Original Article

Outcomes of Newborn Infants with Neonatal Sepsis Receiving IgM-Enriched Intravenous Immunoglobulin as Adjunctive Treatment

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Background: Neonatal sepsis is a major cause of morbidities and mortality in newborn infants. Adjunctive treatment with IgM-enriched intravenous immunoglobulins (IgM-enriched IVIG) may improve the outcomes of the newborn infants with neonatal sepsis. However, there is limited data with regards to the outcomes of newborn infants receiving this treatment.

Objective: To evaluate the outcomes of the newborn infants with neonatal sepsis receiving IgM-enriched IVIG.

Materials and Methods: A retrospective cohort study was done in newborn infants aged 28 days or younger diagnosed with either culture-proven sepsis or clinical sepsis at Srinagarind Hospital between 2012 and 2018. The outcomes with regards to death and morbidities were compared between newborn infants received IgM-enriched IVIG versus a control group.

Results: Ninety-six newborn infants were eligible for the present study. Culture-proven sepsis group consisted of 20 newborn, which five of them had early-onset sepsis (EOS) and 15 had late-onset sepsis (LOS). There were 76 newborn infants in clinical sepsis group, which 36 had EOS and 40 had LOS. IgM-enriched IVIG was given to 12 (60%) newborn infants with culture-proven sepsis and 10 (13.2%) newborn infants with clinical sepsis. Among newborn infants diagnosed with culture-proven EOS and LOS, there was no significant differences in morbidities, mortality, length of hospital stay, and hospital cost between the intervention and the control group. In newborn infants diagnosed with clinical sepsis, subgroup analysis showed that in clinical LOS, the intervention group had significantly higher rate of death at 25% versus 0% (OR 6.3; 95% CI 3.0 to 13.2, $p<0.05$) and hospital cost with a mean of 601,155 versus 279,777 Baht ($p<0.05$) in comparison to the control group.

Conclusion: IgM-enriched IVIG failed to demonstrate benefit as an adjunctive treatment for newborn infants with neonatal sepsis. It also failed to show reduction in length of hospital stay and hospital cost. Routine prescription of IgM-enriched IVIG in neonatal sepsis is not recommended.

Keywords: Neonatal sepsis; IgM-enriched IVIG; Outcomes

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Neonatal sepsis is a major cause of mortality and morbidity among newborn infants worldwide and responsible for more than 300,000 neonatal deaths per year[1]. Preterm and very low birth weight (VLBW) infants are more susceptible to neonatal sepsis and have higher rates of death and disability in comparison to term infants[2,3]. Standard treatment for this condition is to provide adequate antibiotics and other supportive treatments.

Newborn infants, especially preterm or VLBW infants, have lower level of immunoglobulin IgG and IgM than children and adults, which may contribute to their higher mortality and morbidity rates[4]. International Neonatal Immunotherapy Study (INIS study) published in 2011 and Cochrane review showed that using standard immunoglobulins (S-IVIG), which does not contain IgM, as adjunctive therapy to the standard treatment in neonatal sepsis had no effect on death or major disability at two years of age[5,6]. However, since IgM has a key role in clearing pathogens and enhancing immune responses, IgM enriched immunoglobulins or IgM-enriched IVIG formula may have better therapeutic potential in neonatal sepsis[7-10].

Srinagarind Hospital, Khon Kaen University, a supra-tertiary university hospital in northeastern Thailand, has been using IgM-enriched IVIG as adjunctive therapy in neonatal sepsis since 2012, but

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there was limited data about the outcomes of newborn infants treated with IgM-enriched IVIG. Thus, the aim of the present study was to determine the outcomes of newborn infants with neonatal sepsis who received versus who did not received IgM-enriched IVIG at the present study hospital.

Materials and Methods

The present study was a retrospective cohort study conducted by reviewing the medical records of newborn infants at 28 days or younger diagnosed with either culture-proven sepsis or clinical sepsis, admitted to level III neonatal intensive care unit (NICU) at Srinagarind Hospital between January 1, 2012 and December 31, 2018. To minimized variation in newborn care, the authors enrolled only inborn newborn infants. Newborn infants with severe congenital anomalies, genetic or chromosomal disorder, or incomplete records were excluded from the study.

Eligible newborn infants were categorized into culture-proven sepsis and clinical sepsis groups, and further divided into subgroups of early-onset sepsis (EOS) and late-onset sepsis (LOS) for each group. Intervention group consisted of newborn infants receiving IgM-enriched IVIG (Pentaglobin®, Biotest AG, Germany) adjunctively to the standard treatment consisting of intravenous antibiotics and supportive treatments. The control group was newborn infants who did not receive IgM-enriched IVIG. Each milliliter of IgM-enriched IVIG contained 38 mg of IgG, 6 mg of IgA, and 6 mg of IgM. Recommended dose is 5 mL/kg per dose every 24 hours for three doses. There was no established guideline indicating the use of IgM-enriched IVIG for neonatal sepsis, thus, decision to use IgM-enriched IVIG was at the neonatologists' discretion.

Definition of neonatal sepsis

The present study adopted The Brighton Collaboration Neonatal Infections Working Group guideline to standardize the diagnosis and classifications of neonatal sepsis[11]. Neonatal sepsis is a systemic infection or systemic inflammatory response syndrome (SIRS) occurring in infants younger than 28 days that can be chronologically classified into EOS, which occurs prior to 72 hours of life, and LOS, which occurs from 72 hours to 28 days of life. This reflects different etiologies and causative pathogens of neonatal sepsis[11-15].

Neonatal sepsis is also classified as culture-proven sepsis, defined as sepsis with positive bacterial culture from sterile-site specimens such as blood, cerebrospinal fluid (CSF), or catheterized urine, and the culture identifies a single causative pathogen[11-15].

Clinical sepsis is defined as newborn infants not meeting with culture-proven sepsis criteria but having at least two abnormal clinical symptoms and at least one abnormal laboratory result and have been receiving antibiotics treatment for at least five days.

Abnormal clinical symptoms are increased oxygen requirement or ventilator support, increase in apneic or bradycardic episodes, persistent tachycardia, hypotension or prolonged capillary refill time, glucose intolerance, lethargy, temperature instability, feeding intolerance, bowel ileus, or abdominal distension.

Abnormal laboratory results are metabolic acidosis with base deficit of more than 5 mmol/L, raised C-reactive protein (CRP) of more than 6 mg/L, raised immature-to-total neutrophil ratio of more than 0.2, leukocytosis with white blood cells (WBC) of more than $20,000\times10^6$/L, leukopenia with WBC of less than $7,000\times10^6$/L, and neutropenia with absolute neutrophil count (ANC) of less than $5,000\times10^6$/L.

Outcomes of the present study included demographic data, rates of death, rates of morbidities, which were intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP), length of hospital stay, and total cost of treatment, in comparison between the intervention and the control group.

Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Percent, ratio, mean ± standard deviation (SD), and median with interquartile range were used to present descriptive data. Correlation analyses were performed by using chi-square test, Fisher's exact test, Student t-test, or Mann-Whitney U-test and presented in odd ratio. A p-value of less than 0.05 was considered to be statistically significant.

The present study was approved by the Ethics Committee for Human Research at Khon Kaen University (HE611317).

Results

One hundred sixty-nine newborn infants were diagnosed with neonatal sepsis and admitted to the NICU during the study period. Twenty-two outborn newborn infants and 40 newborn infants with severe congenital anomalies or chromosomal disorder were excluded. Another 11 newborn infants with incomplete medical records were also excluded. Finally, there were 96 newborn infants included in

Table 1. Characteristics of newborn infants

Group 1	Culture-proven sepsis								
	Overall (n=20)			Culture-proven EOS (n=5)			Culture-proven LOS (n=15)		
	I (n=12)	C (n=8)	p-value	I (n=4)	C (n=1)	p-value	I (n=8)	C (n=7)	p-value
Sex: male; n (%)	5 (41.6)	5 (62.5)	0.361	1 (25.0)	0 (0.0)	0.576	4 (50.0)	5 (71.4)	0.398
BW; mean±SD	1,550±1,105	1,742±920	0.430	1,141±1,140	1,050	0.287	1,755±1,104	1,922±978	0.530
GA; mean±SD	30.6±5	32.6±4.5	0.350	29.5±6	27.0	0.599	31.2±4.7	34.1±4.0	0.404
Group 2	**Clinical sepsis**								
	Overall (n=76)			Clinical EOS (n=36)			Clinical LOS (n=40)		
	I (n=10)	C (n=66)	p-value	I (n=2)	C (n=34)	p-value	I (n=8)	C (n=32)	p-value
Sex: male; n (%)	4 (40.0)	39 (59.1)	0.256	1 (50.0)	21 (61.8)	0.740	3 (37.5)	18 (56.2)	0.342
BW; mean±SD	1,447±1,079	1,327±523	0.570	2,810±311	1,412±575	0.002*	1,106±905	1,237±454	0.561
GA; mean±SD	29.8±5.6	29.8±3.2	0.968	37.0±2.8	30.0±3.5	0.009*	28.0±4.5	29.7±2.9	0.194

EOS=early-onset sepsis; LOS=late-onset sepsis; I=intervention; C=control; BW=birth weight; GA=gestational age; SD=standard deviation

* Statistically significant

the present study, of which, 22 newborn infants (22.9%) received IgM-enriched IVIG.

There were 20 newborn infants diagnosed with culture-proven sepsis. Five of them had EOS and 15 had LOS. Of the 20 newborn infants, 12 of them (60%) received IgM-enriched IVIG, which were four out of five (80.0%) in culture-proven EOS and eight out of 15 (53.3%) in culture-proven LOS groups. In the culture-proven EOS group, time-to-receive IgM-enriched IVIG was one to three days (mean 1.7 days) after the diagnosis of neonatal sepsis while in the culture-proven LOS group, the timing was zero to three days (mean 1.3 days). There was no significant difference in gender, birth weight and gestational age among the newborn infants with culture-proven sepsis.

Among 76 newborn infants diagnosed with clinical sepsis, there were 36 clinical EOS and 40 clinical LOS. Of the 76 newborn infants, 10 of them (13.2%) received IgM-enriched IVIG. In clinical EOS group, two out of 36 newborn infants (5.5%) received IgM-enriched IVIG, while eight out of 40 newborn infants (20.0%) in clinical LOS group received the treatment. Time-to-receive IgM-enriched IVIG in clinical EOS group was zero to one day (mean 0.5 day), and zero to eight days (mean 1.6 days) in clinical LOS. In clinical EOS subgroup, birth weight and gestational age in newborn infants who received IgM-enriched IVIG were significantly higher than in the control group, in contrast to the newborn infants in clinical LOS subgroup that had no significant difference in birth weight and gestational age. Newborn infants' characteristics are shown in Table 1.

Among the newborn infants with culture-proven sepsis, there was no significant difference in the rates of death, all grade IVH, definite or ≥ stage II NEC, BPD, all stage ROP, length of stay, and hospital cost between the intervention and the control groups. Subgroup analyses of culture-proven EOS and LOS continued to show similar result with no significant different of outcomes between the intervention and the control groups. Outcome results are shown in Table 2.

Among the newborn infants with clinical sepsis, the present study revealed that death rate in the intervention group was significantly higher than the control group at 20.0% versus 0.0% (OR 9.2, 95% CI 4.8 to 17.8; p=0.016). In addition, hospital cost was significantly higher in the intervention group compared to the control group at 558,614 versus 300,262 Baht (p=0.023).

In subgroup of clinical EOS, there was no significant difference in the rates of death, all grade IVH, definite NEC, BPD, all stage ROP, length of stay, and hospital cost between the intervention and the control group. However, in clinical LOS subgroup, intervention group had significantly higher death rate at 25.0% versus 0.0% (OR 6.3, 95% CI 3.0 to 13.2; p=0.004), and hospital cost at 601,155 versus 279,777 Baht (p=0.007) in comparison to the control group. Results are shown in Table 3.

The most common causative organisms for culture-proven sepsis were *Enterobacter* species (27.0%), *Acinetobacter baumannii* (26.0%), *Escherichia coli* (26.0%), *Enterococci* species (8.6%), *Pseudomonas aeruginosa* (8.6%), and *Candida albicans* (3.8%), respectively.

Antibiotics used in newborn infants with culture-proven sepsis were meropenem (66.7%) and

Table 2. Outcomes of newborn infants with culture-proven sepsis

	Overall culture-proven sepsis (n=20)			Culture-proven EOS (n=5)			Culture-proven LOS (n=15)		
	I (n=12)	C (n=8)	p-value	I (n=4)	C (n=1)	p-value	I (n=8)	C (n=7)	p-value
Death; n (%)	3 (25.0)	0 (0.0)	0.229	1 (25.0)	0 (0.0)	0.576	2 (25.0)	0 (0.0)	0.155
IVH; n (%)	9 (75.0)	4 (50.0)	0.445	4 (100)	1 (100)	N/A	6 (75.0)	3 (42.9)	0.205
NEC; n (%)	2 (16.7)	0 (0.0)	0.486	1 (25.0)	0 (0.0)	0.576	1 (12.5)	0 (0.0)	0.333
BPD; n (%)	5 (41.7)	2 (25.0)	0.164	2 (50.0)	1 (100)	0.361	3 (37.5)	1 (14.3)	0.310
ROP; n (%)	3 (25.0)	0 (0.0)	0.360	2 (50.0)	0 (0.0)	0.361	1 (12.5)	0 (0.0)	0.333
Length of stay (day); mean±SD	79±63	47±25	0.205	83 (11, 155)†	62	1.000	76±58	45±26	0.217
Hospital cost (Baht); mean±SD	464,728±345,005	435,310±298,321	0.863	611,962±470,969	N/A	N/A	380,595±254,490	435,310±298,321	0.728

EOS=early-onset sepsis; LOS=late-onset sepsis; I=intervention; C=control; IVH=intraventricular hemorrhage; NEC=necrotizing enterocolitis; BPD=bronchopulmonary dysplasia; ROP=retinopathy of prematurity; SD=standard deviation; IQR=interquartile range; N/A=not applicable

† Median (IQR)

Table 3. Outcomes of newborn infants with clinical sepsis

	Overall clinical sepsis (n=76)			Clinical EOS (n=36)			Clinical LOS (n=40)		
	I (n=10)	C (n=66)	p-value	I (n=2)	C (n=34)	p-value	I (n=8)	C (n=32)	p-value
Death; n (%)	2 (20.0)	0 (0.0)	0.016*	0 (0.0)	0 (0.0)	N/A	2 (25.0)	0 (0.0)	0.004*
IVH; n (%)	5 (50.0)	36 (54.5)	0.788	0 (0.0)	21 (61.8)	0.085	5 (62.5)	15 (46.8)	0.429
NEC; n (%)	1 (10.0)	22 (33.3)	0.134	0 (0.0)	7 (20.6)	0.475	1 (12.5)	15 (46.8)	0.082
BPD; n (%)	4 (40.0)	28 (42.4)	0.885	0 (0.0)	14 (41.2)	0.246	4 (50.0)	14 (43.8)	0.751
ROP; n (%)	4 (40.0)	13 (19.7)	0.151	0 (0.0)	8 (23.5)	0.437	4 (50.0)	5 (15.6)	0.059
Length of stay (day); median (IQR)	38 (30, 109)	53 (31, 84)	0.969	28±4#	53 (23, 84)	0.369	61 (34, 155)	53 (34, 86)	0.660
Hospital cost (Baht); mean±SD	558,614±320,152	300,262±320,711	0.023*	388,451±20,034	319,959±383,094	0.806	601,155±348,402	279,777±246,067	0.007*

EOS=early-onset sepsis; LOS=late-onset sepsis; I=intervention; C=control; IVH=intraventricular hemorrhage; NEC=necrotizing enterocolitis; BPD=bronchopulmonary dysplasia; ROP=retinopathy of prematurity

Mean±SD, * Statistically significant

vancomycin (66.7%). In clinical sepsis, newborn infants received ampicillin (94.0%) and gentamicin (79.0%) for clinical EOS. In newborn infants with clinical LOS, ampicillin (46.3%) and cefotaxime (64.3%) were commonly prescribed.

Discussion

The present study's purpose was to evaluate the outcomes of the newborn infants that received IgM-enriched IVIG at a single supra-tertiary hospital. Overall usage of IgM-enriched IVIG was low at 22.9% in comparison to the previous studies, which had higher usage rate between 31.8% and 50.6%[7-9]. Administration of IgM-enriched IVIG was higher in culture-proven sepsis group at 60.0% in contrast to clinical sepsis group, which was only 13.2%. Low prescription of IgM-enriched IVIG in newborn infants with clinical sepsis may hinder the effect and outcomes of the treatment.

In the present study, the newborn infants with culture-proven sepsis group had no significant differences in death and morbidities between the intervention and the control group. The present study result was similar to a randomized controlled study conducted by Akdag et al and found no difference in mortality rate among the newborn infants with neonatal sepsis between control group, IgM-enriched IVIG group, and IgM-enriched IVIG in combination with pentoxiphylline group[16]. The present study result was also similar to the retrospective studies by Erdem et al and Boonsopa et al that found no difference in mortality rate between the infants receiving IgM-enriched IVIG compared to the control group[17,18].

However, these results contrasted with studies that showed benefit of IgM-enriched IVIG in reduction of mortality rate in newborn infants with sepsis. In the studies conducted by Capasso et al and Haque et al, they found that most organisms causing neonatal sepsis were gram-positive bacteria and candida species[7,10], unlike the present study, which most causative organisms were gram-negative bacteria comprising 87.6% of the culture-proven sepsis. It is known that gram-negative bacteria were more virulent and associated with higher mortality rate. Therefore, different causative organisms could

play a key role in the effectiveness of IgM-enriched IVIG. Since gram-positive bacteria consisted of only 8.6%, it was difficult to compare IgM-enriched IVIG effectiveness between the newborn infants with gram-positive and gram-negative sepsis.

A study conducted by El-Nawawy et al showed significant reduction in mortality in patients with sepsis receiving IgM-enriched IVIG[19]. However, the population age group in that study was between 1 and 24 months, in contrast to the present study, which was conducted in preterm newborn infants whose immune status were compromised. This could affect the effectiveness of IgM-enriched IVIG causing the differences in mortality rate.

The timing of IgM-enriched IVIG initiation may also affect the outcomes. Ideally, the treatment should be given as soon as the diagnosis of neonatal sepsis was made. Since there was no consensus guideline about when to start IgM-enriched IVIG, the timing varied between zero and three days among the newborn infants, and up to eight days after the diagnosis was made. These heterogenous outcomes had made the benefit of IgM-enriched IVIG in newborn infants with culture-proven sepsis inconclusive.

In newborn infants with clinical sepsis, death rate was significantly higher in those receiving IgM-enriched IVIG. Hospital cost was also significantly higher in the intervention group in comparison to the control group. Subgroup analysis found that in the newborn infants with clinical LOS, death rate was significantly higher in the intervention group, as well as higher hospital cost. Higher death and hospital cost in intervention group were associated with the newborn infants presenting with more severe clinical features that prompted neonatologists to prescribe IgM-enriched IVIG as adjunctive treatment and required more intensive medical interventions. In contrary, there was no significant differences in death, morbidities, length of stay, and hospital cost in the clinical EOS subgroup.

Studies showed conflicting results about IgM-enriched IVIG role in improving mortality and morbidities in neonatal sepsis. The present study failed to demonstrate the benefit of IgM-enriched IVIG as adjunctive treatment. Cochrane review in 2015 had concluded that either S-IVIG or IgM-enriched IVIG did not reduce mortality in newborn infants with sepsis and routine use of S-IVIG or IgM-enriched IVIG was not recommended[6]. Lack of significant morbidities among newborn infants in the intervention and the control groups showed that IgM-enriched IVIG could be used safely without adverse outcomes, similar to the studies conducted by Salihoglu et al and Hamilcikan et al[20,21].

Cost analysis found that using IgM-enriched IVIG as adjunctive treatment could not demonstrate reduction in length of hospital stay or hospital cost. Conversely, intervention group tended to have longer hospitalization and higher hospital cost, although not statistically significant.

Limitation

The present study had limitations due to its retrospective design. There was no standard guideline about when to start IgM-enriched IVIG, causing delays in the treatment. The present study was also prone to selection bias since neonatologists were likely to prescribe IgM-enriched IVIG to newborn infants with more severe clinical features, affecting the outcomes between the control and the intervention groups. IgM-enriched IVIG was not covered by universal health coverage and had to be paid by the newborn infants' parents and some parents were unable to afford. This reduced the number of newborn infants who could benefit from the treatment. Using standard guideline of using IgM-enriched IVIG, providing financial coverage of the treatment, and conducting a prospective randomized controlled study could provide better insights and more reliable information about the effectiveness of the IgM-enriched IVIG.

Conclusion

Using IgM-enriched IVIG as adjunctive treatment in neonatal sepsis did not result in significant reduction of mortality rate, length of hospital stays, or hospital cost. Despite it had been shown to be safe in newborn infants, routine prescription of IgM-enriched IVIG is not recommended.

What is already known on this topic?

Neonatal sepsis is a major cause of morbidities and mortality in newborn infants even though adequate antibiotics were given. Cochrane review showed that using S-IVIG did not result in improvement of death or major disability at two years of age. However, studies had shown benefits of adjunctive treatment with IgM-enriched IVIG in improving the outcomes.

What this study adds?

Using IgM-enriched IVIG as adjunctive treatment in newborn infants with neonatal sepsis did not show improvements in short-term outcomes comparing to

newborn infants who did not receive this treatment. This finding discouraged routine use of IgM-enriched IVIG in newborn infants with neonatal sepsis.

Conflicts of interest

The authors declare no conflict of interest.

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