Comparison of Adjunctive Treatment with IgM-Enriched IVIG and Antibiotics Alone in Treatment of Neonatal Sepsis

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ABSTRACT

Objective: The primary objective of this study was to compare the clinical and laboratory outcomes and the mortality rate of neonatal sepsis treated with antibiotics and IgM-enriched IVIG as adjunctive therapy versus antibiotic alone. In addition, the secondary objective was to determine the morbidities and safety following the IgM-enriched IVIG treatment and the duration of mechanical ventilation and length of hospital stay.

Methods: A retrospective cohort study was conducted between January 2016 to December 2018 in Naresuan University Hospital, Thailand. All eligible neonates were divided into 2 groups. The control group received antibiotics alone. The intervention group received both antibiotics and IgM-enriched IVIG. The clinical, laboratory parameters and morbidities were collected and compared.

Results: There were 28 neonates enrolled in the study. There were 14 in each group. In the intervention group, after receiving the 3-day course of IgM-enriched IVIG concurrently with antibiotics, the patients had significantly decreased respiratory rates (p=0.022), increased mean arterial pressure (p=0.049) and increased serum pH (p=0.017). The incidence of intraventricular hemorrhage, necrotizing enterocolitis, periventricular leukomalacia and patent ductus arteriosus in preterm neonates were not found to be significantly changed in both control and intervention groups. No adverse effects recorded.

Conclusion: The use of IgM-enriched IVIG as adjunctive treatment in neonatal sepsis showed evidence of improvement in some clinical and laboratory parameters in neonates presented with hypotension and DIC. The mortality rate improvement was inconclusive and the use of IgM-enriched IVIG was not found to reduce morbidities in preterm neonates.

Keywords: Neonatal sepsis; intravenous IgM-enriched IVIG; intravenous immunoglobulin; antibiotics (Siriraj Med J 2021; 73: 84-91)

INTRODUCTION

In 2015, the World Health Organization (WHO) reported that there were almost 2.6 million newborn deaths per year and most of them were caused by neonatal sepsis.[1] The Expert Meeting on Neonatal and Pediatric Sepsis in 2010 defined that neonatal sepsis is a condition of which clinical manifestations and laboratory investigations compatible with infection, although no evidence of infection (through microbiological cultures or polymerase chain reaction (PCR).[1] Premature birth and newborn with extremely low birthweight are prone to have a severe infection. Moreover, premature neonates are susceptible to pathogens especially from gram-negative bacteria requiring maternal serum immunoglobulin G (IgG) for opsonization to activate phagocytic activity. However, maternal serum IgG is inadequate in premature neonates and the immune system,

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integumentary system, and thymus glands are not fully developed.[2] There were some evidence reported that the use of intravenous immunoglobulins (IVIG) can enhance immunity functions such as opsonization, complement activity, antibody dependent-cytotoxicity, and neutrophil chemoluminescence.[3-6] The newer studies found that the IgM- enriched IVIG have a higher opsonization activity, specific complement activation and phagocytic activity, and more potent agglutination strength than IVIG.[5,7]

The diagnosis of neonatal sepsis is through comprehensive assessment when a newborn exhibits at least two clinical manifestations and two main laboratory findings. Clinical manifestations involve temperature instability, cardiovascular instability, skin and subcutaneous lesions (petechial rash, sclerema), respiratory instability, gastrointestinal disturbances, and other non-specific symptoms such as irritability and hypotonia. The main laboratory findings include but not limited to leukopenia or leukocytosis, increased immature to total neutrophil (I/T) ratio, thrombocytopenia, increased serum C- reactive protein (CRP) or procalcitonin, glucose intolerance and metabolic acidosis.[1]

Timely antibiotic therapy of neonatal sepsis is necessary without the need for positive microbiological cultures to reduce the delay of treatment. Antibiotics are still the most important specific treatment of neonatal sepsis. Various studies reported substantial outcome improvement, especially in severe cases who received intravenous immunoglobulin (IVIG), and IgM-enriched IVIG as adjunctive treatment.[2,4-6,8-19] However, in 2015, the International Neonatal Immunology Study Group (INIS Collaborative Group) and Cochrane Review published that certain studies showed no distinction in mortality rates between newborns with neonatal sepsis treated with antibiotics alone compared to those treated with both IVIG and antibiotics.[20] In contrast, IgM-enriched IVIG proved to considerably reduce the mortality rate of neonatal sepsis when incorporated as a concomitant to antibiotics.[2-3,5,10-11,13,21-22] Newer studies reported positive changes in symptoms and laboratory results among severely underweight newborns with suspected or confirmed neonatal sepsis after receiving IgM-enriched IVIG. IgM-enriched IVIG also found to decrease mortality rates on day 7 and day 28.[13,21-23] Currently, there are very few studies involving the effectiveness of IgM-enriched IVIG with antibiotics for treatment of neonatal sepsis in Thailand.

The primary objective of this study was to compare the clinical and laboratory outcomes and the mortality rate of neonatal sepsis treated with antibiotics and IgM-enriched IVIG as adjunctive therapy versus antibiotic alone. In addition, the secondary objective was to determine the morbidities and safety following the IgM-enriched IVIG treatment and the duration of mechanical ventilation and length of hospital stay.

MATERIALS AND METHODS

The retrospective cohort study was conducted between January 2016 to December 2018. Data were collected from all infants in Naresuan University Hospital, Phitsanulok, Thailand. The Institutional Review Board of Naresuan University (COA No. 296/2019 IRBNo. 0364/2020) approved this study. The inclusion criteria were neonates with a gestational age of 24 to 40 weeks and 500 to 4,000 grams birthweight diagnosed with neonatal sepsis by ICD-10 and admitted in NICU. The exclusion criteria were neonates with prenatal diagnosis of chromosomal abnormalities, congenital anomalies and congenital infections (TORCH). Neonates included in the study received the standard antibiotic treatment whereas some eligible neonates were given intravenous IgM-enriched IVIG (Pentaglobin®) 5 ml/kg per day for three consecutive days as an adjunctive treatment. The subjects were divided into 2 groups. The first group (the intervention group) comprised of neonates who received antibiotics and IgM-enriched IVIG as an adjunctive treatment while the second group (the control group) consisted of neonates who received antibiotics alone. The decision to prescribe an adjunctive treatment depended on the physician's assessment and the family's financial capability. Data records collected contains the demographic details of the infants (gestational age, sex, birth weight, mode of delivery, age at diagnosis of sepsis and age at treatment initiated), maternal antenatal corticosteroid and antibiotic uses, timing of membrane ruptured and maternal chorioamnionitis. The clinical characteristics collected at time of the sepsis diagnosis consists of feeding intolerance, respiratory distress, hypotension and Disseminated Intravascular Coagulation (DIC). The data collected were analyzed according to the source of infection, clinical and laboratory parameters, culture results before and after the treatment in both groups. The clinical and laboratory information obtained from the control group were 48-72 hours after antibiotic administration, whereas, data gathered in the intervention group were 24 hours after the 3-day course IgM-enriched IVIG infusion. Other comorbidities and complications recorded were grade 2 intraventricular hemorrhage, necrotizing enterocolitis, periventricular leukomalacia, and patent ductus arteriosus. Additional data monitored were the duration of mechanical ventilation, length of hospital stay, and mortality rate on the 7th day and 28th

day. The notable IgM-enriched IVIG adverse effects evaluated were hypotension, anaphylaxis, and rashes.

Statistical analysis

Data were analyzed using SPSS version 22 (IBM Corp., Armonk, NY). Continuous data were shown as mean ± standard deviation (SD). Categorical data were shown as frequency and percentage. The pair t-test was used to compare the results before and after treatment. Independent T-test, Chi-square tests and Fisher's exact test were used to compare data between control and intervention groups. The comparison of changes of parameters between the two groups was performed by mixed linear regression. The absolute differences between the two groups of treatment with the p- value < 0.05 are considered to be statistically significant.

RESULTS

There were 166 neonates diagnosed with neonatal sepsis from 1,860 infants born between January 2016 and December 2018. There were 14 neonates in the intervention group given IgM-enriched IVIG as an adjunctive treatment while the other 152 received antibiotic alone. The 14 neonates in control group were taken from the 152 neonates through by blocked randomization. Table 1 provides the demographic details and information of each group. After comparing between the two study groups, there were no differences found related to patient characteristics and timing of antibiotic received.

Table 2 shows the clinical characteristics at the time of neonatal sepsis diagnosis. These clinical characteristics were quite similar between these two groups. 9 out of 14 (64.3%) patients in the intervention group had hypotension, whereas 2 out of 14 (14.3%) in the control group (p-value 0.007). Disseminated intravascular coagulation (DIC) was frequently found in the intervention group (9 vs. 0 with P-value <0.001). Necrotizing enterocolitis (NEC) and hospital-acquired pneumonia (HAP) were found to be the source of infection in the intervention group (5 vs. 0 with P-value 0.014). Early neonatal sepsis was found more in the control group (9 vs. 14 with P-value 0.014).

After the 3-day course of IgM-enriched IVIG along with antibiotics, patients in the intervention group had significantly decreased respiratory rates (68.18±10.94 vs. 60.80±4.13 with p-value 0.022), increased mean arterial pressure (MAP) (40.36±15.36 vs. 46.43±15.04 with p-value 0.049) and serum pH (7.28±0.11 vs. 7.36±0.09 with p-value 0.017) comparable to the value prior to treatment. In the control group, white blood cell count was significantly decreased after antibiotic treatment (15,709.29±1,601.15 vs. 10,792±1,206.88 with p-value 0.041) as shown in Table 3.

There was no remarkable difference in microbiological culture values after treatment was administered in both study groups (Table 4).

Duration of mechanical ventilation and length of hospital stay in the intervention group were found to be longer than those in the control group (50.85±12.62 vs. 8.14±5.71 with P- value 0.007, 97.00±16.93 vs. 21.79±8.80 with P-value 0.001). No difference in mortality rate at day 7 and day 28 was recorded in both groups (0(0%) vs. 0(0%)). After the mixed linear regression analysis, the estimated difference between the intervention and control groups on account of the duration of mechanical ventilation and length of hospital stay (adjusted for changes in respiratory rate, mean arterial pressure, and pH) was 29.03 days (95%CI -7.10 to 65.17, p = 0.108) and 42.98 days (95%CI -1.99 to 87.95, p = 0.060) respectively, resulting to insignificant change between groups as shown in Table 5.

After performing subgroup analysis, the results of morbidities in preterm neonates were shown in Table 6. The incidence of intraventricular hemorrhage at least grade 2, necrotizing enterocolitis, periventricular leukomalacia and patent ductus arteriosus were not found to be significantly changed in both groups.

No adverse effects consisting of hypotension, anaphylaxis and rash found during and 24 hours after IgM- enriched IVIG therapy.

DISCUSSION

This study was initiated to evaluate the efficacy of IgM-enriched IVIG as adjunctive treatment for neonatal sepsis in Thailand. A previous study conducted by Kola E, et al. showed that neonates with sepsis who received IgM-enriched IVIG had a significant increase in survival rate and a significant reduction in length of hospital stay as compared to neonates who were given antibiotics and placebo.[12] In Capasso et al. study, similar findings were also reported regarding the IgM-enriched IVIG therapy in infants and showed a reduction in short - term mortality in neonates (OR 0.16; 95% CI 0.3-0.7).[2,13,21] In the meta-analytical study conducted by Kreymann et al., they found that from 12 trials on 710 neonates, polyvalent immunoglobulins (IgGAM) had a significant effect on mortality in sepsis and septic shock.[5] On the other hand, Ohlsson A and Lacy JB reported no evidence for the reduction of mortality or other relevant outcomes of 3,973 neonates who received IVIG. In addition, subgroup analysis for IgM- enriched IVIG from this study was performed (N = 266) and there was no indication that

TABLE 1. Demographic data.

Characteristics	Intervention n=14 (%)	Control n=14 (%)	P-value
Gestational age (week)			
< 37	12 (85.7)	10 (71.4)	0.357
≥ 37	2 (14.3)	4 (28.6)	
Sex			0.131
Male	9 (64.3)	5 (35.7)	
Female	5 (35.7)	9 (64.3)	
Birth weight (gram)			0.115
< 2,500	11 (78.6)	7 (50.0)	
≥ 2,500	3 (21.4)	7 (50.0)	
Mode of delivery			0.303
Normal labor	3 (21.4)	1 (7.1)	
Cesarean section	10 (71.4)	13 (92.9)	
Vacuum extraction	1 (7.2)	0 (0.0)	
Antenatal corticosteroid received	7 (50.0)	2 (14.3)	0.103
Maternal prolonged PROM (>18 hour)	1 (7.1)	5 (35.7)	0.065
Maternal received antibiotic	2 (14.3)	6 (42.9)	0.094
Maternal chorioamnionitis	2 (14.3)	0 (0.0)	0.142
Timing of antibiotic received (hour)	7.77±2.85	8.43±2.87	0.871

its use would significantly reduce mortality in infants with suspected infection (Risk ratio 0.68; 95% CI 0.39-1.20).[20] However, the results of this study only revealed the mortality outcome.

Our study did not find a difference in the mortality rate as there were no recorded deaths on day 7 and day 28. The length of hospital stay was longer in the intervention group. This may be caused by the more severity (hypotension and DIC) in the intervention group at time of sepsis. However, the duration of mechanical ventilation and the length of hospital stay were insignificant between groups as revealed in the mixed linear regression analysis.

In a study conducted by Salihoglu O, et al., I/T ratio and CRP level were significantly decreased and a substantial increase in the pH and base excess were recorded following IgM- enriched IVIG therapy.[22] This result is similar to this study as the intervention group had significantly decreased respiratory rates, increased mean arterial pressure (MAP) and serum pH after treatment. Whereas no significant decline in preterm morbidities was observed in both groups.

It is inconclusive to state that IgM-enriched IVIG provides benefits to any specific microbial organism as presented in this current study. Furthermore, randomization between groups could not be performed because of the retrospective nature of the study. Thus, it may be difficult to compare the baseline characteristics such as severity of neonatal sepsis between groups. Further prospective study with precise protocols should be conducted to substantiate the results of this current study.

This research study was designed to offer information about the new adjunctive treatment for neonatal sepsis, therefore providing physicians feasible treatment alternatives in the care of patients with neonatal sepsis.

TABLE 2. Clinical characteristics at time of neonatal sepsis diagnosis and source of infection.

	Intervention n=14 (%)	Control n=14 (%)	P value
Clinical characteristics at time of neonatal sepsis diagnosis			
Feeding intolerance	7 (50.0)	5 (35.7)	0.445
Respiratory distress	12 (85.7)	13 (92.9)	0.541
Cyanosis/desaturation	6 (42.9)	5 (35.7)	0.699
Hypotension	9 (64.3)	2 (14.3)	0.007*
Apnea	2 (14.3)	2 (14.3)	1.000
Abdominal distension	6 (42.9)	2 (14.3)	0.094
Jaundice	3 (21.4)	3 (21.4)	1.000
Bradycardia	1 (7.1)	1 (7.1)	1.000
Lethargy	2 (14.3)	1 (7.1)	0.541
Disseminated intravascular coagulation (DIC)	9 (64.3)	0 (0.0)	<0.001*
Source of infection			
Necrotizing enterocolitis (NEC)	5 (35.7)	0 (0.0)	0.014*
Early neonatal sepsis	9 (64.3)	14 (100.0)	0.014*
Septicemia (hemoculture positive)	3 (21.4)	0 (0.0)	0.067
Congenital pneumonia	5 (35.7)	4 (28.6)	0.686
Hospital acquired pneumonia (HAP)	5 (35.7)	0 (0.0)	0.014*

TABLE 3. Clinical and laboratory parameters.

Clinical and laboratory parameters	IgM- enriched IVIG treatment (n=14)			Control (n=14)		
	Before	After	P-value	Before	After	P value
Body temperature (°C)	37.16± 0.78	37.09±0.78	0.727	37.16±0.44	37.29±0.31	0.334
Respiratory rate (bpm)	68.18±10.94	60.80±4.13	0.022*	61.21±10.14	55.79±9.74	0.150
Heart rate (bpm)	169.79±34.22	164.21±12.53	0.520	157.00±22.87	143.00±27.22	0.198
Systolic blood pressure (mmHg)	57.14±17.83	62.43±17.39	0.111	60.14±8.18	60.36±8.88	0.928
Mean arterial pressure (mmHg)	40.36±15.36	46.43±15.04	0.049*	46.29±9.24	45.07±9.64	0.666
Diastolic blood pressure (mmHg)	32.36±14.90	37.43±14.68	0.068	38.50±10.18	36.36±9.60	0.494
SpO_2 (%)	87.79±12.78	91.86±6.32	0.286	95.57±9.20	95.86±8.01	0.923
pH	7.28±0.11	7.36±0.09	0.017*	7.28±0.06	7.34±0.09	0.135
pO_2	41.65±19.40	41.22±14.13	0.940	74.30±18.63	51.60±6.30	0.296
pCO_2	56.43±17.59	46.29±11.00	0.093	42.87±5.62	51.60±19.92	0.146
HCO_3 (mEq/L)	26.36±7.18	25.56±4.07	0.560	20.54±3.28	22.89±4.59	0.182
Base excess	-0.31±2.22	0.77±1.41	0.538	-6.00±3.97	-2.40±4.67	0.062
WBC count (/mm^3)	12,012.14 ±1,897.50	8,472.14 ±2,155.73	0.133	15,709.29 ±1,601.15	10,792 ±1,206.88	0.041*
Platelet count (/mm^3)	191,321.43 ±25,912.66	199,071.43 ±29,303.35	0.812	259,714.29 ±23,819.47	257,555.56 ±42,699.89	0.884
Hemoglobin (g/dL)	12.59±0.50	12.26±0.45	0.658	17.06±2.21	17.23±1.97	0.428
I:T ratio	0.37±0.07	0.17±0.09	0.127	0.25±0.08	0.14	NA
C- reactive protein (mg/dL)	7.83±5.02	11.30±5.70	0.645	1.79±0.89	2.89±0.24	0.401

TABLE 4. Microbiological cultures.

Laboratory	IgM- enriched IVIG treatment (n=14)			Control (n=14)		
	Before n (%)	After n (%)	P value	Before n (%)	After n (%)	P value
Hemoculture			1.000	0 (0.0)	0 (0.0)	NA
Staphylococcus aureus	1 (7.1)	1 (7.1)		0 (0.0)	0 (0.0)	
Staphylococcus spp.	1 (7.1)	1 (7.1)		0 (0.0)	0 (0.0)	
Gram negative bacilli	1 (7.1)	1 (7.1)		0 (0.0)	0 (0.0)	
Sputum culture			0.376			NA
Acinetobacter baumannii	3 (21.4)	4 (28.5)		0 (0.0)	1 (7.1)	
Enterococci spp.	1 (7.1)	1 (7.1)		0 (0.0)	0 (0.0)	
Pseudomonas aeruginosa	2 (14.3)	1 (7.1)		0 (0.0)	0 (0.0)	
Stenotrophomonas maltophilia	1 (7.1)	1 (7.1)		0 (0.0)	0 (0.0)	
Staphylococcus coagulation negative				1 (7.1)	0 (0.0)	
Urine culture	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Cerebrospinal fluid culture	0 (0.0)	1 (7.1)	0.733	0 (0.0)	0 (0.0)	NA
Fungus				0 (0.0)	0 (0.0)	NA
Hemoculture for fungus	0 (0.0)	1 (7.1)	0.733	0 (0.0)	0 (0.0)	NA
Sputum for fungus	0 (0.0)	1 (7.1)	0.733	0 (0.0)	0 (0.0)	NA
Urine for fungus	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA

TABLE 5. Outcome measurement.

Outcome measurement	IgM-enriched IVIG treatment (n=14)	Control (n=14)	P- value
Duration of mechanical ventilation (day)	40.33 ±15.82	11.30 ± 7.89	0.108[a]
Length of hospital stay (day)	70.78 ±18.17	27.80 ±11.93	0.060[a]
Mortality rate			
At day 7 (n (%))	0 (0.0)	0 (0.0)	NA
At day 28 (n (%))	0 (0.0)	0 (0.0)	NA

[a] adjusted for changes in respiratory rate, mean arterial pressure, pH

TABLE 6. Morbidities in preterm.

Morbidity	IgM- enriched IVIG treatment (n=12)			Control (n=10)		
	Before n (%)	After n (%)	P value	Before n (%)	After n (%)	P value
Intraventricular hemorrhage grade ≥ 2	6 (50.0)	6 (50.0)	1.000	0 (0.0)	1 (10.0)	0.305
Necrotizing enterocolitis	5 (41.7)	5 (41.7)	1.000	0 (0.0)	1 (10.0)	0.305
Periventricular leukomalacia	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Patent ductus arteriosus	6 (50.0)	5 (41.7)	0.682	0 (0.0)	1(10.0)	0.305

CONCLUSION

Following a 3-day course of IgM-enriched IVIG concurrently with antibiotics, improvements in clinical and laboratory parameters were recorded. Mortality rate was inconclusive as there was no reported patient death on day 7 and day 28. However, improvements on respiratory rates, mean arterial pressure (MAP) and serum pH are beneficial indicators to monitor sepsis in neonates and there were found to be improved after using IgM-enriched IVIG as adjunctive treatment in the neonates presented with hypotension and DIC. Nevertheless, the use of IgM-enriched IVIG was not found to reduce morbidities in preterm neonates.

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