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Intravenous immune globulin in the management of sepsis in PICU RSAB Harapan Kita, Jakarta

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Abstract

Background Sepsis is a major health problem and a leading cause of death among children. Intravenous immune globulin (IVIG) has been reported in systemic inflammatory conditions.

Objective To determine the effectiveness of IVIG in the treatment of sepsis in children.

Methods This was a hospital-based, retrospective study conducted from 2000-2001. Sixty neonates and children under 18 years old with sepsis were classified to either received or not received IVIG. The IVIG and the non-IVIG groups were compared. Data was obtained from medical records.

Results Of 60 sepsis cases, 16 were neonates (7 received IVIG, 9 did not), and 44 were infants and children (25 received IVIG and 19 did not). In neonates, IVIG had no influence on mortality (P=0.838), while in non-neonatal cases, it improved the survival rate (P=0.010). The suitability of the 1st antibiotic influenced the outcome and length of stay in neonatal cases (P=0.005), but not in the non-neonatal group (P=0.111). Although in some cases the 1st antibiotic was not suitable, IVIG seemed to hold the process for a while, giving more time to adjust to a suitable antibiotic according to the culture result.

Conclusions The addition of IVIG to standard therapies revealed minimum effect but showed benefit in holding the process, and seemed to improve survival in children, but not in neonates. **[Paediatr Indones 2007;47:226-228]**.

Keywords: *children, intravenous immune globulin, sepsis*

Sepsis is defined as the systemic inflammatory response syndrome that occurs during infection. Sepsis represents an uncontrolled inflammatory response, a response to the presence of microorganisms that causes the disease.[1] Sepsis is a major health problem among children in both developing and industrialized countries, and a leading cause of death, with more than 42,000 cases of severe sepsis annually in the United States and millions worldwide. There were an estimated 4,400 pediatric deaths from sepsis every year in the United States. Half of the children with severe sepsis in the United States are infants, and half of infants are low- or very low-birth-weight newborns.[2-4]

Intravenous immune globulin (IVIG) has been used for more than 25 years. It is a safe preparation with no long-term side effects. Benefits have been reported in many systemic inflammatory conditions. The mode of action of immune globulin is complex, involving: 1. Modulation of the expression and function of Fc receptors, 2. Interference with the activation of complement and the cytokine network, 3. Provision of antildiotypic antibodies, and; 4. Effects

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on the activation, differentiation, and effector functions of T cells and B cells.[5] This broad range of activities reflects the importance of immunoglobulins in the immune homeostasis of healthy people.

We reviewed our experience in using intravenous immunoglobulin (IVIG) in infants and children with sepsis.

Methods

This was a hospital-based, retrospective analysis conducted at the Department of Child Health, Mother and Child Harapan Kita Hospital, Jakarta, from 2000-2001. Neonates and children aged from one month to 18 years old with sepsis were eligible for this study. Sixty subjects were enrolled and classified to either received or not received IVIG. Data was obtained from neonatal and pediatric medical records. The IVIG and the non-IVIG groups were compared based on survival and non-survival, suitability of the first antibiotic and the length of hospital stay.

Results

During the study period there were 16 neonates with sepsis; 7 received IVIG, while the rest 9 did not. From the 7 neonates who received IVIG, 2 survived compared to 3 from the 9 babies who did not receive IVIG. Out of 44 patients under 18 years old, 25 patients received IVIG, while 19 did not. Among those sepsis patients, infants and children aged above 1 month old who received IVIG, 56% survived, compared to only 26% survival rate in the group that did not receive IVIG (**Table 1**).

Table 1 shows that in neonates, IVIG had no influence (P=0.838), while in cases of infants and children, it seemed to improve their well being (P=0.010). Overall, without defining patients' age, IVIG improved survival (P=0.027)

Table 4 shows that the suitability of the 1st antibiotic influenced the outcome and also the length of stay (P=0.005).

The table above shows that although the 1st antibiotic did not influence the outcome (P= 0.111) in non-neonatal cases. In cases where first antibiotic was not suitable, IVIG seemed to hold the process for a while, giving more time to adjust to a suitable antibiotic according to the culture result.

Table 1. Distribution of sepsis cases according to age, IVIG, and outcome

Outcome	0-1 month (n=16)		1 month-18 years old (n=44)	
	IVIG (n=7)	Non IVIG (n=9)	IVIG (n=25)	Non IVIG (n=19)
Survive	2	3	14	5
Died	5	6	11	14

Table 2. Cross tabulation Count of IVIG and non IVIG group

		Survive		
		Yes	No	Total
IVIG	Yes	17	15	32
	No	7	21	28
Total		24	36	60

Table 4. Distribution of neonatal cases according to the suitability of the 1st antibiotic and the mean of length of stay (LOS)

	IVIG (n=7)		**Non IVIG (n=9)**	
	Survived (n=2)	**Died (n=5)**	**Survived (n=3)**	**Died (n=6)**
1st Atb suitable	1	1	3	0
1st Atb not suitable	1	4	0	6
Mean LOS days	42.5	22.4	21.7	12.8

Note: Atb = antibiotic; LOS = length of stay

Table 3. Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.922(b)	1	.027		
Continuity Correction(a)	3.820	1	.051		
Likelihood Ratio	5.034	1	.025		
Fisher's Exact Test				.036	.025
Linear-by-Linear Association	4.840	1	.028		
N of Valid Cases	60				

a Computed only for a 2x2 table

b 0 cells (.0%) have expected count less than 5. The minimum expected count is 11.20.

Table 5. Distribution of non-neonatal cases according to the suitability of the 1st antibiotic and the mean of length of stay (LOS).

	IVIG (n=25)		Non IVIG (n=19)	
	Survived (n=14)	Died (n=11)	Survived (n=5)	Died (n=14)
1st Atb suitable	5	1	3	4
1st Atb not suitable	9	10	2	10
Mean LOS (days)	12.2	11.3	12	3.5

Note: Atb = antibiotic; LOS = length of stay

Discussion

One of the strategies in the management of sepsis is augmentation of the host defence and inhibition of the inflammatory process. In this study, IVIG was tend to augment the host defence, with a result of increasing survival in the IVIG group (P=0.027).

Normally, a potent, complex immunologic cascade ensures a prompt protective response to microbial invasion in human. A deficient immunologic defence may allow infection to become established; however, an excessively or poorly regulated response may harm the host through a maladaptive release of endogenously generated inflammatory compounds. Conceptually, one approach is to prevent infection in patients at high risk with the timely use of immune stimulants and then provide brief, targeted immunosuppressive therapy if sepsis ensues.[6]

A major shift has occurred in the way investigators view the problem of sepsis. Sepsis may not be attributable solely to an "immune system gone haywire" but may indicate an immune system that is severely compromised and unable to eradicate pathogens. Mechanisms of organ failure and death in patients with sepsis remain unknown, and autopsy studies do not reveal widespread necrosis. Current clinical advances in the treatment of sepsis include therapy with activated protein C, tight control of blood glucose, and early goal-directed therapy to treat the cellular oxygen deficit. Future therapy may be directed at enhancing or inhibiting the patient's immune response, depending on genetic polymorphisms, the duration of disease, and the characteristics of the particular pathogen.[7]

Khalid *et al*[8] did a systematic review of prophylactic use of nonspecific IVIG in 15 randomized controlled trials (RCTs) with a total of 5054 preterm infants of low birth weight has demonstrated that prophylactic nonspecific IVIG reduced sepsis (RR=0.83; 95%CI 0.72;0.97) and was safe with no major adverse effects, but showed no reduction in mortality. The use of IVIG in the treatment of neonatal sepsis has also been subject to systematic review. This review showed a 50% reduction in mortality when 4 RCTs of IVIG therapy in 208 infants with suspected or proven infection was reviewed (RR for mortality= 0.52; 95%CI 0.28;0.98). Using slightly different selection criteria and method for analysis, Jenson and Pollock[9] in this journal came to the conclusion that IVIG should be considered as part of routine therapy for neonatal sepsis. Unfortunately, our result does not show the same thing in the neonatal group, might be due to not enough samples we have in this study. While in the non-neonatal group, it shows the same result. In conclusion, the addition of IVIG to standard therapies for sepsis shows benefit in holding the process, and seems to improve survival in children, but not in neonates. This study should be continued.

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