ORIGINAL RESEARCH

Efficacy of an IgM preparation in the treatment of patients with sepsis: a double-blind randomized clinical trial in a pediatric intensive care unit

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Abstract

Aim: Additional treatments for sepsis to be administered alongside the standard therapy recommended by the Surviving Sepsis Campaign have recently undergone evaluation. Due to its anti-bacterial, anti-inflammatory and immunomodulatory properties, intravenous polyvalent immunoglobulin M (IgM)–enriched immunoglobulins (IgM preparation) has been investigated as one of these potentially valid adjunctive therapies. The aim of this trial was to assess the efficacy of an IgM preparation as adjuvant therapy in the treatment of pediatric patients with sepsis.

Methods: In our study, 78 septic patients admitted to a pediatric intensive care unit (PICU) at the University Hospital Center "Mother Teresa" in Tirana, Albania, were randomized into two groups (intervention and control). All patients were treated according to standard PICU sepsis guidelines. Additionally, patients in the intervention group received the IgM preparation Pentaglobin® while patients in the control group received standard sepsis therapy, but no immunoglobulin administration.

Results: The survival rate was higher in the intervention group (87%, N=34) than in the control group (64%, N=25), and this difference was statistically significant (P=0.03). Length of stay (LOS) was also significantly shorter in the intervention group.

Conclusion: In this study conducted in Albania, use of an IgM preparation, in addition to standard sepsis therapy, led to a significant increase in the survival rate as well as a significant reduction in LOS compared with placebo, when administered in PICU patients with sepsis.

Keywords: bacterial infections, IgM preparation, immunoglobulin, immunotherapy, Pentaglobin®, sepsis.

Introduction
Sepsis is a major cause of morbidity and mortality in critically ill pediatric patients (1,2). About 25% of all PICU admissions are due to life–threatening infections in pediatric patients (2). Although numerous advances in the management of critically ill children with severe infections have occurred in recent years, the mortality associated with severe sepsis and septic shock remains unacceptably high, with a rate between 20% to 56% (1,3-10). Because of its broad and potent activity against bacteria and their exotoxins as well as against the excessively activated pro-inflammatory host response, an IgM preparation was investigated as an adjunctive treatment for patients with severe bacterial infections (11-13). This IgM preparation is the only approved intravenous immunoglobulin for treating severe bacterial infections and contains anti- bacterial, anti-inflammatory and immunomodulatory antibodies from the immunoglobulin classes IgM, IgG, and IgA. In this respect, the preparation differs from all other standard intravenous immunoglobulin preparations, which contain almost only IgG (3,14,15).
To date, there are no studies conducted in Albania assessing the efficacy of IgM preparations in pediatric wards. In this framework, the objective of this trial was to assess the efficacy of an IgM preparation as adjuvant therapy in the treatment of pediatric patients with sepsis in Albania. We hypothesized that administration of the IgM preparation in combination with standard-of-care antibiotics would increase the overall survival rate in septic patients admitted to PICU.

Methods
This was a prospective, double-blinded, randomized, placebo-controlled trial conducted in the PICU of the University Hospital Center "Mother Teresa" in Tirana, Albania, between January 2009 and December 2010.
The Ethics Committee of the University of Tirana approved the study protocol and a written informed consent was obtained from the parents or guardians of all of the patients. The study was conducted in accordance with the Declaration of Helsinki and followed Good Clinical Practice guidelines and national regulations. The study was registered in a clinical trial registry. To increase patient homogeneity and to strengthen internal validity, strict diagnostic criteria were applied. Proven sepsis was defined according to 2001 ACCP/SCCM sepsis criteria (16). Patients with sepsis (SIRS, sepsis, severe sepsis, septic shock) documented infection and dysfunction of an organ or hypotension were enrolled in the study. Patients fulfilling one or more of the following criteria were not included in the study: severe immunosuppression, irreversible end- stage damage of vital organs, a Glasgow coma score of 3/15, comorbidities and/or contraindications to any of the study treatments.
One hundred and three patients were assessed for eligibility in the study. Eighteen children did not meet the inclusion criteria, whereas seven parents declined study participation of their children.

Intervention
The study utilized a parallel-group design whereby patients were stratified by baseline characteristics such as age and gender and also according to diagnosis and severity of disease. Patients were randomly assigned in a 1:1 ratio to the intervention or control group. Treatment assignment was randomly generated by computer in stratified permuted blocks of two. The intervention group received the IgM preparation while the control group did not receive any immunoglobulin administration (Figure 1).
Fluid administration was protocolized. All patients received isotonic intravenous fluid bolus

20-40ml/kg in 1 hr. Repeated boluses were administered depending on clinical parameters, including heart rate, capillary refill, blood pressure, urine output and level of consciousness.

A researcher sealed envelopes labeled only with the patient number and containing the respective study medication. Corresponding envelopes were opened by the researcher only after the enrolled participants had completed baseline assessments and were about to be allocated to a treatment group. Other investigators, staff, parents of the children, the nurse who administered the treatment and endpoint assessors were all blinded to treatment assignment.

Study protocol

All patients received standard sepsis therapy which comprised intravenous antibiotics. Patients in the intervention group received the IgM preparation Pentaglobin® intravenously. Administration of the IgM preparation was started on the day of sepsis diagnosis at a volume of 5 ml/kg body weight per day and was infused over six hours for three consecutive days.

Patients in the control group received standard sepsis therapy, but no immunoglobulin administration.

A detailed clinical history was taken from all cases who were also subjected to physical examination. Demographic data (age and gender), body weight, height, [based on which the body mass index (BMI) was calculated] diagnosis at PICU admission, duration of stay in the PICU and outcome at discharge were recorded for each patient (Table 1). Study treatment was administered within eight hours after randomization. Patients were observed throughout their stay in PICU. Compliance, laboratory parameters, vital signs, hemodynamic data laboratory parameters and organ dysfunction were monitored on a daily basis. Protocol violations were defined before the start of the study. The study endpoint was death in PCIU.

Statistical analysis

Based on literature review and in our previous experience, the expected mortality rate in the control group was anticipated as 60%, whereas the magnitude of the expected treatment effect was set at 40%. Type I error was set as $\alpha=0.05$ in a two-tailed test and type II error as $\beta=0.05$. The 95% confidence interval (CI) for the difference between proportions was calculated as follows: (D) = D - 0.236 to D + 0.236.

After adjusting for a 5% drop-out rate, the sample size was estimated at 39 individuals in each group. The primary efficacy analysis was performed according to intention-to treat (ITT) principles, rather than as an explanatory analysis. All randomized patients were included in the ITT population and the per-protocol population included only patients who completed the treatment originally allocated in both groups.

Normal distribution of continuous variables was tested with the Kolmogorov-Smirnov test.

Mann-Whitney test was used to compare age, height and body weight of patients between the two groups.

Chi-square test was used to compare gender differences and laboratory values in each treatment group and the independent sample t-test was used to compare the length of stay (LOS) in the PICU as well as the BMI.

Mortality rates in the intervention and control group were compared with the chi-square test.

The difference in survival rates between groups was assessed using the Kaplan-Meier method and the log-rank test. The censoring time for the survival analysis was the PICU stay duration.

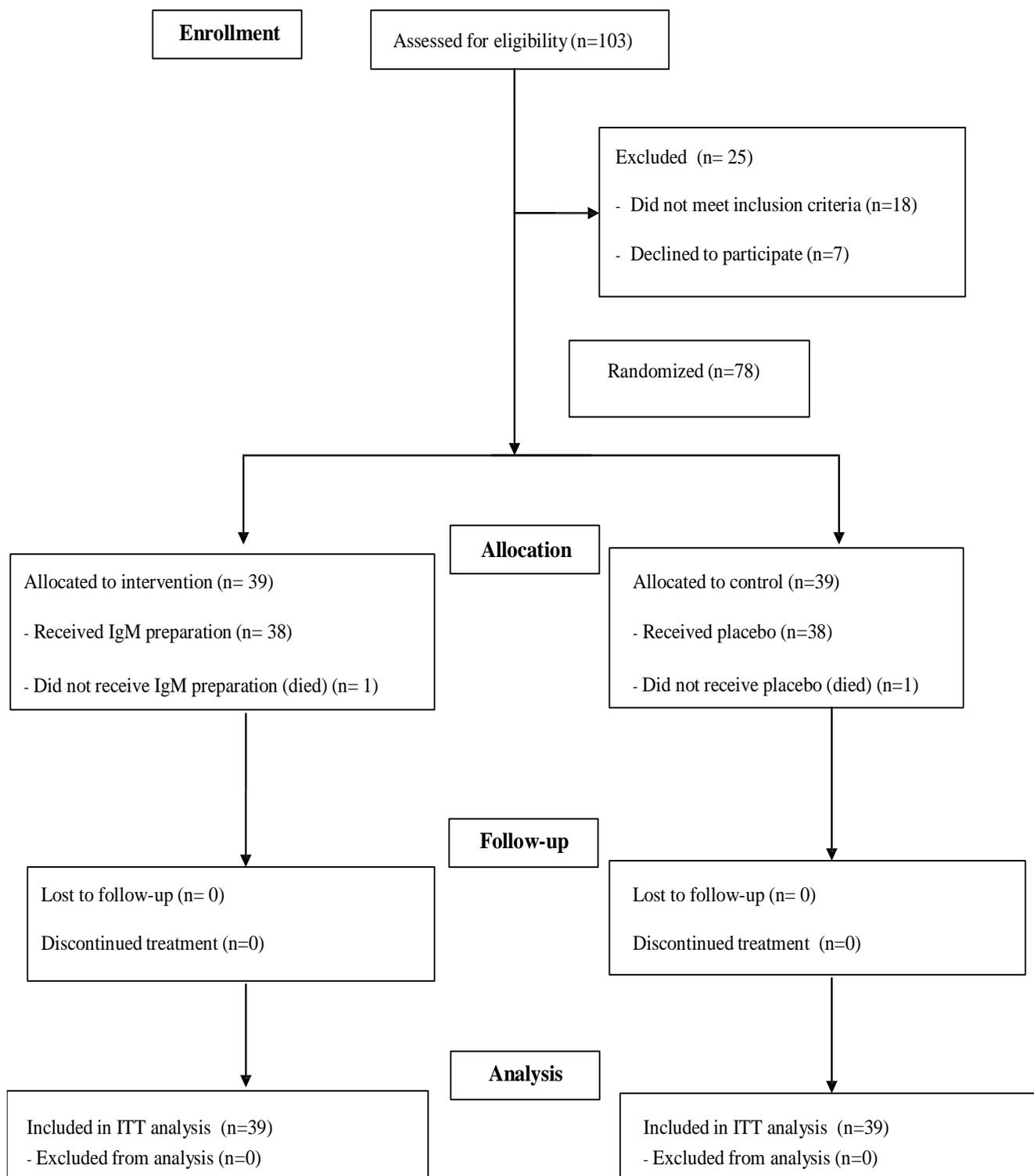All statistical analyses were performed with SPSS, version 16.0.

Figure 1. Patients included in the study

Results

A total of 78 consecutive patients (aged from one month to thirteen years) with proven sepsis were included in the study after adjusting for drop-outs and non-evaluable patients. There were no statistical differences between treatment groups in baseline characteristics at PICU admission (Table 1). One patient in each group died before receiving the full course of therapy. A four-month old patient died on the first day of treatment in the intervention group and a six-month old patient died on the second day of treatment in the control group. There were no major or minor violations of the protocol. No withdrawals, patient exclusions and or losses to follow-up occurred in either treatment group. Mean treatment duration in both groups was three days. No other concomitant treatments were given in addition to the study treatment in both groups.

Table 1. Baseline characteristics in the ITT population

Variable	Intervention group (N=39)	Control group (N=39)	P
Age (years)	2.1 (3.1) (1.07 – 3.08)[*]	1.8 (2.7) (0.87 – 2.66)	0.6
PICU stay (days)	5.1 (3.1) (4.08 – 6.06)[*]	7.1 (2.4) (6.35-7.90)	<0.01
Males (N, %)	25 (64.1) (48.4 – 77.2)[†]	29 (74.4) (58.9 – 85.4)	0.4
Body weight (kg)	12.9 (8.1) (10.4 – 15.6)[*]	12.3 (6.9) (10.0 – 14.5)	0.7
Height (cm)	84.7 (24.8) (76.7 – 92.8)[*]	83.0 (22.6) (69.9 – 87.8)	0.8
BMI	16.7 (0.92) (16.4 – 17.0)[*]	16.8 (24.8) (16.5 – 17.1)	0.8

[*] Data reported as mean (SD) (95%CI).

[†] Number (%) (95%CI).

Intention to treat analysis (ITT)

Overall, of the 78 patients included in this study, 59 (75.6%) individuals survived. However, the survival rate was higher in the intervention group (87.2%, N=34) than in the control group (64.1%, N=25), with the difference of 23.1% being statistically significant (P=0.03).

The odds ratio (OR) for survival was 3.8 (95%CI=1.2-11.9). A Kaplan-Meier survival analysis also showed a statistically significant difference in the survival rate in the intervention group (log-rank=4.0, P=0.04) [Figure 2].

Furthermore, LOS in the PICU was significantly shorter for patients in the intervention group, compared to the control group (5.1±3.1 days vs 7.1±2.4 days; P<0.01).

Twelve (30.8%) children in the intervention group and nine (23.1%) in the control group were mechanically ventilated without a significant difference between them (P=0.6).

Cardiac, pulmonary, renal, CNS (central nervous system) and adrenal dysfunctions were involved, as well as glycemic control disturbances. MODS (multiple organ dysfunction) in our study occurred in 8 (10.3 %) patients.

We used hydrocortisone in 18 (23.1%) cases with catecholamine resistance and suspected or proven adrenal insufficiency (total cortisol concentration <18mg/dL).
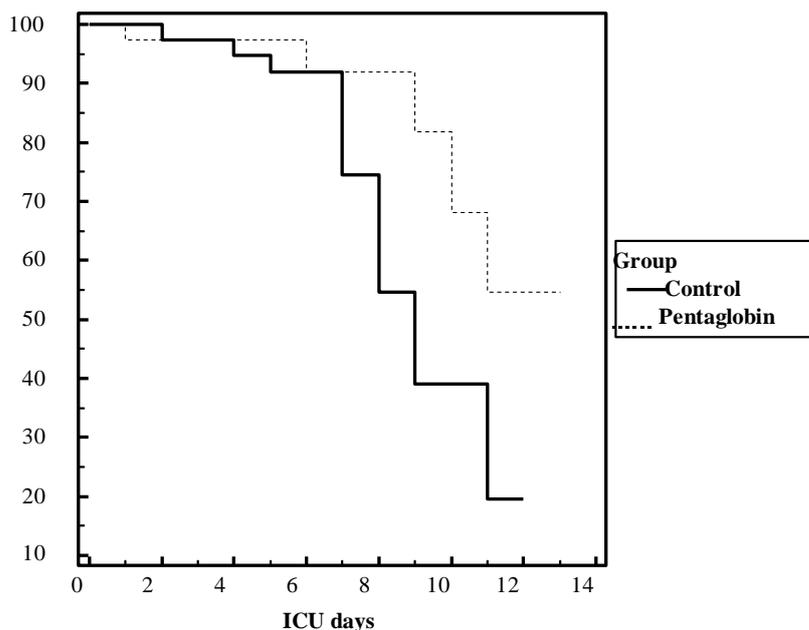
Figure 2. Kaplan-Meier survival analysis

Inotropes and vasopressors were administered in 26 (33.3%) patients. There was no surgical procedure involved during the study period.

The causes of death were renal failure, brain damage, hepatic failure, metabolic derangements, diffuse intravascular coagulation (DIC), ventilator-associated pneumonia (VAP).

No adverse events occurred during the study period. Additionally, no fatalities occurred after discharge from the hospital.

In our study we focused on anaphylactic reaction or anaphylactic shock to define an adverse event. Adverse reactions described in the enclosed leaflet of pentaglobine did not occur.

Blood samples were collected daily from each treatment group for the evaluation of hematological and laboratory parameters (Table 2). There were no statistically significant differences in the total WBC count, platelets, base excess in blood, and C-reactive protein levels between the two groups at baseline.

After treatment, the intervention group had statistically significant improvements in two inflammatory markers. Proportions of patients with C-reactive protein levels and total leucocyte and neutrophil counts <10000 were significantly higher in the intervention group, compared with controls (P=0.04 and P<0.01, respectively).

There were no significant differences in changes in platelet counts and base excess in blood between treatment groups.

Per-protocol analysis

In total, 59 (77.6%) of the 76 patients who completed treatment survived. The survival rate was higher in the intervention group (89.5%) than in the control group (65.8%), with the difference being statistically significant (P=0.03). A Kaplan-Meier survival analysis also demonstrated a statistically significant difference in the survival rate for the intervention group, with a hazard ratio of 3.1 (95%CI=1.1-8.6).

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Table 2. Patients with abnormal laboratory values before and after treatment

Laboratory parameter	Intervention group (N=39) n (%) of patients	Control group (N=39) n (%) of patients	P
Baseline			
WBC <10000	24/39 (61.5%)	25/39 (64.1%)	NS*
Platelets <40000	10/39 (25.7%)	9/39 (23.1%)	NS
Base excess>8	19/39 (48.7%)	20/39 (51.2%)	NS
C-reactive protein >N	29/39 (74.3%)	29/39 (74.3%)	NS
After treatment			
WBC <10000	10/39 (25.6%)	18/39 (46.2%)	<0.01
Platelets <40000	6/39 (15.4%)	8/39 (20.5%)	NS
Base excess>8	11/39 (28.2%)	20/39 (51.2%)	NS
C-reactive protein >N	12/39 (30.8%)	22/39 (56.4%)	0.04

*non-significant.

Discussion

Treatment of sepsis is complicated and typically requires a multidisciplinary approach. In recent years, the immunotherapeutic approach has been extensively studied but the results of both experimental and clinical investigations have been puzzling. The administration of monoclonal antibodies directed against specific sepsis mediators has produced disappointing results, whereas the administration of polyvalent immunoglobulins has been associated with better outcomes across various subgroups of patients (1,4,13). Recently, a number of studies have indicated that an IgM preparation is associated with reduced morbidity and an increased survival rate in patients with sepsis, severe sepsis or septic shock (2,14,17). In children, however, all the trials have been relatively small and the evidence is insufficient to support a robust conclusion of the benefit.

In the present study, administration of an adjunctive IgM preparation in septic pediatric patients resulted in a statistically significant increase in survival rate of 23.1% in the intervention group, compared to control group. Another interesting result was the significantly shorter mean LOS in the PICU for patients receiving the IgM preparation, compared with controls. A similar outcome in LOS was shown in a study by El Nawawy et al. in which the mean LOS in the intervention group who received the adjuvant IgM preparation was significantly shorter than in the control group, with durations of six and nine days, respectively (2). Furthermore, a study published fairly recently showed that early administration of the IgM preparation is crucial. Delay in administration significantly increased the absolute risk of death by 2.8% every 24 hours. Therefore, in this study, the IgM preparation was administered additionally to antibiotics on the day of sepsis diagnosis and study inclusion (18,19).

In a meta-analysis comparing two types of polyvalent immunoglobulin preparations, an IgM preparation was found to be superior over a standard immunoglobulin preparation which contains mostly IgG (20). Statistically significant increases were shown in the survival rates of

adult and neonatal patients with sepsis and septic shock when treated with the IgM preparation in addition to standard sepsis therapy (11). The pooled results showed a relative reduction in mortality of 34% in adult sepsis patients who received the adjunctive IgM preparation (relative risk: 0.66; P=0.0009). The standard adjunctive immunoglobulin preparation showed a relative reduction in mortality of only 15% (relative risk: 0.85; P=0.04). In neonates with sepsis, a relative reduction in mortality of 50% was reported for the adjunctive IgM preparation (relative risk: 0.50; P=0.0003). The standard adjunctive immunoglobulin preparation resulted in a relative reduction in mortality of only 37% (relative risk: 0.63; P=0.03) (11,14,21,22).

A head-to-head clinical trial in neonates with sepsis showed similar results. Haque et al. (20) conducted a clinical trial with these two different polyvalent immunoglobulin preparations (IgM or standard immunoglobulin preparations). A statistically significant increase in the survival rate in the group treated with the IgM preparation was shown when compared with the control group treated with the standard immunoglobulin preparation where no increase in survival rate was observed (8,9). Moreover, other clinical studies in neonates and children have shown increases in survival rates due to administration of an adjunctive IgM preparation of between 28%-56% (11,17,22,23) – further demonstrating a survival benefit from this treatment.

Efficacy of the IgM preparation in patients of all ages is thought to be due to higher antibody titers against a broader variety of bacterial pathogens and their toxic products compared with standard immunoglobulin preparations (7,10,24). Additionally, the immune system initially responds with the production of IgM as the first line of defense against bacterial pathogens and hence IgM antibody titers increase before IgG antibody production starts (23,25). Moreover, IgM is more efficient in activating the complement cascade and leads to a more rapid and specific antibody response, compared with IgG (15,25).

With respect to neonatal sepsis, the efficacy of an IgM preparation is possibly due to the relatively low IgM levels in neonates after birth. During pregnancy, only a low level of IgM is transferred via the placenta to the fetus and endogenous IgM production in neonates starts only gradually.

Conclusion

The use of an adjuvant IgM preparation Pentaglobin® in the treatment of pediatric sepsis patients resulted in an increase in the survival rate, a reduction in the LOS and an improvement in infection severity, all of which were found to be statistically significant in this study conducted in Albania.

Conflicts of interest: none declared.

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