

The association between cortisol dynamics and the course of aneurysmal subarachnoid hemorrhage

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ABSTRACT

Context: One of aneurysmal subarachnoid hemorrhage complication is delayed ischemic neurological deficits (DIND). It is postulated that cortisol dynamics might be associated with the severity of this complication.

Aims: The goal of the study is to investigate whether the peak of morning serum cortisol levels are associated with the severity of its complication during the course of the disease.

Settings and Design: This is a prospective cohort study conducted from January 2009 to June 2011, at our institution.

Materials and Methods: The study follows a consecutive cohort of patients for 14 days after the aneurysmal subarachnoid hemorrhage. Serum cortisols, cortisol binding globulin, adenocorticotrophic hormone (ACTH) were measured pre operatively and then on post operative days (POD) 2, 4, 7, and 10. Blood was drawn to coincide with peak cortisol levels between 08.00-09.00 hours. Neurological examinations were conducted at least twice daily and patient outcome were graded according to modified Ranklin Scale. DIND was defined by a decrease in the Glasgow Coma Scale of two or more points compared to the status on POD 1.

Statistical Analysis: All the results were analyzed using statistical software, Statistical Package for Social Sciences (SPSS v61; SPSS, Inc., Chicago, IL). Logistic regression analysis was used to compare the relationship between the variables.

Results: Thirty six consecutive patients are collected, but only 28 patients (12 M and 16 F) were eligible for the cohort analysis. Average patient age is 50.75 years old (50.75 ± 12.27), and more than 50% (15/28) arrived with World Federation of Neurologic Surgeons grade 3 or better. Elevated total cortisol levels of more than 24 $\mu\text{g/dl}$ on day 2, 4, and 10 were associated with DIND, and the most significant being on day 4 ($P=0.011$). These patients also had a higher grade on the modified Ranklin scale of disability.

Conclusions: This study shows that the elevated levels of morning total cortisol in the serum are associated with the onset of DIND during the disease course, and it's also associated with bad outcomes.

Key words: Aneurysmal subarachnoid hemorrhage, clipping, cortisol, delayed ischemic neurological deficits, outcome

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Introduction

The cortisol dynamics might be associated with the severity and outcome after aneurysmal subarachnoid hemorrhage.^[1] It is well known that the cortisol plays an important role as a defense mechanism for stress conditions such as sepsis, fasting, trauma, pain, and tissue ischemic.^[2] Aneurysmal subarachnoid hemorrhage is a devastating condition which produces severe headache, constitutional symptoms, and neurological deficits. All of those things will precipitate a strong stress response and increase the serum cortisol levels through hypothalamic and autonomic nervous system pathways. Theoretically, cortisol itself may increase the risk of vasospasm through its up-regulating endothelin-1 (vasoconstriction) and its

down-regulating nitric oxide (vasodilatation). Vasospasm has been studied extensively and is a well recognized condition following aneurysmal subarachnoid hemorrhage. It is a major determinant of patient outcome even with appropriate treatment, and clinically, it is recognized as delayed ischemic neurological deficits (DIND). The purpose of the study is to investigate whether the morning serum cortisol level could be associated with changes in the disease course.

Materials and Methods

Thirty six consecutive patients (age > 18 years), with aneurysmal subarachnoid hemorrhage, who underwent craniotomy clipping procedure within the first two days of bleed, were included in this study. Exclusion criteria were pregnancy, pre-existing pituitary insufficiency, and glucocorticoid medication during admission or treatment. This is a prospective cohort study that follows the patients for the first two weeks after surgery. All patients or their next of kin provided consent for this study, which is approved by the Institutional Review Board of Universitas Hassanuddin Makassar. A ten cc sample of venous blood was taken pre-operatively, then every morning (08.00-09.00 hrs) on POD 2, 4, 7, and 10. Serum cortisols, cortisol binding globulin (CGB), and adenocorticotrophic hormone (ACTH) were measured. Daily clinical assessments were done by the investigator and another independent clinician.

All patients were managed in the intensive care unit by the neurosurgical and neurointensivists teams. Nimodipine was routinely given for at least 14 days (2 mg/h). DIND is defined as a decrease in the Glasgow Coma scale (GCS) of two or more points compared to the GCS on POD 1. Patients who died on POD 1 or suffered from severe complication of infection, heart problem, kidney failure, sepsis, or multiple organ failure were removed from the study.

The total serum cortisol levels were measured by immunoassay (electrochemiluminescence immunoassay 'ECLIA') using Elecsys cortisol kit (cat no. 11875116 122); serum CGB levels were measured by radioimmunoassay using CBG (transcortin) RIA (cat no MG13061) (IBL International GmbH, Hamburg, Germany; reference value men 22-55 µg/ml; reference value women 40-154 µg/ml); and serum ACTH measured using ACTH ELISA (cat no ACO18T) (Calbiotech Inc., Spring Valley, CA; reference value: 8.3-57.8 pg/ml). Coolens equation^[3] was used to calculate the amount of free cortisol in the serum. The patient clinical condition and imaging were graded according to World Federation of Neurologic Surgeons (WFNS) grading^[4] and Fisher grading.^[5] Patients outcome was graded according to modified Rankin scale.^[6]

All the data were analyzed using statistical software, Statistical Package for Social Sciences (SPSS v61; SPSS, Inc., Chicago, IL) and reviewed by a professional statistical consultant. Due to the sample size ($n=28$), non-parametric statistics were

used for calculation. To assess whether cortisol variables are distributed normally, we use Shapiro-Wilk test. Data were presented descriptively and underwent univariate analysis. Logistic regression bivariate analysis was used to see the relationship between the total cortisol or free cortisol, and the DIND neurological status. Regression bivariate analysis was used to see the relationship between total cortisol and ACTH. Logistic regression multivariate analysis was used to define the interaction between the variables and DIND.

Results

There are 36 patients collected in this study, but eight patients were withdrawn from analysis because of co-morbid condition or inability to get follow-up data. The analysis cohort was 28 patients (12 M and 16 F). Patients average age is 50.75 years old (50.75 ± 12.27) with the median age of 50.50 years old. The duration of ICU stay in this study was 8-45 days (mean 23 days). Average hospital stay was 32 days (11-69). Over 50% (15/28) of the patients arrived with WFNS grade 3, 35% (10/28) grade 2, and 10% (3/28) with grade 4. Blood distribution on initial computed tomography (CT) scans showed the majority of cases (62.5%) with Fisher grade 3; 25% with Fisher grade 2; and 12.5% with grade 4.

The most common location of aneurysm in this study is anterior communicating artery (10) followed by posterior communicating artery (5), middle cerebral artery (4), internal carotid (IC) artery bifurcation (4), IC-choroidal artery (2), IC-ophthalmic artery (1), vertebral artery (1), and posterior inferior cerebellar artery (1). Patient outcomes based on modified Rankin Scale were fairly good. One patient died on day 16, due to pneumonia.

The basal serum cortisols, on admission (before surgery), ranged between 0.02 to 63.44 (mean 24.69 and median 22.49). The ACTH level represents the function of the hypothalamo-pituitary-adrenal axis, whether it is solely related to baseline cortisol levels or involving extra ACTH cortisol release from the hemorrhage will be analyzed, periodically. Results of cortisol, ACTH, CBG, and free cortisol are presented in [Table 1].

Statistically, total cortisol level on day 2, 4, and 10 shows significant relationship with the clinical worsening (DIND) [Table 2]. It is most significant on day 4 ($P=0.011$). Unfortunately, the free cortisol levels did not show proportional relationship with the DIND ($P>0.083$). The increase total cortisol level is followed by the increased level of CBG. This might be a body compensation to reduce the biological effect of the cortisol. So, in other words, it's not the biological effect of free cortisol that causes the clinical worsening.

One case in our series, a young female of 22-year-old, GCS 15 after surgery, and total cortisol level 37.23 µg/dl on

Table 1: Cortisol dynamics following microsurgical aneurismal clipping

	Day 0	Day 2	Day 4	Day 7	Day 10
ACTH	n=24	n=27	n=28	n=28	n=24
Mean (SD)	29.41 (49.50)	25.89 (32.74)	25.91 (31.58)	32.42 (26.13)	29.45 (26.29)
Median	9.79	14.80	13.53	19.75	23.49
Min	0.46	0.91	0.46	4.45	3.56
Max	195.82	150.65	121.78	89.47	108.89
Cortisol	n=28	n=27	n=28	n=28	n=26
Mean (SD)	24.69 (16.95)	28.22 (12.12)	23.94 (10.40)	26.86 (11.02)	25.22 (12.70)
Median	22.49	27.28	22.55	24.43	24.38
Min	0.02	12.10	2.53	6.16	7.15
Max	63.44	63.60	48.73	63.44	70.12
Free-Cortisol	n=20	n=22	n=23	n=23	n=19
Mean (SD)	1.80 (1.18)	1.54 (0.91)	1.21 (0.91)	1.58 (1.90)	1.17 (0.85)
Median	1.72	1.34	0.93	1.10	1.18
Min	0.00	0.41	0.11	0.19	0.26
Max	3.66	4.25	3.99	9.04	3.94
CBG	n=24	n=27	n=28	n=28	n=24
Mean (SD)	29.06 (10.72)	32.30 (13.87)	37.52 (12.42)	40.96 (15.38)	40.89 (13.39)
Median	27.38	28.75	36.00	40.63	39.00
Min	10.75	12.50	10.75	5.00	19.25
Max	54.50	79.75	61.00	72.75	65.50

ACTH - Adenocorticotrophic hormone; CBG – Cortisol binding globulin

day 4; 63.44 µg/dl on day 7, was release from ICU care, on day 9, to the ordinary ward. She was perfectly well (GCS 15), fully oriented, since POD 1 to 9, but she still suffered from significant headache. Unfortunately, on the evening POD 9, her conscious levels dropped to GCS 12, showing signs of lateralization, and finally we have to perform decompression craniectomy. Just before the surgery, her GCS was 7 with one side pupil dilated. On the next day of the surgery (day 10), her total cortisol level was 50.02. She went through tracheostomie, stayed in ICU for more than one month, accounting for a total hospital stay of 67 days. She went home with lot of assistance, and finally, she recovered very well after three months. Patient with increased level of total cortisol (>24 µg/dl, especially within the first week), although have GCS 15 with only mild headache, should, probably, be kept in ICU or Neuro Step-down Unit (NSU).

The function of hypothalamo pituitary adrenal axis is the primary regulator for cortisol secretion. There is a linear relationship between ACTH and total cortisol release during the first week. ACTH levels continued to rise during the first week, and gradually decreased during the second week. Although the ACTH levels were decreasing in the second week, but the total cortisol levels were persistently high [Figure 1].

Table 2: Relationship between the cortisol, CBG, and ACTH with clinical worsening (DIND)

	Day 2	Day 4	Day 7	Day 10
Cortisol				
LR Chi2	7.08	19.64	1.71	12.77
P>(Z)	0.028	0.011	0.22	0.022
Pseudo R2	0.1938	0.5078	0.0441	0.3979
Free-Cortisol				
LR Chi2	4.04	2.05	0.01	4.31
P>(Z)	0.083	0.198	0.909	0.091
Pseudo R2	0.14	0.06	0.0004	0.1819
ACTH				
LR Chi2	0.41	0.66	1.38	0.09
P>(Z)	0.528	0.431	0.256	0.759
Pseudo R2	0.0112	0.0169	0.0355	0.0032
CBG				
LR Chi2	1.3	0.663	0.46	1.12
P>(Z)	0.297	0.664	0.505	0.298
Pseudo R2	0.0355	0.0049	0.0118	0.00388

ACTH - Adenocorticotrophic hormone; CBG – Cortisol binding globulin

Discussion

There is an evidence showing that the cortisol dynamics might be associated with the severity and outcome after aneurysmal subarachnoid hemorrhage.^[1] Although a previous study on the pituitary adrenal function in acute subarachnoid hemorrhage (SAH) has shown that the SAH severity does not affect cortisol concentration,^[7] that study did not describe the relationship between the total cortisol level and the patient’s neurologic state. Also, they were unable to show any difference in the adrenal response between comatose (GCS<8) and non comatose patients. Vergouwen *et al.* have shown that the increase cortisol level is associated with the DIND, through hyperglycemia and endothelium dysfunction (von Willebrand factor).^[8] Whether the cortisol is just part of the stress process and is unrelated to the ongoing worsening of patient neurologic status, or it is contributing to make the patient worst, is still unclear. In our study, it shows that the total morning cortisol levels were associated with DIND on POD day 2, 4, and 10, and the most significant one is on POD 4 (P=0.011). It is consistent with the fact that most of symptomatic vasospasm (who presented with DIND) usually starts on days three and four, after SAH, and progressively gets worsened until the peak levels of oxy-hemoglobin at day seven, after the SAH.^[9]

Normally, the morning total cortisol level should not exceed 18 µg/dl. During the disease course, the cortisol could reach four times normal value (63.44 µg/dl). The increased level of total serum cortisol was followed by the increase of CBG. The end result was that the free cortisol which was the one that have biological role, does not increase. The increase level of CBG may represent the body compensation to control the biological effect of cortisol. More than 90% of cortisol itself is bound

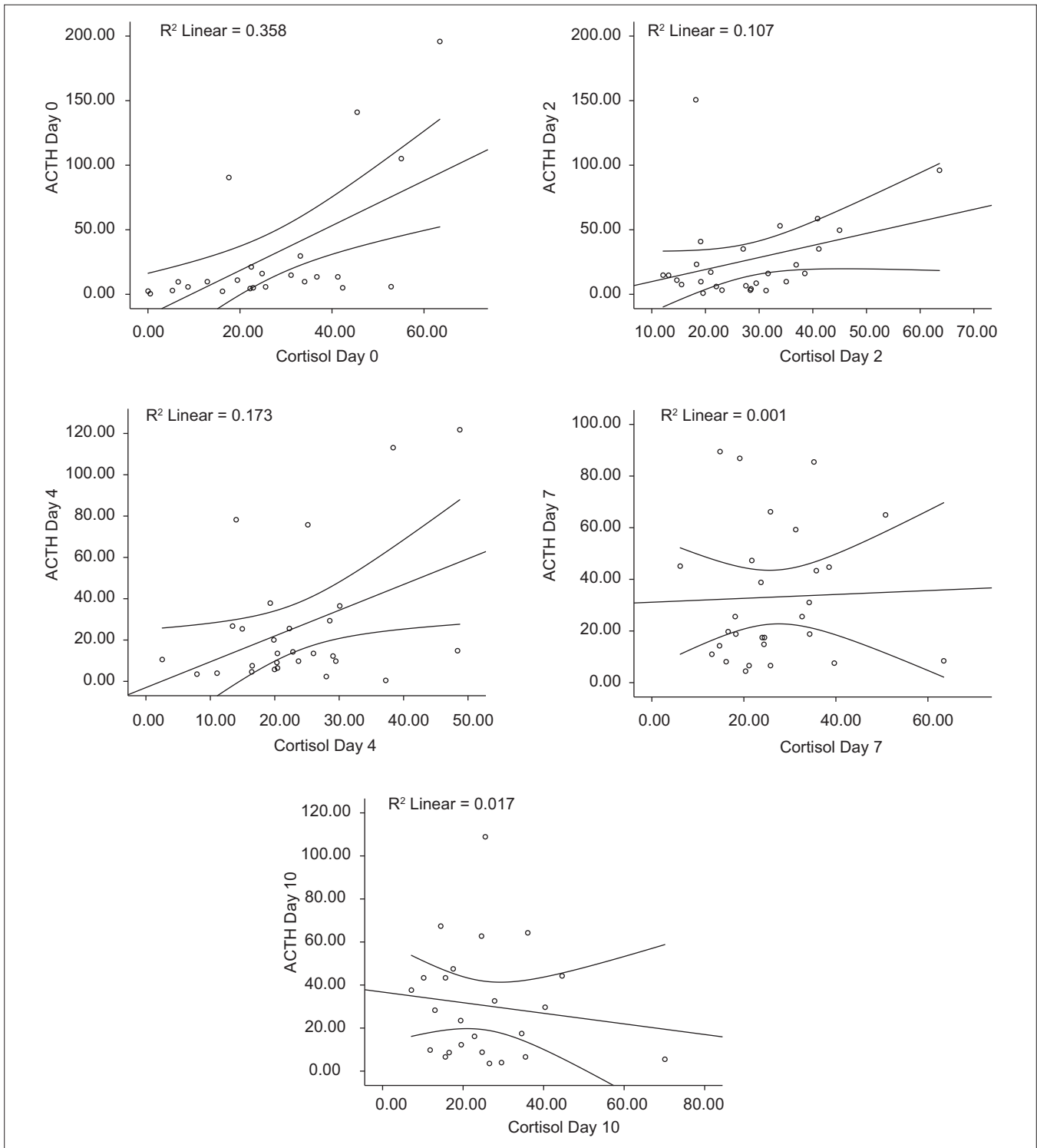


Figure 1: Adenocorticotrophic hormone and cortisol release

to cortisol binding globulin (CBG),^[10] and only unbound free cortisol is responsible for physiological effects. Our result shows that the free cortisol levels do not correlate with the DIND, during the follow-up. This evidence suggests that the cortisol level is only part of the stress process and is not contributing to the clinical worsening of patient with DIND. Although, theoretically, cortisol itself could increase the risk of vasospasm

through its up-regulating endothelin-1 (vasoconstriction) and its down-regulating nitric oxide (vasodilatation).^[11,12] In our study, the CBG were increased proportionally following the total cortisol level, and this might explain why the free cortisols were maintained at a constant level. This supports the observation that although the total cortisol level is increased, but the biological consequences are not great.

Our study supports the evidence that the total morning cortisol level in serum is associated with the onset of DIND. The total cortisol levels frequently elevate within 24 hours prior to the clinical worsening (GCS decrease >2 points), and from our observation, the mild hypoxia usually make it worst (data not presented). It's probably the ischemia at the level of endothelial cells following the hypoxia that turn on the transcription of human endothelin-1 gene in chromosome 6.^[13] The evidence suggests to consider the total cortisol level as one of the factors before releasing the patient from ICU care or NSU to the ordinary ward, especially during the first week after surgery. The patients with high total cortisol level that do not fit the criteria for DIND, very often will show increasing headache. We need to put attention for the increasing headache, since it could be a non localizing finding associated with the early DIND.

Interestingly, three cases in our series with extremely low pre-operative total cortisol levels (<1 µg/dl), showed increase in cortisol level on the following days, but none of them developed DIND, despite the cortisol exceeding 24 µg/dl. In our study, low preoperative cortisol level was not associated with the clinical worsening (DIND). Elevation of cortisol level on the post-operative days suggests that the HPA response function is intact.

During the first few days of SAH, the cortisol level is totally dependent on the Hypothalamo - Pituitary-adrenal (HPA) function. The ACTH is released from the anterior pituitary to stimulate cortisol release from the adrenal gland. It is the major source of the cortisol, but on POD 7, the function is taken over by the extra ACTH cortisol release [Figure 1]. In the second week, although the ACTH level is decreasing, the total cortisol levels were persistently high. It supports the evidence that there is an extra ACTH cortisol release. Interleukin 6 (IL-6) constitutes a potentially important factor of extra-ACTH cortisol release,^[14] besides IL-1 and tumor necrosis factor-alpha.^[15] The role of inflammatory pathway becomes substantial in the second week.

Total cortisol level also correlates with the modified Rankin scale. Patients with total cortisol levels >24 µg/dl are shown to have higher grade of modified Rankin scale. In long term follow-up (>12 months), their grade is likely to improve.

Conclusion

This study shows that the elevated levels of morning total cortisol in the serum are associated with the onset of DIND

during the disease course, and it's also associated with bad outcomes.

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