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SHORT COMMUNICATION

Effects of IgM-Enriched Immunoglobulin Therapy in Septic-Shock–Induced Multiple Organ Failure: Pilot Study

Ildiko Toth · Andras Mikor · Tamas Leiner · Zsolt Molnar · Lajos Bogar · Tamas Szakmany

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Abstract Mortality due to septic-shock–induced respiratory failure remains high. A recent meta-analysis suggested that IgM-enriched immunoglobulin treatment may be beneficial in these patients. In this prospective randomised controlled pilot study we investigated the effects of IgM-enriched immunoglobulin treatment in patients with early septic shock accompanied by severe respiratory failure. 33 patients were randomly allocated to receive 5 ml/kg (predicted body weight) IgM-enriched immunoglobulin (16 patients) or placebo (17 patients), respectively, via 8 h IV-infusion for three consecutive days. Daily Multiple Organ Dysfunction Scores (MODS) were calculated. Serum C-reactive protein (CRP) and procalcitonin (PCT) levels were monitored daily. For statistical analysis two-way ANOVA was used. Daily MODS showed ongoing multiple system organ failure without significant resolution during the 8 days. Median length of ICU stay, mechanical ventilation, vasopressor support during the ICU stay and 28-day mortality were nearly identical in the two groups. Serum PCT levels showed no significant difference between the two groups, however, CRP levels were significantly lower in the IgM-enriched immunoglobulin group on days 4, 5 and 6, respectively. In this study the use of IgM-enriched immunoglobulin preparation failed to produce any improvement in the organ dysfunction as compared to standard sepsis therapy.

Keywords Septic shock · Immunoglobulin · Procalcitonin · Respiratory failure · Mortality · Organ failure · C-reactive protein

I. Toth · A. Mikor · T. Leiner · Z. Molnar · L. Bogar · T. Szakmany
Department of Anaesthesiology and Intensive Therapy, University of Pecs, Pecs, Hungary

A. Mikor · Z. Molnar
Department of Anaesthesiology and Intensive Therapy, Albert Szent-Gyorgyi University of Szeged, Szeged, Hungary

T. Szakmany
Department of Anaesthetics, Theatres and Critical Care, Cwm Taf LHB, Llantrisant CF72 8XR, Wales, UK

T. Szakmany (✉)
Department of Anaesthesia, Intensive Care and Pain Medicine, Medical School, Cardiff University, Cardiff, Wales, UK
e-mail: szakmanyt1@cardiff.ac.uk

Mortality due to acute respiratory failure accompanied by septic shock is around 50–70 % [1]. Although the Surviving Sepsis Campaign bundles showed significant mortality reduction in this patient population over the last decade, the proposed outcome is still poor [2, 3]. A recent meta-analysis suggested that polyclonal immunoglobulin treatment may be beneficial in these patients [4]. However, to date most of the available data are provided by retrospective analysis, rather than high-quality prospective randomised clinical trials [4–6].

In this prospective randomised controlled study we investigated the effects of polyclonal immunoglobulin treatment in patients with acute respiratory failure due to septic shock.

The local ethics committee approved the study protocol and written consent was obtained from the patients' next of kin. We included patients in our 10-bedded tertiary centre between 2003 and 2004 who fulfilled the following criteria: early reversible septic shock. "Septic shock" was defined by the ACCP/SCCM consensus [7]. "Early" was defined as the time from diagnosis of septic shock to study entry <24 h. "Reversible" meant that patients had to become

stable as a response to inotropic and vasopressor support within a few hours. The criterion of severe respiratory failure was defined as the requirement of mechanical ventilation with a $PaO_2/FiO_2 < 225$ mmHg (the limit was decided as determined by the respiratory organ dysfunction score ≥ 2 as monitored by the Multiple Organ Dysfunction Scoring system, MODS) [8]. Patients with chronic cardiovascular, chronic respiratory, chronic renal failure requiring renal replacement therapy, chronic liver failure, or with expected survival <24 h were excluded from the study.

Once included, patients were randomly allocated in a block-of-four fashion to receive 5 ml/kg (predicted body weight) IgM-enriched immunoglobulin (Pentaglobin® IV-IgGMA, Biotest Pharma Hungary. 100 ml contain 3.8 g IgG, 0.6 g IgM, 0.6 g IgA or an equivalent amount of 0.9 % NaCl, respectively, via 8 h IV-infusion. During the first 3 days of the study drug infusions were repeated daily. The investigators were blinded to the treatment allocation, but the attending medical and nursing staff were not.

All patients received routine intensive monitoring and therapy with lung-protective ventilation applying the open-lung concept with a PEEP of 5–25 cmH_2O. All patients received noradrenaline to maintain mean arterial pressure above 65 mmHg, and dobutamine was added to seven patients in each group for improving the cardiac index above 2.5 $l/min/m^2$. Antibiotics were used according to microbiological advice.

MODS scores were obtained daily during the first eight days of the study (t_{1-8}). Blood samples for measuring serum C-reactive protein (CRP) and procalcitonin (PCT) levels on top of routine laboratory tests were taken on inclusion then daily (t_{1-8}).

All data are presented as medians and interquartile range in parentheses. To test normal distribution the Kolgomorov–Smirnov test with the Lilliefors modification was used. Analysis of variance (ANOVA) was used for testing the significance levels between the different groups, and ANOVA for repeated measures was used for testing significance levels between the measurement stages. Data were analyzed comparing patients in the IgM-enriched immunoglobulin group with those in the placebo group on an intention-to-treat basis. For statistical analysis SPSS® version 10.0 was used. Statistical significance was considered at $p < 0.05$.

Prior to the study the number of patients required in each group was calculated by power analysis according to data obtained from a previous study in a similar patient population where the mean MODS was found to be 7 ± 3. The smallest difference between the means we regarded as clinically acceptable not to be overlooked was 50 % reduction in the IgM-enriched immunoglobulin group. With type I alpha of 5 % and type II (power) of 80 % we calculated we would need about 13 patients per group.

Thirty-three white Caucasian patients were recruited during the study period. 16 were randomized to the IgM-enriched immunoglobulin, and 17 to the placebo group.

The two groups were well matched for demographic and clinical characteristics on trial entry (Table 1). Median length of ICU stay, the length of mechanical ventilation, length of vasopressor support during the total interval of ICU stay, number of ventilator and shock-free days, and survival were nearly identical in IgM-enriched immunoglobulin and placebo groups (Table 1). Serum PCT levels were elevated and remained in the pathological range for the rest of the study indicating ongoing septic shock with no significant difference between the two groups (Table 2).

Serum CRP levels were high in both groups on inclusion to the trial, without significant difference. CRP levels were significantly lower in the IgM-enriched immunoglobulin group on days 4, 5 and 6, respectively (Table 2).

Table 1 Demographic variables, morbidity, and outcome in the two groups

	Placebo	IgM group
Age (years)	60 (50–63)	56 (50–65)
Sex (M/F)	4/13	8/8
SAPS II	25 (15–37)	26 (14–35)
Reason for ICU admission		
Pneumonia	5	4
Postoperative sepsis	6	7
Cardiac arrest	1	0
Pancreatitis	2	2
ARDS	3	3
Causative micro-organism		
MRSA	7	7
Eschericia coli	3	4
Candida albicans	1	1
Unkown	6	4
Length of stay on ITU (days)	26 (9–34)	15 (9–30)
Length of mechanical ventilation (days)	17 (6–29)	13 (8–20)
Length of inotropic support (days)	6 (3–9)	5 (1–9)
Ventilator-free days	0 (0–1)	0 (0–1)
Shock-free days	1 (0–4)	3 (1–7)
28-day survival	5/17	4/16
Cause of death		
Septic shock	8	8
ARDS	3	2
Coma	1	1
Uncontrolled haemorrhage	0	1

Data are presented as medians and interquartile ranges in parentheses. SAPS II and diagnoses indicate the severity score and diagnosis on admission to ICU

SAPS II Simplified Acute Physiology Score II, *MODS* Multiple Organ Dysfunction Score, *ARDS* acute respiratory distress syndrome, *MRSA* methoxicillin resistant *Staphylococcus aureus*

Table 2 Procalcitonin and C-reactive protein levels in the two groups

	PCT (ng/ml)		CRP (mg/l)	
	Placebo	IgM group	Placebo	IgM group
Day 1	10.00 (5.12–25.87)	9.44 (4.74–18.33)	216 (43–281)	226 (163–383)
Day 2	11.77 (2.34–24.83)	16.57 (3.51–26.92)	236 (110–426)	234 (105–451)
Day 3	12.96 (3.54–16.14)	16.28 (2.37–30.73)	274 (165–361)	222 (137–266)
Day 4	11.19 (3.11–16.51)	8.71 (2.59–18.97)	339 (174–450)	172 (100–238)[§]
Day 5	10.74 (2.32–36.32)	9.72 (3.56–19.94)	238 (130–266)	128 (74–263)[§]
Day 6	5.93 (0.57–12.88)	4.21 (1.56–15.35)	198 (128–311)	98 (61–151)[§]
Day 7	7.59 (0.68–16.70)	2.71 (1.10–16.16)	172 (148–205)	86 (62–148)
Day 8	6.41 (3.04–13.90)	11.74 (0.34–23.34)	145 (80–181)	102 (55–192)

Data are presented as medians and interquartile ranges in parentheses

[§] $p < 0.05$ between the two groups

Table 3 Clinical and biochemical changes in the two groups over the study period

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
MODS								
Placebo	7 (4–8)	6 (5–10)	8 (5–9)	8 (5–12)	8 (5–12)	6 (4–8)	6 (4–9)	5 (4–8)
IgM	7 (5–10)	9 (5–10)	8 (7–9)	8 (3–10)	9 (6–11)	8 (4–9)	8 (5–11)	9 (5–11)
White cell count (1,000/mL)								
Placebo	12.6 (4.2–15.0)	9.8 (5.8–18.6)	14.8 (11.8–19.1)	14.6 (4.8–20.1)	11.7 (8.7–24.3)	15.0 (10.8–21.7)	14.0 (11.1–23.2)	13.1 (8.1–18.2)
IgM	12.5 (7.9–16.4)	11.0 (99.1–15.9)	12.2 (8.3–15.9)	14.3 (6.0–19.1)	12.2 (7.5–17.3)	11.2 (8.1–11.2)	13.8 (8.6–15.8	14.8 (8.6–20.0)
Platelet count (1,000/mL)								
Placebo	158 (93–248)	154 (77–234)	222 (72–248)	194 (62–280)	166 (93–264)	188 (150–270)	223 (133–298)	206 (120–248)
IgM	129 (85–207)	110 (66–137)	88 (71–177)	97 (45–185)	116 (45–203)	156 (63–270)	105 (67–334)	119 (47–322)
PTT (s)								
Placebo	59 (46–73)	56 (45–77)	64 (53–83)	66 (53–71)	58 (52–74)	61 (51–74)	68 (59–83)	67 (57–69)
IgM	48 (36–58)	51 (41–66)	59 (47–70)	58 (45–79)	63 (46–79)	58 (45–79)	61 (51–74)	68 (59–83)
Total protein (g/l)								
Placebo	40 (34–59)	44 (36–46)	43 (36–47)	47 (40–53)	45 (42–48)	46 (35–50)	47 (41–51)	44 (42–54)
IgM	42 (32–49)	43 (40–48)	50 (39–52)	50 (38–54)	45 (38–52)	49 (42–54)	46 (42–54)	42 (39–53)
Albumin (g/l)								
Placebo	18 (14–24)	17 (13–22)	19 (18–24)	19 (14–21)	18 (13–20)	17 (13–21)	18 (15–24)	17 (11–26)
IgM	16 (14–23)	18 (15–21)	20 (12–23)	18 (13–22)	18 (15–24)	18 (15–25)	21 (15–25)	20 (15–25)

Data are presented as medians and interquartile ranges in parentheses

MODS Multiple Organ Dysfunction Score

Daily MODS showed multiple system organ failure, which did not change significantly during the 8 days of observation (Table 3). Other conventional markers of organ dysfunction such as platelet count, prothrombin time, total protein and albumin levels and markers of infection such as white blood cell count were nearly identical in the two groups throughout the study period (Table 3). Blood gas parameters such as pH and base excess were also similar, together with temperature (data not shown).

In this study we observed a similar degree of organ dysfunction with the use of IgM-enriched immunoglobulin preparation as compared to standard sepsis therapy in patients with septic shock accompanied by severe respiratory failure.

Our results are in line with the findings of the recent meta-analysis by the Cochrane group, where pooled data from high-quality trials failed to support the routine use of polyclonal immunoglobulins in severe sepsis [4]. High-

quality trials showed a relative risk of 1.02 (95 % CI 0.84–1.24), whereas other trials with inadequate or unclear concealment of allocation showed a relative risk of 0.61 (95 % CI 0.50–0.73) [4]. Laupland et al. reached similar conclusions in their meta-analysis which included data from the very recent SBITS trial [9, 10]. On the other hand Kreymann et al. [11] found that IgM-enriched immunoglobulins reduced mortality by 34 % in adults and by 50 % in neonates in their systematic review. If we examine possible explanations for inconsistency of the literature, the dosage, the timing of immunomodulatory therapy and the etiology of infection should be taken into consideration. In previous trials most investigators applied a total amount of approximately 500 ml IgM-enriched immunoglobulin for 3 consecutive days [9]. In this study we applied a predicted bodyweight-based approach and administered approximately 300 ml IgM-enriched immunoglobulin daily. There are some data available to indicate that higher doses for a longer duration might yield better results, however, the correct dose of polyclonal immunoglobulins in septic shock has yet to be established [12].

Compared to the trials where immunoglobulin was administered as a prophylactic adjuvant and was able to show risk reduction in patients with postoperative infections, our patients received the treatment in a later stage of the septic process [13, 14]. Although we included patients with early septic shock, it is possible that the administration of IgM-enriched immunoglobulins was too late, as the evolution of organ dysfunction was driven by the host response rather than the infective pathogen itself [15].

Most of the trials, where there was an improvement in the patient's clinical course, investigated sepsis caused by predominantly Gram negative bacteria [16]. In our study the patients' admission diagnoses to ICU were diverse. This means they had varied clinical backgrounds and likely pathogens causing sepsis. In fact, in both groups the causative organism was MRSA in 7 patients, which again might explain the lack of effect (Table 1). In contrast to recent trials, we have failed to demonstrate any clinically significant effect on the inflammatory markers in the IgM-enriched immunoglobulin group [17]. Namely, PCT levels were nearly identical in the two groups and did not change during the course of the study, signifying ongoing septic shock. Although we have seen a steady state in the CRP levels during the IgM-enriched immunoglobulin treatment then a continuous decline compared to the raised CRP levels in the placebo group, this did not correspond with the clinical course of septic shock, reflected by the unchanged MODS scores throughout the study. Therefore, the clinical importance of the observed statistically significant difference in the CRP levels between the IgM-enriched immunoglobulin and placebo groups is questionable.

There are several limitations in our study which should be considered. Our trial was a pilot study performed in a relatively small group of patients with septic shock accompanied by severe respiratory failure. Although the predicted and observed MODS scores on inclusion were identical (7 ± 3 in both groups), giving strong internal validity to our data, increasing the number of patients could confirm a change in the severity of organ dysfunction as a result of using IgM-enriched immunoglobulin. The all-cause mortality seems to be high, however, as multiple organ failure affecting 4 or more organs was not resolved during the study period, the 28-day outcome is comparable with other trials [18].

To show a significant impact on mortality of polyclonal immunoglobulin administration in septic shock, according to our power calculations, a large, transparently reported, multicentre randomized study with $\sim$850 patients per group would be needed, which could only be accomplished with international collaboration. In conclusion, our results do not support the routine use of polyclonal immunoglobulins in early septic shock and respiratory failure until such trial is reported in the literature.

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