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Original Article

Multiple organ dysfunction syndrome associated with hyperglycemia in children requiring intensive care

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Abstract

Background Hyperglycemia can be caused by three or more organ dysfunctions and occurs in children requiring intensive care in the first 48 hours. Blood sugar level higher than 140 mg/dl is considered as hyperglycemia in children requiring intensive care.

Objective To determine the association between multiple organ dysfunction syndrome (MODS) in children requiring intensive care and hyperglycemia with blood sugar level higher than 140 mg/dl.

Methods This case control study without matching was conducted on children aged 1 month-12 years from pediatric ward at Sanglah hospital during June-August 2012. We used consecutive sampling to recruit subjects, which then were screened by *Pediatric Risk of Hospital Admission* (PRISA) 2 score. All subjects were enrolled for blood sugar test, then divided into 2 groups; hyperglycemia with blood sugar level > 140 mg/dl as case and normoglycemia as control. We used organ dysfunction criteria to determine multiple organ dysfunction. The association between MODS and hyperglycemia was assessed by Chi-square test with 95% confidence interval and a statistical significance value of $P < 0.05$.

Results Fifty two subjects were enrolled in this study. We excluded two subjects, hence each group consisted of 25 subjects. We found 18 subjects under and 7 subjects above five years old in hyperglycemia group. The association between multiple organ dysfunction and hyperglycemia was significant with an odds ratio of 10 (95% CI 3 to 38), $P < 0.0001$.

Conclusion Multiple organ dysfunction syndrome had a significant association with hyperglycemia. Multiple organ dysfunction syndrome with hyperglycemia occurs ten times greater than with normoglycemia. **[Paediatr Indones. 2015;55:231-5]**.

Keywords: *MODS, children requiring intensive care, hyperglycemia*

Multiple organ dysfunction syndrome (MODS) is presence of altered organ function in an acutely ill patient that homeostasis cannot be maintained without intervention.[1,2] The prevalence of MODS in Indian children is 10.6%.[3] Cell damage caused by MODS can activate the hypothalamic-pituitary-adrenal axis (HPA), hence releases cortisol that acts as a counter-regulatory hormones (CRH), and it will increase blood sugar levels (hyperglycemia).[4-7] Hyperglycemia occurs approximately 19-23.5 hours after MODS in children.[8] The prevalence of MODS with hyperglycemia in American children is 16.7-75%.[9] Previous studies reveal an association between three or more organ dysfunctions and intermittent hyperglycemia with a duration of 24 hours or longer, and an odds ratio (OR) of 6.1 (95% CI 1.8 to 21.2), $P = 0.004$.[10] Hyperglycemia is a strong pro-inflammatory factor that can promote further organ damage.[5,6] Studies have revealed the association between MODS with hyperglycemia in children requiring intensive care and mortality,[10,11] while insulin therapy decreases mortality rate and length of

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stay.[12,13] A study in America revealed that children requiring intensive care with blood sugar higher than 140 mg/dL as a criteria of hyperglycemia had a positive predictive value of 51% and a negative predictive value of 94%, and was set up as the foundation of insulin therapy in children.[12,14]

The purpose of this study was to determine the association between MODS in children requiring intensive care and hyperglycemia. The secondary purpose of this study was to prove that a blood sugar level of > 140 mg/dL can be applied as a value of hyperglycemia due to MODS.

Methods

A case control design without matching was conducted in the pediatric ward (intensive care, emergency room and nursing wards) in Sanglah Hospital during June-August 2012. The souce population was children aged 1 month-12 years requiring intensive care. Subjects were collected by consecutive sampling using questionnaires and medical records. The amount of sample required in this study was calculated using the one way two proportion hypothesis test formula with α 5%, power 20%, effect size 35%, and the proportion of MODS in children requiring intensive care with hyperglycemia was 55%. Based on calculation, the minimal sample amount for this study was 22 children for each group. Subjects were classified into 2 groups: case group and control group. The case group included children aged 1 month-12 years who met the inclusion criterias, such as needed intensive care with suffering from hyperglycemia, and parents or guardian had agreed to participate in the study. Exclusion criterias were having diabetes mellitus and history of corticosteroid administration in 24 hous before blood sugar test. The control group were children aged 1 month-12 years with intensive care admitted at the same time of study and had normal blood sugar level.

This study began with a screening done by pediatric-residency doctors to children in pediatric wards, using *Pediatric Risk of Hospital Admission* (PRISA) 2 score.[15] The subjects were assumed as children requiring intensive care when the total score of PRISA 2 was greater than 11. Subject was recruited as a study sample when the parents or guardian had signed the informed consent. The subjects were then assigned for blood sugar test obtained from venipuncture by nurses. Blood sample was immediately examined by Sanglah Hospital laboratory using one of these three machines; the Cobas Integra® 400 plus or Cobas® 6000 analyzer series or *UniCel® DxC 600*. All three machines were calibrated daily with the control by the Sanglah Hospital Laboratory staff before operation. Test results were analyzed by a pathologic clinician before it was inserted to the medical record. The study was continued by grouping of the samples based on the blood sugar levels. Case group consisted of samples with hyperglycemia, whereas control group consisted of samples with normoglycemia. Then the organ dysfunctions were evaluated according to the *2005 Intenational Consensus*[16] and was noted in the questionnaires available in the medical record by the pediatric-residency doctor. The questionnaires were then collected by the researcher and analyzed after the minimal amount of sample was obtained.

The independent variable of this study was multiple organ dysfunction, whereas the dependent variable was hyperglycemia. Multiple organ dysfunction syndrome was a dysfunction affecting two or more organs. Hyperglycemia was blood sugar level higher than 140 mg/dL and normoglycemia was blood sugar level between 65-140 mg/dl. Disease classification was evaluated from the main diagnosis at the time the subject was admitted and was based on organ systems suffered namely cardiovascular, respiratory, neurology, gastroenterology, nephrology, liver, and others.

Distribution of samples according their variable was analyzed using univariate test. The association between multiple organ dysfunction syndrome and hyperglycemia was analyzed with Chi-square test, and an OR analysis with a confident interval 95% and P value less than 0.05. The entire sample data was analyzed using a computer statistical software.

Evaluation and ethical clearance were granted by the Research Ethics Commission of Udayana University Medical Faculty/Sanglah Hospital Denpasar.

Results

The total amount of subjects who participated in this study during June -August 2012 was 52 children; 25 subjects with hyperglycemia, 25 subjects with

normoglycemia, one subject was excluded due to history of steroid administration in 24 hours prior to blood sugar test, and another one was excluded due to diabetes mellitus. There was no difference between boys and girls in this study. Median age in the hyperglycemia group was younger than normoglycemia group (**Table 1**). Hyperglycemia was seen more frequent in children under five year old.

The association between MODS in children requiring intensive care and hyperglycemia are shown in **Table 2**. The MODS with hyperglycemia in children requiring intensive care was significantly higher than those with normoglycemia.

Table 1. Baseline characteristics of subjects

Characteristic	Hyperglycemia n = 25	Normoglycemia n = 25
Gender, girl, n	13	14
Median age (IQ), months	16 (4-65)	70 (8-96)
Age group		
< 5 year old, n	18	12
≥ 5 year old, n	7	13
Median blood sugar level (IQ), mg/dL	164 (149-197)	106 (87-119)
Primary category of illness on admission		
Infection, n	15	16
No infection, n	10	11
Organ system of primary disease on admission		
Cardiovascular system, n	1	3
Respiratory system, n	6	6
Neurology system, n	10	11
Gastroenterology system, n	4	0
Nephrology system, n	0	1
Hepatic system, n	1	0
Others, n	3	4

IQ = interquartile

Table 2. Association between MODS and hyperglycemia

Variable	Hyperglycemia	Normoglycemia	P value	OR	CI 95%
MODS, n	18	5	< 0.0001	10	3 to 38
No MODS, n	7	20			

MODS = multiple organ dysfunction syndrome

Discussion

This study was conducted to reveal the association between MODS and hyperglycemia in children requiring intensive care. There were 72% subjects with MODS who had hyperglycemia. This was in concordance with a previous study which have revealed that in critically ill children, the prevalence of hyperglycemia was approximately 16.7-75%.[9] This study showed that there was a significant difference between MODS with hyperglycemia and MODS with normoglycemia. It revealed an OR of 10 (CI 95% 3 to 38) and P = 0.0001. This association was consistent with previous studies. In a previous study revealed a relative risk of 14-50 for hyperglycemia in intensive care children,[14] whereas other study revealed an OR of 6.8.[10] Hyperglycemia caused by MODS is due to stress. Stress will activate HPA, hence releases cortisol which is a main CRH. Other CRH includes catecholamine (norepinephrine, epinephrine), glucagon, and growth hormone are also released during stress. These hormones will cause peripheral insulin resistance, and then glycolysis and gluconeogenesis disorder in liver, muscle and fat tissue, and eventually hyperglycemia.[5,6]

The criteria of hyperglycemia in this study was > 140 mg/dL. The criteria was accordance to the

previous study.[12] In this study, we found a significant relationship between MODS and hyperglycemia. Therefore, a blood sugar level of > 140 mg/dL could be used as a criteria for hyperglycemia that need further therapy.

A previous study did not reveal an age difference in MODS with hyperglycemia.[10] Our study revealed that median age of MODS with hyperglycemia was younger compared to those with normoglycemia, and hyperglycemia was seen more often in children under 5 years. This could be due to younger age children are more vulnerable to diseases that require intensive care with MODS complication, hence the hyperglycemia is higher.

A study in adults has shown a significant relationship between sepsis, lung, cardiac, and neurologic disorders. In sepsis, there is a release of proinflammatory cytokines that have important role in the occurrence of hyperglycemia. This can happen directly or through a stimulation of glucoregulatory hormones.[6] A study showed that septic patients would produce tumor necrotizing factor-R55 and R75 which caused insulin resistance and eventually hypoinsulinemia.[17] Lung disorders would stimulate CRH which suppressed pancreatic beta cell functions.[5] Hyperglycemia has closely relation to lung disorders and usually followed by a cardiac disorder. One study has revealed a low production of endogenous C-peptide in critically ill patients with lung and cardiac disorders.[18] A study in stroke patients with insular cortical ischemia has revealed a significant relationship with hyperglycemia.[19] Our study revealed that infection, respiratory system, and neurology system have a high proportion, but they had no significant association, hence further study is needed to reveal the association between various diseases and hyperglycemia in children requiring intensive care.

Several studies have proven that hyperglycemia has caused acute inflammation, acute myocardium infarction, and stroke.[5,6] Insulin administration for maintaining blood sugar levels between 80-140 mg/dL is proven to reduce mortality and length of stay.[11] This is because insulin can act as a potent acute anti-inflammation and hence limit further damages.[5,6] There are two methods of insulin therapy for hyperglycemic patients due to organ dysfunctions; strict and standard therapy.[13,20] A previous study has showed a low incidence of hypoglycemia with the strict insulin therapy.[13] Therefore, we recommend the strict insulin therapy for hyperglycemia caused by MODS in children requiring intensive care.

The limitation of this study was blinding of the oblood sugar erver which could cause information bias. The researcher used objective criteria to determinate organ dysfunctions to reduce bias. The pitfall of this study was that we did not conduct an analysis for the onset and fluctuations of hyperglycemia, therefore a selection bias was likely to happen.

Multiple organ dysfunction syndrome had a significant association with hyperglycemia. This study reveals that MODS with hyperglycemia was ten times greater than with normoglycemia.

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Conflict of interest

None declared.

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