HUMAN VACCINES & IMMUNOTHERAPEUTICS
2020, VOL. 16, NO. 8, 1997–2002
https://doi.org/10.1080/21645515.2019.1711298

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RESEARCH PAPER

Clinical, laboratory features and prognosis of children receiving IgM-enriched immunoglobulin (3 days vs. 5 days) as adjuvant treatment for serious infectious disease in pediatric intensive care unit: a retrospective single-center experience (PIGMENT study)

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ABSTRACT

Introduction: Although there are studies about sepsis treatment in different age groups, data on immunoglobulin-M (IgM)-enriched intravenous immunoglobulin use in pediatric intensive care units (PICUs) are limited. The aim of this study was to evaluate the clinical features and prognoses of children receiving IgM-enriched intravenous immunoglobulin to treat sepsis, septic shock, and multi-organ failure.

Method: We extracted data from the medical records of 254 children who received IgM-enriched intravenous immunoglobulin infusion (104 children for 3 days, 150 children for 5 days) in addition to standard treatment between 2010 and 2017.

Results: When the 5-day vs. 3-day IgM-enriched immunoglobulin treatments were compared, the mortality rate was shown to be lower in patients who received the longer duration of treatment ($p < .001$). Better outcomes were observed among children with septic shock ($p < .01$).

Conclusion: Our clinical work with 5-days IgM-enriched intravenous immunoglobulin may reveal a survival benefit of this treatment for children with septic shock.

ARTICLE HISTORY
Received 15 July 2019
Revised 14 December 2019
Accepted 27 December 2019

KEYWORDS
IgM-enriched intravenous immunoglobulin; sepsis; septic shock; children

Introduction

Sepsis and septic shock are significant problems worldwide, leading to high morbidity and mortality rates among children and adults every year, regardless of underlying health problems.[1,2] Sepsis also contributes to sequelae and financial losses all over the world. Current treatment of sepsis syndrome, although nonspecific, is focused primarily on supporting organ function and administering intravenous fluids, antibiotics, and oxygen.[1-4] In recent years, the major causes of sepsis in children and adults have been attributed to a significant number of multi-drug-resistant (MDR), mainly gram-negative, bacteria (*Acinetobacter baumannii, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*).[4-6] High resistance rates, especially for nosocomial infections in intensive care units (ICUs), may result in the failure of antibiotic treatment, which may in turn result in poor prognosis.[4,6]

Previously published guidelines for treating sepsis among child patients reveal a lack of evidence for many interventions and treatments.[3,4,7,8] In the treatment of sepsis, the primary goal is to fight infection through the early administration of appropriate antibiotics and via the elimination of causal factors. However, antibiotic treatment is not always sufficient; in some cases, endotoxin might lead to endothelial damage and to the progression of sepsis and organ dysfunction. These serious infections are also characterized by impaired innate immune defenses for the effective phagocytosis of bacteria.[4,9,10] Many studies on the treatment of sepsis have been carried out with appropriate fluid and inotropic support and supportive therapies other than antibiotic treatments.[11]Results from recent trials and systemic meta-analyses seem more promising with regard to the use of IgM-enriched intravenous immunoglobulin in septic patients.[12-14] In addition to the effects of polyclonal standard intravenous immunoglobulins (IVIGs) – e.g., providing specific antibodies, inactivating endotoxin, and inhibiting complementary activation by blocking Fc receptors – immunoglobulin-M (IgM)-enriched intravenous immunoglobulin increases the bactericidal activity of leukocytes and inhibits the effects of cytokines.[15,16] It is thought that strengthening opsonization with IgM-enriched intravenous immunoglobulin may be beneficial in combatting MDR pathogen infections.[17]

Since studies on the use of IgM-enriched intravenous immunoglobulin in intensive care patients are generally performed on adult or newborn patient groups, data for pediatric patients are limited.[12-14] Due to the high heterogeneity of the immune inflammatory response, it is implausible that a single supportive therapy will be effective for all populations with sepsis. Therefore, it is crucial to identify which patient phenotypes can receive special advantages from each specific adjuvant therapy.[11] The clinical and laboratory characteristics of hospitalized pediatric patients who receive polyclonal IgM-

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enriched intravenous immunoglobulin therapy may provide a guide for future sepsis protocols. In this retrospective study, we aimed to determine the effects of IgM-enriched intravenous immunoglobulin use, when administered in addition to standard therapy, on the survival rate of patients with serious infections, including sepsis, septic shock, and multi-organ failure.

Patients and method

This retrospective study included pediatric patients who were "*at any stage of sepsis and were treated with IgM-enriched intravenous immunoglobulin*" in the Eskisehir Osmangazi University Faculty of Medicine between January 2010 and December 2017. The study was approved by the Eskisehir Osmangazi University Local Ethical Committee (21 December 2017, numbered 45425468–48).

A list of patients who received IgM-enriched intravenous immunoglobulin, including 38 g/L (76%) immunoglobulin-G (IgG), 6 g/L (12%) immunoglobulin-M (IgM), and 6 g/L (12%) immunoglobulin-A (IgA) (Pentaglobin®, Biotest AG, Dreieich, Germany), between January 1, 2010 and December 31, 2017 was retrieved from the hospital's pharmacy records and used to determine the study group. The medical records of patients between 28 days and 18 years of age who had received IgM-enriched intravenous immunoglobulin treatment for sepsis, septic shock, and multi-organ failure were then evaluated according to the criteria of previously defined sepsis guidelines.[1] Patients who were in the neonatal period and who had received standard IVIGs at any time in the treatment protocol were excluded from the study.

The day on which the first dose of IgM-enriched intravenous immunoglobulin treatment was given in addition to standard sepsis therapy was accepted as the first day of the study, and the data were recorded from this time point. All patients were given 5 mL (250 mg/kg/day) of IgM-enriched intravenous immunoglobulin within a 6-hour infusion. In our pediatric ICU (PICU) setting, a 3-day IgM-enriched intravenous immunoglobulin treatment protocol was used until 2012, at which time the treatment protocol was switched to five days, at the same daily dose, due to results from our previous clinical work.

Clinical and laboratory findings within 28 days from the initiation of IgM-enriched intravenous immunoglobulin treatment were noted from the enrolled patients' medical records. Demographic (age and gender) and medical data obtained before the patients' admission, including underlying diseases, were also recorded. The cause of hospitalization, detailed physical findings at enrollment (temperature, blood pressure, respiratory data, heart rate, peripheral oxygen saturation), and the Glasgow Coma Score (GCS) were noted, and the Pediatric Risk of Mortality (PRISM) score was calculated for the severity of the disease. On the first day of polyclonal IgM-enriched intravenous immunoglobulin treatment, venous blood gas analysis, complete blood counts (hemoglobin, white blood cell count, absolute neutrophil count, abscess lymphocyte number, platelet count), blood biochemistry (urea nitrogen, creatinine, bilirubin, transaminases, albumin), coagulation values (International Normalization Ratio-INR, D-dimer), and procalcitonin and lactate levels were recorded. To determine the expected infection locus, a sterile sample of urine, peripheral and catheter blood cultures, and cerebrospinal fluid cultures – as well as imaging results in patients with a body temperature of ≥38°C – were collected from each patient. Microbiological culture results obtained throughout the treatment period were also evaluated. Both proven and suspected infection conditions were considered as breakthrough infections in the follow-up. The microbiologically proven infection types were grouped as *gram-negative, gram-positive, fungal*, and *mixed* types. Antimicrobial data, including empirical treatments, combinations, and changes, were also recorded.

The primary aim of this study was to determine the effects of IgM-enriched intravenous immunoglobulin treatment, when administered in addition to standard therapy, on the survival of patients with sepsis, septic shock, and multi-organ failure. We also aimed to compare the survival rate of patients who received a 3-day course of IgM-enriched intravenous immunoglobulin treatment with that of patients who received a 5-day course of IgM-enriched intravenous immunoglobulin treatment. Secondary end points included the potential effects of IgM-enriched intravenous immunoglobulin treatment on mortality rates according to the etiological causes of sepsis and comparisons between age groups.

Statistical method: Normally distributed data were presented as mean ± standard deviation (mean ± SD), while non-normal data were given in medians (min-max). For comparison, Fischer's Exact test and the Mann-Whitney U test were used. $p < .05$ was considered statistically significant. All statistical analyses were performed using SPSS 16.5 for Windows (Chicago, IL, US).

Results

A total of 254 children (119 girls and 135 boys) aged between 1 month and 18 years who were hospitalized in Eskisehir Osmangazi University Medical Faculty Hospital and had received IgM-enriched intravenous immunoglobulin between January 2010 and December 2017 were included in the study. The median age was 13 months (range 1–216 months). The age distribution of the enrolled patients was as follows: 169 patients aged between 1 and 24 months (66.5%), 85 patients aged between 25 and 216 months (33.5%).

On the first day of IgM-enriched intravenous immunoglobulin therapy, 100 (39.4%) of the 254 patients had sepsis, 95 (37.4%) had septic shock, and 59 (23.2%) had multi-organ failure. The number of patients who required respiratory support on the first day of treatment was 161 (63.4%). Of these, 143 (88.8%) required invasive mechanical ventilation, while the remaining 18 (11.2%) did not. Regarding system involvement, 77.2% (n = 196) of the patients had respiratory system involvement, 16.5% (n = 42) had cardiovascular system involvement, 22% (n = 56) had liver failure, 22.8% (n = 158) had renal failure, and 39.4% (n = 100) had central nervous system involvement. Coagulopathy was observed in 102 (40.2%) patients, and metabolic acidosis (pH < 7.35, HCO3 < 16mmol/L) was shown in 89 (35%) patients. Stress hyperglycemia was observed in 66 (26.6%) patients. The number of patients using vasopressor drug infusion was 162

(63.8%; dopamine alone, 18.1%; dobutamine alone, 0.8%; adrenaline alone, 1.2%; and more than one inotropic agent, 43.7%). Hydrocortisone (steroid) treatment was given to a total of 83 (32.7%) children. Blood product transfusion (erythrocyte suspension, fresh frozen plasma, thrombocyte suspension, etc.) was given to a total of 220 (86.6%) patients. Hemodialysis was performed in 22 patients (8.7%) (Table 1). The percentages of system involvement and all interventions, as shown in Table 1, were similar between children who received the 5-day IgM-enriched intravenous immunoglobulin treatment and those who received the 3-day IgM-enriched intravenous immunoglobulin treatment ($p > .05$).

Pediatric patients were evaluated using the GCS on the first day of treatment and PRISM scoring for critical disease severity. The median GCS was 7 (minimum 3 and maximum 14), and the median PRISM score was 18 (1–46). Hematological and biochemical findings of the patients are summarized in Table 1. The clinical scores and hematological and biochemical findings were similar between children who received the 5-day IgM-enriched intravenous immunoglobulin treatment and those who received the 3-day IgM-enriched intravenous immunoglobulin treatment ($p > .05$). Regarding the microbiological evaluation of the enrolled patients, 47 (18.5%) patients were infected with gram-positive agents, 40 (15.7%) with gram-negative agents, 17 (6.7%) with fungal agents, and 54 (21.3%) with more than one microorganism; 96 (37.8%) patients, on the other hand, showed no growth in their cultures from sterile sites (Table 1).

When hospitalization periods were evaluated, it was noted that 120 (47.2%) patients had been hospitalized for fewer than 28 days, whereas 134 (52.8%) patients had been hospitalized for more than 28 days. When the mortality rates of the patients in the first 28 days of polyclonal IgM-enriched intravenous immunoglobulin treatment were evaluated, the survival rate in the sepsis group stood at 96%. Meanwhile, the survival rate for the septic shock group was 65.3%, while that for the multi-organ failure group was 39%. The mortality rate across the entire study population was 28.7%. Regarding age groups, in the 1–24 month age group, the mortality rate was 29.6%; for the 25–216 month group ($p > .05$), the mortality rate was 28%.

In this study, 104 patients received IgM-enriched intravenous immunoglobulin treatment for 3 days, while 150 received the same treatment for five days. The mortality rate for the 3-day treatment group was 40.3% – importantly, however, the mortality rate decreased to 20.6% among patients in the 5-day treatment group (OR: 0.51 (95% CI 0.34–0.75; $p < .001$).

In the evaluation of treatment regimens (i.e., 3 days vs. 5 days) according to sepsis staging, the mortality rate among patients in the septic shock group who received 5-day IgM-enriched intravenous immunoglobulin treatment was 19.2% ($n = 52$), while the mortality rate among those in the same

Table 1. Clinical features of children receiving IgM-enriched intravenous immunoglobulin treatment.

	3-day course of IgM-enriched intravenous immunoglobulin treatment (n = 104)	5-day course of IgM-enriched intravenous immunoglobulin treatment (n = 150)	Total IgM-enriched intravenous immunoglobulin treatment (n = 254)
Sepsis	37.5% (n = 39)	40.6% (n = 61)	39.4% (n = 100)
Septic shock	41.3% (n = 43)	34.6% (n = 52)	37.4% (n = 95)
Multi-organ failure	21.1% (n = 22)	24.6% (n = 37)	23.2% (n = 59)
System involvement			
Respiratory	77.8% (n = 81)	76.6% (n = 115)	77.2% (n = 196)
Hepatic	20.1% (n = 21)	23.3% (n = 35)	22% (n = 56)
Cardiovascular	23.0% (n = 24)	12% (n = 18)	16.5% (n = 42)
Renal	21.1% (n = 22)	24.0% (n = 36)	22.8% (n = 58)
Central nervous	42.3% (n = 44)	37.3% (n = 56)	39.3% (n = 100)
Mechanical ventilation	66.3% (n = 69)	61.3% (n = 92)	63.4% (n = 161)
Coagulopathy	37.5% (n = 39)	42% (n = 63)	40.2% (n = 102)
Metabolic acidosis	34.6% (n = 36)	35.3% (n = 53)	35% (n = 89)
Stress hyperglycemia	24.0% (n = 25)	27.3% (n = 41)	26.6% (n = 66)
Vasopressor agents			63.8% (n = 162)
Dopamine	14.4% (n = 15)	20.6% (n = 31)	18.1% (n = 46)
Dobutamine	0.15% (n = 1)	0.66% (n = 1)	0.8% (n = 0.2)
Adrenaline	0.15% (n = 1)	0.66% (n = 1)	1.2% (n = 3)
Combined	49.0% (n = 51)	34.0% (n = 51)	43.7% (n = 111)
Steroid use	33.6% (n = 35)	32.0% (n = 48)	32.7% (n = 83)
Blood product transfusion	84.6% (n = 88)	88.0% (n = 132)	86.6% (n = 220)
Hemodialysis/CRRT	8.6% (n = 9)	8.6% (n = 13)	8.7% (n = 22)
Plasmapheresis	0.15% (n = 1)	4.6% (n = 7)	3.1% (n = 8)
PRISM score	19 (2–46)	18 (1–43)	18 (1–46)
Glasgow Coma Scale (GCS)	7 (3–14)	7 (3–14)	7 (3–14)
Hemoglobin (g/dl)	10.0 (6.2–17.2)	10.1 (4.4–14.8)	10.1 (4.4–17.2)
White blood cell count (mm^3)	11630 (100–70700)	12500 (680–58230)	11950 (100–70700)
Absolute neutrophil count (mm^3)	7400 (0–61400)	7200 (0–51670)	7250 (0–61400)
Absolute lymphocyte count (mm^3)	2050 (0–27730)	2945 (200–19800)	2505 (0–27730)
Platelet count (mm^3)	178000 (10000–1113000)	137000 (6000–1083000)	154000 (6000–1113000)
Procalcitonin (ng/mL)	3.77 (0.11–124.4)	5.7 (0.06–200)	5.45 (0.06–200)
Lactate (mmol/L)	2.19 (0.4–16)	2.13 (0.6–35)	2.18 (0.4–35)
D-dimer (ng/L)	3.32 (0.44–36.6)	4.50 (0.29–36.8)	3.82 (0.29–36.8)
Albumin (g/dl)	2.9 (0.9–5.0)	3.2 (1.4–4.8)	3.1 (0.9–5.0)
Microbiological results			
• Gram-negative	16.3% (n = 17)	15.3% (n = 23)	18.5% (n = 47)
• Gram-positive	19.2% (n = 20)	18.0% (n = 27)	15.7% (n = 40)
• Fungal	9.6% (n = 10)	4.6% (n = 7)	6.7% (n = 17)
• Mixed	20.1% (n = 21)	22.0% (n = 33)	21.3% (n = 54)
• No positive results	34.6% (n = 36)	40.0% (n = 60)	37.8% (n = 96)

Table 2. Mortality rate comparison between 5 days vs. 3 days of IgM-enriched intravenous immunoglobulin treatment according to clinical stage of the study group.

	3-day course of IgM-enriched intravenous immunoglobulin treatment (n = 104)	5-day course of IgM-enriched intravenous immunoglobulin treatment (n = 150)	OR (95% CI, p)
Sepsis	7.6% (3/39)	1.6 (1/61)	0.21 (0.02–1.97; $p > .05$)
Septic shock	53.4% (23/43)	19.2% (10/52)	**0.35 (0.19–0.67; $p = .0013$)**
Multi-organ failure	72.7% (16/22)	54.0% (20/37)	0.74 (0.50–1.10; $p > .05$)
Total	40.3% (42/104)	20.6 (31/150)	**0.51 (0.34–0.75; $p = .0008$)**

group who received the 3-day treatment was 53.4% ($n = 43$) ($p < .01$). Among those in the sepsis group, the mortality rate was 1.6% ($n = 61$) for those who received the 5-day treatment, compared to 7.6% ($n = 39$) for those who received the 3-day treatment ($p > .05$). Among those in the multi-organ failure group, the mortality rate was lower among those who received the 5-day treatment than among those who received the 3-day treatment, without statistical significance (54.6% vs. 72.6%, $p > .05$) (Table 2).

We evaluated all medical records for the 254 children who received IgM-enriched intravenous immunoglobulin for safety purposes (regarding our blood product infusion records). There were no recorded adverse events related to the infusion, and we did not observe no cessation of treatment due to adverse events was observed.

Discussion

In this study, the medical records of children who received IgM-enriched intravenous immunoglobulin therapy as a treatment for sepsis, septic shock, or multi-organ failure were evaluated retrospectively. Consequently, 254 patients who received IgM-enriched intravenous immunoglobulin therapy for at least three days between 2010 and 2017 were included. Since the study center was the reference center in the region, most of the patients had an underlying disease, and most also had severe clinical and laboratory conditions related to shock and multi-organ failure (60.6%) that required several interventions in the PICU. When patient mortality was evaluated during the first 28 days of IgM-enriched intravenous immunoglobulin treatment, the mortality rate was found to be 4% in the sepsis group, 34.7% in the septic shock group, 61% in the multi-organ failure group, and 28.7% overall. The all-cases mortality rate in our PICU was 5% per year, while the mortality rate in the sepsis group was lower than that for the overall intensive care population and was, additionally, similar to that for sepsis groups in other studies. In one such study, Schlapbach et al.[18] evaluated sepsis and septic shock mortality rates in Australia and New Zealand between 2002 and 2013. They found a sepsis mortality rate of 5.6% and a septic shock mortality rate of 17.5%.

A significant decrease of IgM serum levels has been reported during septic shock, specifically in those cases that progress from severe sepsis to septic shock, with lower IgM levels among non-surviving patients.[19] The combined presence of low levels of the endogenous immunoglobulin-G1 (IgG1) and IgA, in addition to IgM, in plasma was associated with reduced survival in patients affected by severe sepsis and septic shock.[20] These results clearly indicate that IgM plays an important role in the patient's outcome.[21] Results from recent trials and systemic meta-analyses seem more promising with regard to the use of IgM-enriched intravenous immunoglobulin in septic patients.[13,14,22,23] IgM-enriched intravenous immunoglobulin in different dosing schemes has been used in retrospective or prospective studies of adults and newborns, generating different 28-day mortality results. Alejandria et al.[24] evaluated seven studies on the use of IgM-enriched intravenous immunoglobulin as an adjuvant therapy in adult patients with bacterial sepsis or septic shock and showed a significant reduction in mortality when compared with placebo or nonintervention.[24] Kakoulis et al.[13] evaluated 16 studies on the use of IgM-enriched intravenous immunoglobulin in adult patients with sepsis and its subsequent effects on mortality. While six studies showed no effects of IgM-enriched intravenous immunoglobulin on mortality, nine studies showed that IgM-enriched intravenous immunoglobulin administration increases survival in patients with sepsis or septic shock.[13] Cui et al.[14] conducted a meta-analysis that included 15 randomized controlled clinical trials ($n = 712$) and four observational cohort studies ($n = 818$) and showed that IgM-enriched intravenous immunoglobulin reduced mortality in adults with sepsis by 40%. Cavazutti et al.[25] evaluated whether an association existed between adjunctive therapy with IgM-enriched immunoglobulin and a 30-day mortality rate in 92 adult patients with septic shock in an ICU between 2008 and 2011. They found that the mortality rate was reduced by 21.1% in those patients receiving IgM-enriched intravenous immunoglobulin as an early adjuvant treatment (number needed to treat was five).[25]

In the present study setting, for the first 3-year period of the study, standard IgM-enriched intravenous immunoglobulin treatment (5 ml/kg/day, infusion rate was given as 6 hours) was applied for three days. Since 2012, however, the same dose was given for five days, according to our previous clinical results. The mortality rate of the 104 patients who received the 3-day IgM-enriched intravenous immunoglobulin treatment was 40.3%, yet this rate decreased to 20.6% among the 150 patients who received the 5-day treatment. The relative risk for mortality was 0.51 (0.34–0.75; 95% CI). Other reports regarding the 5-day IgM-enriched intravenous immunoglobulin treatment[14] are as follows: Giamarellos-Bourbolis et al.'s[22] placebo-controlled study in adult patients with sepsis; Rodirigues et al.'s two

studies[26] in an adult sepsis setting; and Welte et al.'s[27] recent placebo-controlled clinical trial with a new trimodulin formulation, which includes 23% IgM and 21% IgA. Cui et al.'s[14] meta-analysis compared the relative risk of mortality for <3 days of treatment and >3 days of treatment. Their results showed a relative risk for mortality at 0.58 (CI 0.48–0.69) for <3 days of treatment and at 0.66 (0.47–0.81) for >3 days of treatment. Our study represents the first pediatric study on the use of a 5-day IgM-enriched intravenous immunoglobulin treatment.

Few studies have focused on the use of IgM-enriched intravenous immunoglobulin therapy in infants and children aged 28 days or more. Popov et al.[28] evaluated the effectiveness of a procalcitonin-guided strategy involving the use of 3-day IgM-enriched intravenous immunoglobulin therapy in children with congenital heart disease who had experienced systemic inflammation during the early post-operative period. They found that the rate of infectious complications was lower (3.3% vs. 26.7%) and that both the length of hospital stays and the time spent in the ICU were shorter in the IgM-enriched intravenous immunoglobulin therapy group than in the control groups.[28] Kola et al.[29] evaluated the effect of IgM-enriched intravenous immunoglobulin on the survival rate of children with sepsis and found a higher survival rate than when compared to the control group (87% vs. 64%), in addition to shorter hospital stays. In a follow-up study of 100 septic children, aged between 1 and 24 months, in a PICU, El-Nawawy et al.[30] found that, in addition to the standard treatment, 8ml/kg/day of IgM-enriched intravenous immunoglobulin treatment shortened the intensive care period, decreased mortality, and disseminated intravascular coagulation development. In our study, we showed that the 5-day IgM-enriched intravenous immunoglobulin treatment was associated with a reduced mortality rate in children with septic shock. While we observed a decline in the mortality rate in children with multi-organ failure (without statistical significance), our results suggest that starting all treatment options in the early stages of the disease will contribute to greater treatment success. Berlot et al.[31] concluded that the efficacy of IgM therapy is time-dependent and is greater in the early phase of severe sepsis and septic shock. This effect is also shown in patients with septic shock caused by MDR pathogens.[31] Recently, an expert panel identified three levels of support for Pentaglobin® use according to PIRO scores (the **P**redisposition component, **I**nsults component, **R**esponse component, and **O**rgan failure component). A TO-PIRO score <5 indicates an uncertain benefit from the use of IgM: individual assessments should be performed according to guidelines. A TO-PIRO score in the range of 6 to10 suggests a potential benefit of IgM, when initiated after antibiotic therapy and within 24 hours after the infection has been identified. Finally, when the TO-PIRO score is >10, the use of IgM is strongly recommended within six hours of identification because the therapy may significantly decrease the mortality risk.[21] Although the PIRO score has not yet been validated for pediatric settings, we plan to evaluate future study groups according to this scoring system.

The incidence of side effects associated with immunoglobulin administration has been, hypersensitivity, and anaphylactic reactions from vasomotor or cardiovascular findings. In this study, there were no recorded adverse events related to the infusion of IgM-enriched intravenous immunoglobulin, nor did we observe the cessation due to adverse events of either the 5-day or 3-day therapy due to polyclonal IgM-enriched intravenous immunoglobulin treatment.

Our study had some analytical limitations. First, it was a retrospective study, and thus even though the 3-day and 5-day treatments were compared in two different periods, the effect of changes in intensive care conditions over time was not evaluated. Moreover, we did not establish a control group for the study, i.e., a group that did not receive IgM-enriched intravenous immunoglobulin, because our standard treatments for severe infection and sepsis were administered instead.

In this study, among children with sepsis, the mortality rate was lower for those children who received the 5-day IgM-enriched intravenous immunoglobulin treatment, and this treatment seemed to be both safe and well-tolerated. Further largest prospective studies on the effects of IgM-enriched intravenous immunoglobulin treatment in children, would help to define mechanism of action.

Author contributions

This study is part of the specialty thesis of Dr. Abdullayev for Pediatric Residency, with Prof. EC Dinleyici serving as the scientific advisor of the thesis. EA and ECD participated in protocol development, statistical analysis, primary data analysis, and interpretation, and they both wrote the first version of the manuscript and finalized the last version. Dr. Kilic, Dr. Bozan, Dr. Kiral, and Dr. Iseri-Nepesov participated in the data analysis and in the writing of the manuscript.

Disclosure of potential conflicts of interest

This study was an investigator-initiated study, and the authors have no financial disclosures related to this publication. ECD serves as a consultant and speaker for GSK, Pfizer, Sanofi Pasteur, Merck, and Biotest. The other authors have no conflict of interest.

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