The Impact of High Cortisol Level in Increasing Incidence of Infection Cases among Acute Stroke Patients

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Abstract

Background: Infection in the stroke was a treatment major problem, because it determines the prognosis. In the acute phase of stroke, high level cortisol may lead to a decreased immune system and patients tend to be more susceptible to infection. The correlation of serum cortisol level among acute stroke patients with incidence of infection was not fully investigated.

Objective: The aim of this study was to determine the relationship between initial serum cortisol levels and the incidence of infection in acute stroke patients.

Method: A prospective cohort study was conducted on 32 of acute stroke patients who admitted in RSUD Dr. Soetomo Surabaya during the period December 2015 to February 2016. Total of 2 cc to the venous blood within 48 hours in onset of stroke being examined of serum cortisol. During the 7 days of hospitalization, the patient was observed for signs of infection, both clinically and the investigation in accordance with the operational definition.

Results: In the infected group there were 8 people (50%) with high cortisol levels (p = 0.015; RR 15,000; 95% IK 1.583-143,171); 6 people were (50%) using urine catheter (p = 0.049; RR 6,667; 95% IK 1.067-30.085); And 6 people were (54.5%) using NGT (p = 0,035; RR 7,200; 95% IK 1.311 - 39,557). In multivariate analysis obtained that Odds Ratio (OR) 15,468 based on high cortisol and OR 7,469 based on NGT usage.

Conclusion: High cortisol levels and the use of NGT had the effect on the incidence of infection in acute stroke.

Keywords: *Acute Stroke, Serum Cortisol Level, Infection Incidence*

Introduction

Stroke was a major health problem in Indonesia. According to the National Basic Health Research data on 2013, the prevalence of stroke in Indonesia was 12.1 for each 1000 population, the number has revealed an increase in stroke prevalence when it was compared to the national data in 2007 which was 8.3 for each 1000 population [1]. Based on Registry Stroke data 2014 infarct stroke was noted as the most frequent cases (67.1%), followed by bleeding stroke (32.9%) [2].

In acute stroke, the systemic infection after the brain damage could be a symptom of the reduction competence of the immune system, that mediated by the central nervous system. The following period of stroke might be considered as a reaction to the stressful event. The red thread that links these two supersystems was the hypothalamus-pituitary-adrenal (HPA) axis [3]. The main characteristics of the response to stress were the activation of the sympathetic nervous system and the HPA axis [4].

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There were several hypotheses that attempt to explain the effect of stroke on the HPA axis, one of them was the structural injury in the brain regions that play a role in the regulation of HPA axis, such as the brainstem, hypothalamus, pituitary, terminal lamina, Limbic hippocampus. Additionally, the lateralization of the nervous system also helps in explaining the several locations that affect the metabolic changes post stroke. In addition, recurrent stress might increase the adrenal sensitivity to ACTH, which turn to leads to the prolonged hyper cortisol. [5] Cortisol was the responsible of primary hormone for the responses to the stress. In the event of exposure to stress the increased of circulating cortisol were inhibits the HPA activity at the hypothalamus and pituitary levels [6].

Increased cortisol suggests a severe inflammatory process that will lead to increased temperature, fibrinogen, leukocyte count, β thromboglobulin and IL-6[11]. Cortisol levels remain high within 7 days post-acute stroke and return to the normal limits approximately after 3 months. The highest cortisol levels were estimated to occur in the first 48 hours marked by the highest deactivation of monocytes [7].

Whereas, In acute stress conditions, cortisol also facilitates the release of anti-inflammatory mediators such as IL-4 and IL-10 that have apoptotic effects on immune cells[13].However, in chronic exposure, high levels of cortisol prevent this effect. The effect of cortisol on these cytokine signals was likely to optimize the occurrence of inflammation [8]. Complications of infection in stroke was a major problem in the treatment of stroke patients. Reported that 5-65% of acute stroke patients with the most common types of infection were urinary tract infections (16%) and pneumonia (12%). Factors that caused the Incidence of infection in high stroke includes: (1) frequent invasive medical procedures such as surgery, catheterization, mechanical ventilation, nasogastric tubing, (2) bed rest, (3) exposure to various drug-resistant bacteria, and (4) the swallowing disorders resulting from the lesions in the central nervous system and causing aspiration. However, the correlation of serum cortisol level among acute stroke patient with incidence of infection was remain unclear [9].

Materials and Method

This study was prospective cohort with analytic observational design. Affordable populations as the sample of this study were an acute stroke patients who admitted in Department of Neurology, Dr. Soetomo hospital, Surabaya, Indoensia during the period December 2015 to February 2016. [2]. The subjects were divided into two groups, namely the subject group of acute stroke patients with high cortisol levels and acute stroke subjects group with normal cortisol levels. Of total 32 samples, 16 samples were included in the high cortisol group and 16 were included in the normal cortisol group. In this study, several variables that measured were serum cortisol levels, the incidence of infection, age, body temperature, use of urine catheter, use of nasogastric tube (NGT) [10].

Serum corticol level are measured by blood samples collection as much as 3 ml from the study subjects within the first 48 hours of stroke onset, at 6-8 am then being examined in laboratory. High serum cortisol levels, when the results obtained on the examination more than 22.40 µg / dL. Normal cortisol serum levels, when the results obtained on the examination between 4.30 - 22.40 µg / dL.

Age based on official self-proof, from date of birth to date of data retrieval. The patient's body temperature was measured in the axilla for 2 minutes with a digital thermometer and expressed in degrees Celsius [8]. Statistical analysis was performed with SPSS version 22.0. The collected data was analyzed by Chi Square test for categorical data and unpaired t test for normal distributed numerical data. Differences in the proportion of infections in both groups were tested using Chi Square test [11].

Results

Tabel 1. Correlation between NGT usage and infection incident

	Group		Total	p	RR (IK 95%)
Variable	**Infection (+)**	**Infection (-)**			
NGT					
Yes	6 (54,5%)	5 (45,5%)	11 (100%)	0,035	7,200
No	3 (14,3%)	18 (85,7%)	26 (100%)		(1,311-39,557)
Total	9	23	32		

In the group of subjects infection, 6 (54.5%) was got NGT and 3 people (14.3%) did not use NGT. The chi square test showed statistically significant difference of proportion with p = 0,035 and relative risk (RR) was 7,200 (95% IK 1,311 - 39,557) (Table 3). This means that subjects with the use of NGT had a relative risk for infection 7.2 times compared to the subjects without NGT use.

Table 2. Correlation between cortisol rate and infection incident

	Group		**Total**	**p**	**RR (IK 95%)**
Variable	**Infection (+)**	**Infection (-)**			
Cortisol Rate					
High	8 (50%)	8 (50%)	16 (100%)	0,015	15,000
Normal	1 (6,25%)	15 (93,75%)	16 (100%)		(1,583-143,171)
Total	9	23	32		

In the group of subjects infection, 8 (50%) had high cortisol and 1 person (6.25%) with normal cortisol levels. By using chi square test statistically significant difference with p = 0,015 and Relative Risk equal to 15,000 (IK 95% 1,583 - 143,171). This means that subjects with high cortisol levels had a relative risk for infection of 15,000 times compared to the subjects with normal cortisol levels (Table 3).

Tabel 3. Analysis result of multivariate logistic regression

	Coefisien	**SE**	**Wald**	**Df**	**P Value**	**OR**	**IK 95%**	
							Min	Max
Cortisol rate	2,739	1,232	4,941	1	0,026	15,468	1,382	173,073
NGT	2,011	1,020	3,887	1	0,049	7,469	1,012	55,131
Constanta	-3,597	1,254	8,222	1	0,004	0,027		

In this study subjects based on the cortisol content obtained the value of Odds Ratio (OR) 15.468 with the interpretation that subjects of high cortisol content have the possibility for the occurrence of infection 15,468 times compared to the subjects with normal cortisol levels. In the study subjects based on the use of NGT obtained the value of Odds Ratio 7,469, with the interpretation that subjects with the use of NGT have the possibility for the occurrence of infection of 7.469 times compared to the subjects without the use of NGT. Based on this multivariate analysis (table 4), it revealed that the variables affecting the incidence of infection cortisol levels and the NGT use with the greatest relation strength was cortisol content with OR = 15,468.

Discussion

In this study, we found 20 subjects with infarct stroke and 12 subjects with intracerebral hemorrhage stroke. There was no significant difference of cortisol

content based on the stroke type with p = 0,716. This was consistent according to the results of a meta-analysis of various studies that found elevated cortisol levels were more associated with morbidity, mortality and stroke severity, compared to the stroke types. In this study, we obtained acute stroke patients with high cortisol levels of 16 subjects or 50% of the total subject. In the patients with acute stroke, there was an increase or abnormality of ACTH secretion and cortisol associated with extensive infarction, poor functional outcome and increased mortality [12].

In this study, 8 subjects with diabetes mellitus and 24 subjects did not suffer from the diabetes mellitus. There was no significant difference in the proportion of diabetes mellitus status between the two groups in this study (p = 0.220). Chiodini in his study also mentioned that the increase in cortisol levels was more related to the complications of diabetes mellitus and it was the degree of complication. Meanwhile in this study was not studied about the complications and degrees of complications in diabetes mellitus that occurred in the study subjects.

Glucocorticoids affect vascular tone by increasing vascular resistance and causing secondary hypertension [13]. However, there was no significant difference in proportion between the two groups in our study (p = 0.5654). This might be due to our study, that the hypertension was thought to be primary hypertension that was more associated with vascular risk factors and not secondary to the high levels of glucocorticoids.

Urinary catheter insertion action could bring the organisms from the urethra directly into the bladder. Most strains of bacteria entering through the urinary catheter could multiply rapidly within a day and persist for up to weeks causing urinary tract infection (UTI) [26]. This was consistent with our results where in the group with infection there were 6 subjects (50%) using catheters and 3 subjects (15%) did not.

The analysis with chi square test showed the statistically significant difference in proportion with p = 0,049 and relative risk of 6,777 (95% IK 1,067-30,085). Based on these data it could be said there was a significant relationship between the use of urine catheter with the incidence of infection, where subjects who use urine catheter have a risk of 6,777 times to experience the incidence of infection than subjects who did not use urine catheter. Thus it could be said that the use of urinary catheters in this study was a significant confounding factor for the occurrence of infection [14].

Pneumonia occurs in 44% of acute stroke patients with dysphagia using NGT. NGT was associated with the buildup and aspiration of pharyngeal secretions and gastric contents leading to the high incidence of gram-negative pneumonia in patients with NGT use. This was consistent with our results that in the infected group there were 6 subjects (54.5%) with NGT use and 3 subjects (14.3%) did not. From the analysis with chi square test, there was a statistically significant difference of proportion with p = 0,035 and relative risk was 7,200 (95% IK 1,311-39,557) [15]. Based on these data it could be said there was a significant relationship between the use of NGT with the incidence of infection, where subjects who use NGT have a risk of 7.2 times to experience the incidence of infection than subjects who did not use NGT. The use of NGT in this study was a significant confounding factor for the occurrence of infection [2].

Chen et al mention that the brain infarction could lead to the systemic immunodepression which was predisposes to the infection. Stroke induces widespread apoptosis of lymphocytes and a shift in the production of Th1 to Th2 with immune-system depression [16]. Choi et al mentioned in his research that cortisol exposure was known to reduce the telomerase activity in human T lymphocytes. Meanwhile, Mavoungou et al found that cortisol decreased the ability of NK cells to kill target cells. Cortisol inhibits the expression of cytotoxic receptors from NK cells Transcription level of the regulating gene [14].

Although several studies have examined the relationship between the post-stroke and the incidence of infection, there have been no specific studies that been examining the association between serum cortisol levels and the incidence of infection in acute stroke patients [17]. Therefore, this study was the first study to find the relationship between serum cortisol levels and the incidence of infection in patients with acute stroke. The limitations in this study were the presence of the other confounding factors that could not be controlled, such as the use of urine catheter and NGT. The advantages of this research were to use a prospective cohort research design which was the best observational research design to find the cause and the effect relationship.

Conclusions

In conclusion, this study revealed that high serum cortisol levels and the use of NGT among stroke patients

may contributed to the incidence of infection.

Ethical Clearance: This research process involves participants in the survey using a questionnaire that was accordant with the ethical research principle based on the regulation of research ethic committee. The present study was carried out in accordance with the research principles. This study implemented the basic principle ethics of respect, beneficence, nonmaleficence, and justice.

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