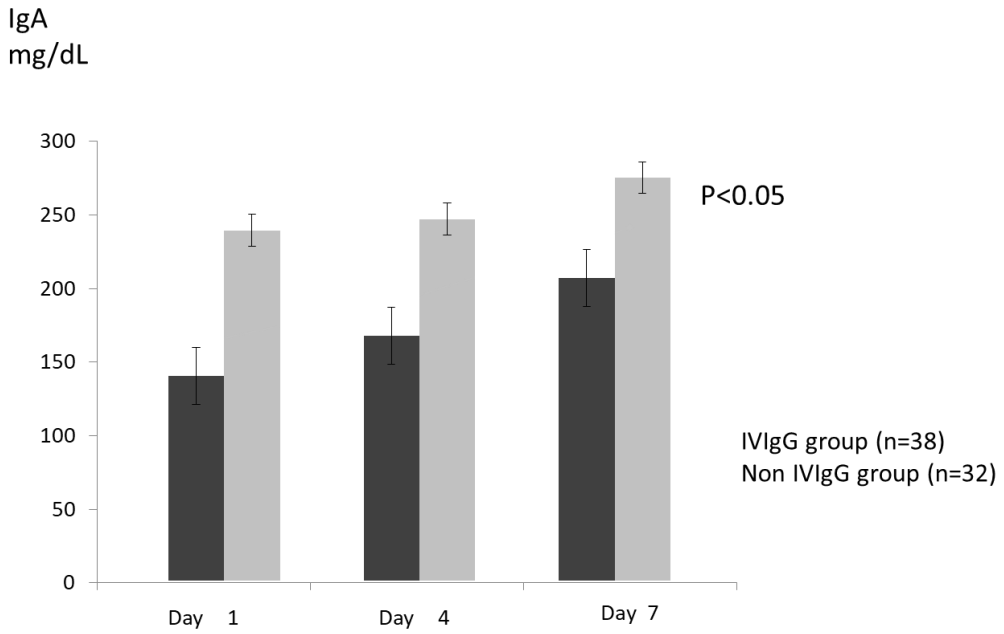
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Additional Information



Additional Figure 1: Analysis of variance results showing the effect of IVIgG treatment on the serum IgG level.
Two-way repeated ANOVA was performed to determine the main effects of IVIgG and time (Days 1, 4 and 7), as well as the interaction between these two factors. Differences in the serum immunoglobulin levels between the IVIgG and non-IVIgG groups were compared using a Mann-Whitney U test.
ANOVA, analysis of variance; IVIgG, intravenous immunoglobulin G



Additional Figure 2: Analysis of variance results showing the effect of IVIgG treatment on the serum IgA level in sepsis patients.
Two-way repeated ANOVA was performed to determine the main effects of IVIgG and time (Days 1, 4 and 7), as well as the interaction between these two factors. Differences in the serum immunoglobulin levels between the IVIgG and non-IVIgG groups were compared using a Mann-Whitney U test.
ANOVA, analysis of variance; IVIgG, intravenous immunoglobulin G