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ORIGINAL ARTICLE

IgM and IgA enriched polyclonal immunoglobulins reduce short term mortality in extremely low birth weight infants with sepsis: a retrospective cohort study

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ABSTRACT

BACKGROUND: Immunoglobulin supplementation is a debated strategy in fighting sepsis. We evaluated a polyclonal IgM and IgA enriched immunoglobulin (IgMeIVIG) preparation in reducing the short-term mortality in extremely low birth weight neonates (ELBW) with proven infection.

METHODS: ELBW infants born from January 2008 to December 2014 were eligible for this retrospective case-control analysis if they were symptomatic and had a positive blood culture after 72 hours of life. Patients received antibiotic treatment with or without IgMeIVIG (intravenously, 250 mg/kg/day for 3 days) within the 24 hours from clinical suspicion as per indication of the attending physician. Short-term (7 and 21 days) mortality was the study primary outcome while secondary outcomes were: mortality at discharge, intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, periventricular leukomalacia, and retinopathy of prematurity.

RESULTS: Each group was composed by thirty-nine infants. Both groups were similar for antenatal steroids, mode of delivery, birth weight, gestational age and SNAPII score as indicator of disease severity. Infants receiving IgMeIVIG had a significantly lower short-term mortality compared with neonates receiving antibiotics alone: 6/39 (15%) *vs.* 14/39 (36%); P=0.038. No differences in other outcomes were found.

CONCLUSIONS: This study shows that IgMeIVIG may have a role as adjuvant therapy in ELBW infants with proven sepsis. We warrant future prospective, blinded RCT studies where IgMeIVIG can be consistently used if needed throughout the NICU admission in ELBW septic neonates to appropriately evaluate its effect on mortality at discharge.

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KEY WORDS: Immunoglobulins, intravenous; Neonatal sepsis; Infant, extremely low birth weight.

Immunoglobulin supplementation has long been used against systemic infection. Opsonization and complement activation are among the mechanisms by which immunoglobulins can adjuvate the effects of antibiotics. Compared to standard immunoglobulins, these functional properties are potentiated by the use of polyclonal IgM and IgA enriched immunoglobulins (IgMeIVIG) that have been showed to have better bacterial antigen or toxin binding and streptococcal super antigen neutralization.[1, 2] IgMeIVIG are, therefore a potentially useful choice for a disease that still carries a high mortality rate. Along the years, the scientific community has kept an alternating attitude toward passive immunotherapy differentiating adult *versus* neonatal patients and standard

versus IgMeIVIG.[3-6] Current recommendations advice against this strategy, irrespectively of patient age or immunoglobulin preparation. Yet, this stern change of policy stems from a relatively small number of papers that have either a small power and weak design[7] or disputable primary outcomes.[8] In the INIS study, a large randomised, placebo controlled, double blind trial, treatment with standard immunoglobulins was given at an average age of 8 days for suspected sepsis but the primary endpoint was set as mortality and disability at 2 years of corrected age. Theoretically, a definitive conclusion can be drawn by an appropriately powered, prospective, randomized controlled trial with coherent methodology but such an expensive and time-consuming work is hardly likely to be conducted withstanding the current recommendations. We present a proof of concept, retrospective, cohort study focusing on the effect of administration of IgMeIVIG on the short-term mortality of a population of symptomatic extremely low birth weight neonates (ELBW) with sepsis confirmed by positive blood culture.

Materials and methods

A retrospective case-control cohort study was conducted at the Neonatal Intensive Care Unit of the University "Federico II" of Naples Italy, a level III unit serving the largest delivery place in the Naples regional area, from January 2008 to December 2014.

All charts of infants with a birth weight less than 1000 grams were reviewed and were included in the investigation all symptomatic neonates who had a positive blood culture after 72 hours of life that confirmed the late onset sepsis.

The definition of sepsis was taken from the Vermont Oxford Network (VON) criteria,[9] *i.e.*:

• sepsis by coagulase negative staphylococcus: pathogen recovered from either a central line, or peripheral blood sample in association to one or more signs of generalized infection and treatment with 5 or more days of intravenous antibiotics after the above cultures were obtained;

• sepsis by other bacteria: bacterial pathogen recovered from blood culture;

• sepsis by fungi: fungus recovered from a blood culture obtained from either a central line or peripheral blood sample.

Clinical signs for the diagnosis of systemic infection that led physicians to obtain a blood culture were: apnea, mottled skin, temperature instability, feedings intolerance, significant abdominal distension, respiratory distress and hemodynamic instability. Laboratory criteria suspected for sepsis were: elevated CRP (cut off =1 mg/dL), abnormal leucocyte count (cut off less than 5000/μl or more than 20000/μl) and I/T ratio(cut off >0.2). We calculated the SNAP II Score to evaluate the clinical gravity of sepsis. This score is an accurate mortality predictor of severe neonatal sepsis[10] including six physical parameters (hypotension, hypothermia, acidosis, PO2/FiO2 ratio, multiple seizures, urinary output); we calculated it for each patient at the onset (in the first 24 hours) of clinical signs of sepsis.[11]

Exclusion criteria were major congenital anomalies and TORCH group infections.

After sepsis was suspected, intravenous antibiotic therapy was started with amikacin and vancomycin as NICU protocol. The attending physician had the faculty to additionally prescribe IgMeIVIG (Pentaglobin® Biotest Germany - a preparation of polyclonal IgG immunoglobulins enriched with IgM and IgA) 250 mg/kg/die for 3 days IV, to be administered shortly after (and always within 24 hours) clinical sepsis suspicion.

Primary outcome was short-term mortality (*i.e.* death within 7 and 21 days from treatment onset), while secondary outcomes were: mortality at discharge, rate of intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) at discharge.

Meticulous care was exerted to ascertain that no other major change had been made that could have been relevant to the outcome (*i.e.* central lines managing and duration; fluconazole prophylaxis against invasive fungal infections; handwashing and other general prophylactic measures; enteral nutrition protocol) during the study period.

Statistical analysis

Statistical Package for Social Sciences (SPPS) 19.0 was used to evaluate the main characteristics

of study population and the differences between groups. *t*-test for independent variables was used to compare quantitative parameters between two samples. Mann-Whitney Test was used to analyze qualitative variables and a P value less than 0.05 was considered statistically significant. Multivariate logistic regression analysis was applied to identify independent risk factors of mortality between the main characteristics of the study population (gestational age, birth weight, Snap II score, prenatal steroids, CRP positive). Kaplan-Meier analysis was conducted to plot the survival curves.

Results

During the study period 319 ELBW neonates were admitted to the NICU and 78 were symptomatic for sepsis confirmed by a positive blood culture after 72 hours of life. Demographic characteristics are shown in Table I. Comparing treated (N.=39) *versus* untreated (N.=39) infants, no difference was found in birth weight, gestational age, mode of delivery while a non statistically significant difference was noted in SNAP II score and CRP positivity, both higher in the treated group. Pathogens responsible for systemic infection were more frequently Staphylococci and Candida sp. (Figure 1). The rate of Candida sp. sepsis was similar between groups. Mortality after 7 and 21 days from therapy onset were identical and significantly decreased in the passive immunotherapy group: 6/39 (15%) *vs.* 14/39 (36%); P=0.038. No differences in mortality at discharge, IVH, PVC, NEC, ROP and BPD was found between treated and untreated groups (Table II). Multivariate logistic regression analysis did not identify independent risk factors of short-mortality. Kaplan-Meier curves are shown in Figure 2, 3.

Discussion

Our data show that administration of IgMeIVIG is effective in reducing the short-term mortality in ELBW babies with documented systemic infection. Our observations substantially contradict recent Cochrane Library recommendations.[5] The latter discourage passive immunotherapy drawing 80% of the evidence from the INIS study.[8] Besides the already mentioned long distance in time between a punctual intervention and the study primary outcome, this large, international RCT raises several methodological concerns. Not all centers used the same standard immunoglobulin preparation. The study took 6 years to completion, a time interval when, according to VON, the global rate of late onset sepsis decreased significantly in preterm neonates. It is not clear how soon after the clinical suspicion was the drug given and it is known that exogenous IgG has a serum half-life around 2 weeks in

TABLE I.—*Main characteristics of the whole study population.*

IgM-IVIG	Treated N.=39	Untreated N.=39	P
Gestational age (weeks)	26.1±1.9	25.7±2.2	NS
Birth weight (grams)	744±142	692±152	NS
Snap II score	18 (46%)	14 (35%)	NS
Prenatal steroids	21 (53%)	21 (53%)	NS
CRP positive	34 (87%)	25 (64%)	NS

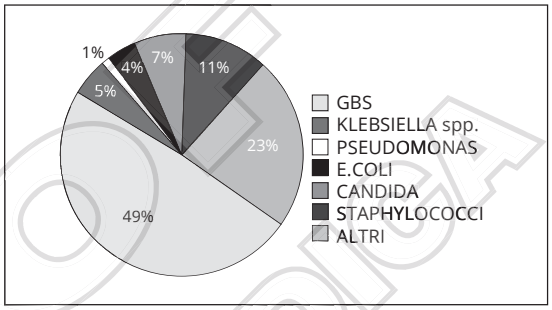

Figure 1.—Main pathogens isolated from blood cultures.

TABLE II.—*Primary and secondary outcomes of the whole study population.*

IgM-eIVIG	Treated N.=39	Untreated N.=39	P
Short term mortality	6 (15%)	14 (36%)	0.038*
Antibiotictherapy (days)	30±29	14±25	0.019*
Hospitalization (days)	95±72	65±61	0.048*
Mortality at discharge	14 (35%)	15 (38%)	NS
IVH	12 (30%)	9 (23%)	NS
PVL	4 (10%)	3 (7%)	NS
NEC	2 (5%)	2 (5%)	NS
BPD	13 (33%)	6 (15%)	NS
ROP	16 (41%)	11 (28%)	NS

P<0.05.

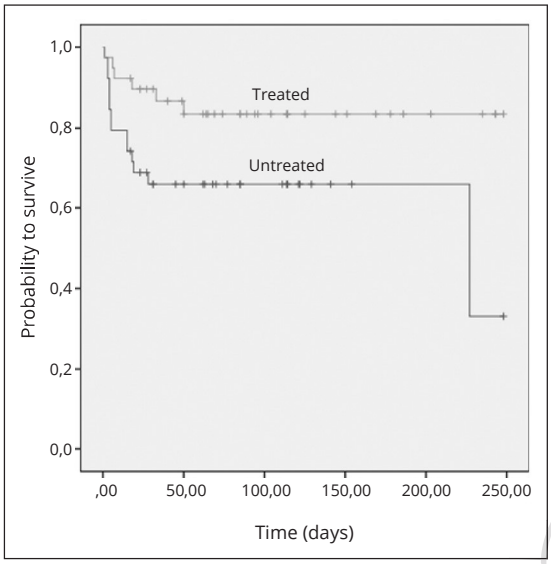

Figure 2.—Kaplan Meier plot for short term survival in patients stratified for treatment with IgM enriched polyclonal immunoglobulins.

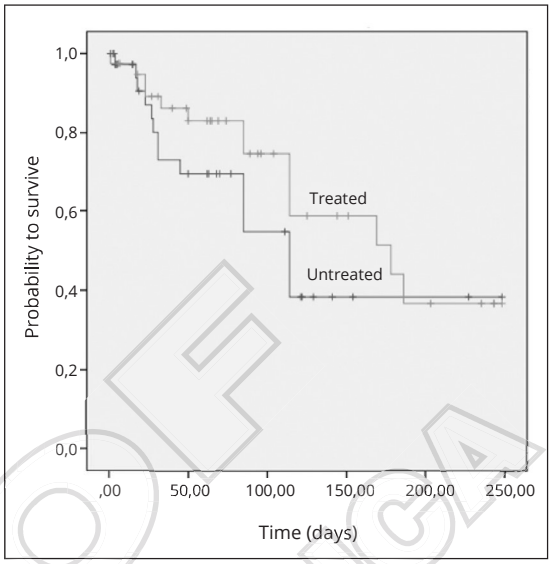

Figure 3.—Kaplan Meier plot for overall survival in patients stratified for treatment with IgM enriched polyclonal immunoglobulins.

preterm[12] while the average admission lasted 64 days and 28% treated infants had at least a second sepsis episode, where immunoglobulins were not administered, that might have been a significant confounder. Finally, the authors do not explain why they did not consider IgMeIVIG for their investigation. Adults patients receiving IgMeIVIG within 24 hours from the onset of severe sepsis or septic shock show a significantly lower mortality, demonstrating a time dependence of such treatment.[13, 14] Also, a recent retrospective study showed in 100 adults that IgMeIVIG added to antimicrobial treatment for septic shock caused by multidrug-resistant Gram-negative bacteria decreased the mortality at 28 days.[15] Giamarellos-Bourboulis showed that endogenous IgM levels decreased in adult patients deteriorating from severe sepsis to septic shock; in the study population the endogenous IgM distribution over time was significantly greater for survivors than for non-survivors and the IgM production by peripheral blood mononuclear cells was significantly lower at all stages of sepsis compared with healthy controls.[16] These interesting new results underline the pivotal role of IgM in sepsis defense and suggest a customized approach in supplementing promptly with IgMeIVIG.[17] Studies in the septic neonate with IgMeIVIG have been underpowered and contradictory. In a randomized trial of 60 Saudi septic neonates of various gestational ages, Hacque *et al.* showed that IgMeIVIG significantly decreased total mortality.[18] In a second paper, the same authors showed in a larger cohort that IgM-eIVIG, but not S-IVIG, was effective in reducing mortality.[19] However, a more recent paper by Akdag *et al.* came to opposite conclusions, inducing the 2015 Cochrane review[5, 7] not to recommend IgMeIVIG as routine adjuvant therapy in neonatal sepsis and to discourage further studies. We underline that Akdag *et al.* in their study enrolled both premature and term neonates with proven or suspected sepsis, they calculated the sample size on mortality for NEC (that is approximately zero among term infants) during a clinical episode of sepsis with a statistical power of 50%. Our current data, as our previous paper on a cohort of VLBW neonates,[20] show the efficacy of a prompt IgMeIVIG supplementation, in keeping with the earliest observations. We provide a similar patient population with the lowest birth weight and certainly affected by systemic infection where the demonstrated short term benefit has a strong biological rationale. The higher number of days on antibiotics for treatment group may be related to the lower short-term mortality for this group.

The retrospective character of our approach is an obvious and significant limitation. However, the trend to a higher SNAP-II score and CRP positivity rate in the treated group might indicate that physicians used IgMeIVIG when they perceived a more severe disease, acting as a bias against the treatment group.

Conclusions

In conclusion, this study shows that IgMeIVIG may have a role as adjuvant therapy in ELBW infants with proven sepsis. We warrant future prospective, blinded RCT studies where IgMeIVIG can be consistently used if needed throughout the NICU admission in ELBW septic neonates to appropriately evaluate its effect on mortality at discharge.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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