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Original Article

Insulin therapy for hyperglycemia in critically ill patients

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Abstract

Background Hyperglycemia in critically ill patients is associated with higher mortality. Insulin therapy may improve outcomes, not only by preventing deleterious effects of hyperglycemia, but by improving the molecular dynamics in organ dysfunction.

Objectives To assess the effects of insulin therapy on critically ill patients in an intensive care unit (ICU) setting and the risk of hypoglycemia.

Methods An open-label, clinical trial was conducted in the Pediatric Intensive Care Unit (PICU) of Dr. Moh. Hoesin Hospital, Palembang, from November 2011 to March 2012. Subjects were consecutively assigned to receive either regular insulin at a dose of 0.05 U/kg/h if the blood glucose level reached >200 mg%, or standard therapy (control group). Blood glucose levels were measured hourly until they reached 80-110 mg%. Dose adjustments were made when the blood glucose level reached 145 mg%, by reducing the insulin dose to 0.025 U/kg/h. Outcomes of therapy were measured by *Pediatric Logistic Organ Dysfunction* (PELOD) score improvement, mortality rate and the occurrence of hypoglycemia.

Results Forty subjects were enrolled in this study, with 20 subjects assigned to the insulin therapy group and 20 subjects to the standard therapy group. Two subjects, one from each group, were not included in the final analysis due to their deaths within 24 hours. There was no significant difference in distribution of PELOD scores before intervention between the groups (OR=0.5; 95%CI 0.1 to 1.9, P=0.32). However, after intervention, the PELOD scores was significantly lower in insulin therapy group compared to control group (OR 0.2; 95% CI 0.05 to 0.8, P=0.02). In the insulin group after intervention, fewer subjects had scores >20.5 and more subjects had scores ≤20.5, indicated a lower risk of organ dysfunction. There was also a significantly lower mortality rate in the insulin group compared to the control group (OR 0.2; 95% CI 0.05 to 0.8, P=0.02). None of the subjects suffered hypoglycemia.

Conclusion Insulin is beneficial in improving organ dysfunction and decreasing mortality for critically ill patients.
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Keywords: *critically ill, intensive care unit, hyperglycemia, insulin therapy*

Hyperglycemia in critically ill patients is associated with higher mortality rates and longer intensive care unit (ICU) stays. Insulin therapy may improve outcomes, not only by preventing deleterious effects of hyperglycemia, but by improving the molecular dynamic of organ dysfunction.[1-4]

Many studies showed that intensive insulin therapy reduced mortality in surgical and medical patients in the ICU. The overall hypothesis regarding treatment of hyperglycemia is that critically ill children will likely benefit from maintaining normoglycemia with exogenous insulin, as in critically ill adults.

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But, along with the rapid change in blood glucose concentration, the risk of hypoglycemia in insulin therapy is substantial.[4,5,6]

The aim of this study was to assess the effect of insulin therapy in critically ill patients in an intensive care unit setting, and their risk of hypoglycemia.

Methods

We conducted an open-label, clinical trial at the PICU of Dr. Moh. Hoesin General Hospital, Palembang, from November 2011 to March 2012. Subjects were assigned consecutively. We included all critically ill patients with hyperglycemia (defined as blood glucose >200 mg%) and without a history of diabetes mellitus. Patients with long-term use of steroids or growth hormone therapy were excluded. The severity of disease was assessed by *Pediatric Risk of Mortality* score III (PRISM III) at the time of admission. Patients with PRISM III scores above 8 were considered to be at increased risk of mortality. Organ dysfunction was assessed by PELOD scores twice, at the time of hyperglycemia diagnosis and 24 hours after the blood glucose level reached 80-110 mg%. A PELOD score above 20.5 was considered to be linked to an increased risk of organ dysfunction.

All subjects were assigned to case or control groups. In the case group, subjects received regular insulin (*Humulin®*) at 0.05 U/kg/h when blood glucose level was >200 mg%. The control group received standard therapy for the primary underlying diseases except the insulin therapy. Blood glucose levels were measured hourly until they reached 80-110 mg%. Dose adjustment was made when blood glucose level reached 145 mg%, by reducing insulin to 0.025 U/kg/h. If blood glucose decreased to <47 mg%, a bolus of 2 mL/kg 10% dextrose was administered intravenously. Hypoglycemia was defined as blood glucose level either <72 mg% with symptoms, or <47 mg% regardless of the presence of symptoms. Capillary blood glucose samples were measured by *Prodigy®* (USA).

Infants who died within 24 hours after the baseline of the study, were considered to be dropped out. The Ethics Committee of Sriwijaya University Medical School, Palembang, Indonesia, approved this study. An informed consent was obtained from all parents.

A 95% confidence interval and P value <0.05 were considered to be statistically significant. Differences in distribution of PELOD scores and mortality rates were analyzed by Chi square test or Fisher's exact test.

Results

Seventy-two patients were admitted to the PICU at Mohammad Hoesin Hospital, Palembang, during the study period. Forty subjects were assigned, hence each group consisted of 20 subjects, the insulin therapy group and the standard therapy group. One subject from each group was not included in the analysis due to deaths within 24 hours after the baseline of the study. Subjects' characteristics are shown in **Table 1.**

The distribution of PRISM III scores is shown in Table 1. Most subjects were in the PRISM III score >8 category. There was no significant difference in distribution of PRISM III scores between the two groups.

PELOD score was assessed twice, at the time of hyperglycemia diagnosis and at 24 hours after the blood glucose level reached 80-110 mg%. There was no significant difference in the distribution of PELOD scores before intervention between the groups (OR 0.5; 95%CI 0.1 to 1.9, P=0.32). However, PELOD scores were significantly improved in the insulin group after intervention (OR 0.2; 95%CI 0.05 to 0.8, P=0.02) (**Table 2**).

Seven subjects died in the insulin therapy group, while 14 subjects died in the standard therapy

Table 1. Characteristics of subjects (n=38)

Characteristics	Insulin therapy group (n=19)	Standard therapy group (n=19)
Gender, n		
Males	10	9
Mean age (SD), years	1.96 (2.97)	2.07 (3.24)
Nutritional status, n		
Well-nourished	10	14
Undernourished	6	5
Severely undernourished	3	0
Inotropic agents use, n	11	10
PRISM III score at the time of ICU admission		
>8, n	16	18
≤8, n	3	1

Table 2. Distribution of PELOD scores before and after intervention

PELOD scores	Insulin therapy group (n=19)	Standard therapy group (n=19)	OR (95% CI)	P value
Before, n				
>20.5	10	13	0.5 (0.1 to 0.9)	0.32
≤20.5	9	6		
After, n				
>20.5	7	14	0.2 (0.05 to 0.8)	0.02
≤20.5	12	5		

group. No subjects had hypoglycemia. There was a significantly lower mortality rate in the insulin therapy group than in the standard therapy group (OR 0.2; 95% CI 0.05 to 0.8, P=0.02).

Discussion

We identified 38 out of 40 patients with hyperglycemia who met the inclusion criteria. In this study, the mean age of subjects was 1.96 (SD 2.97) years in the insulin therapy group and 2.07 (SD 3.24) years in the standard therapy group. Our findings were similar to that of Gupta *et al*. who showed that the prevalence of hyperglycemia was 4.7% in 758 critically ill children aged between 1 month to 6 years.[1]

The PRISM III test is a third generation scoring system that allows assessment of illness severity and mortality risk.[7] In our study, the number of subjects with PRISM III score >8 was larger in the study group. Similarly, Kyle *et al*. reported that there was no relationship between hyperglycemia and disease severity.[8] Dewi reported that PRISM III score >8 correlated with the occurrence of organ dysfunction and mortality risk was 3.5 times compared with PRISM III score ≤8.[7]

The PELOD score is an assessment for detecting any organ dysfunction, even in patients with a low risk of death.[9] In this study, the proportion of PELOD score of >20.5 before intervention was higher in the study groups. After intervention, proportion of PELOD score of ≤ 20.5 in study group increased. Statistical analysis revealed no significant difference in distribution of PELOD scores before intervention between the two groups. But after intervention, there was significant difference in distribution of PELOD scores between the two groups. The results are consistent with research by Patel *et al*., where there were several mechanisms that potentially explained the benefits of insulin therapy and glycemic control in critically ill patients, including:[10] 1) improved immune function and decreased susceptibility to infection; 2) decreased systemic and cellular inflammation; 3) improved endothelial function (through improvement in vasomotor function and stimulation of nitric oxide production; 4) improved coagulable state owing to enhanced fibrinolysis and platelet function; 5) decreased triglyceride and increased high-density lipoprotein cholesterol levels; 6) anabolic effects of insulin; 8) improved myocardial function; 9) decreased circulation of free fatty acids; 10) suppression of free fatty acid uptake; 11) increased glucose uptake; 12) improved contractility; and 13) direct effect of potassium in glucose insulin-potassium solutions on myocardial function. Honna also reported PELOD score >20.5 can be used as a cut-off point for insulin intervention because PELOD scores >20.5 had a higher mortality prediction.[9]

A side effect of insulin therapy is hypoglycemia.[11] In our study, none of the subjects suffered hypoglycemia because we determined dose and duration of insulin therapy through tight serial blood glucose concentration monitoring. Verhoeven *et al*. reported that if hypoglycemia occurs because of a late glucose measurement, insulin is not properly set and to change parenteral to enteral nutrition without insulin setting.[11]

Mortality rate was higher in the standard therapy group than in the insulin therapy group (14 vs 7, respectively). There was a significant difference in mortality rate between the two groups, suggesting that insulin therapy in critically ill patients with hyperglycemia may decrease mortality. Our results were consistent with two studies by Van den Berghe *et al*. who showed that hyperglycemia was associated with high morbidity and mortality rates and insulin

therapy may decrease these morbidity and mortality rates in ICU patients.[5,6]

A limitation of this study was its small sample size. Also, insulin therapy was given at low doses of 0.05 U/kg/h with the cut-off point for hyperglycemia defined as blood glucose level of > 200 mg%.

In conclusion, insulin therapy for critically ill PICU patients may reduce organ dysfunction and decrease mortality.

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