

SALIVARY CORTISOL LEVELS AS A PROGNOSTIC OUTCOME MARKER IN PATIENTS WITH ACUTE ANEURYSMAL SUBARACHNOID HAEMORRHAGE

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Abstract

The physiological stress response to aneurysmal subarachnoid haemorrhage (aSAH) may trigger not only beneficial effects. Production of corticosteroids and catecholamines can induce cerebral vasospasm. Cortisol secretion levels were used to assess physiological stress. However, the appropriate measurement method remains controversial. Our study aimed to establish the relationship between cortisol levels measured in the saliva of patients with aSAH, neurological status, and mortality rates. Our study included 128 patients with aSAH treated with endovascular embolization for cerebral aneurysm with a daily examination of the cortisol level in saliva at 08.00 AM and 08.00 PM until ICU discharge or death. Daily salivary cortisol levels, haemodynamic parameters (mean arterial pressure), neurological status, and the level of consciousness (GCS) were monitored. This study included 53 women and 75 men. The mean patient age was 64.2 years (range: 42–77 years). Eighteen (14.06%) patients died. Salivary cortisol levels were significantly higher in deceased patients, both in the morning (31.8 nmol/l for deceased patients vs. 16.8 nmol/l for patients discharged alive; $p < 0.001$), and in the evening during the follow-up period (5.2 nmol/l for deceased patients vs. 3.6 nmol/l for patients discharged alive; $p < 0.001$). We found a statistically significant correlation between an increase in morning salivary cortisol levels and neurological deterioration. Similar observations of evening cortisol levels were observed in only five patients.

Measurement of salivary cortisol levels in patients with aSAH provides additional information about prognosis. Patients who die during the acute phase of aSAH have higher morning and evening salivary cortisol levels than those who survive. Patients who died demonstrated a progressive increase in salivary cortisol levels in the morning.

Key words: cortisol, saliva, mortality, subarachnoid haemorrhage (SAH), intensive care unit (ICU), Glasgow Coma Scale (GCS)

Introduction. Aneurysmal subarachnoid hemorrhage (aSAH) has an annual incidence of 5–6 per 100 000 person-years. The 30-day mortality rate is 20–25% and has not changed significantly in recent years. The most common cause of death and disability following aSAH is cerebral ischemia from cerebral vasospasm [1, 2]. The stress response to aSAH has beneficial effects and may be an additional cause of vasospasms. The stress response is mediated by the endogenous production of corticosteroids and catecholamines, and measurement of blood cortisol levels, which have been the most widely used to assess stress responses, is characterized by certain limitations. The process of obtaining blood samples from the vein is accompanied by additional stress, resulting in false-positive results. Another disadvantage is that cortisol measured from serum or plasma represents total cortisol, not free, biologically active cortisol. The measurement of morning and evening salivary cortisol levels may monitor free cortisol levels in the serum and may be an effective and convenient screening test for stress responses [3]. Elevated levels of cortisol in the saliva are associated with a higher stress-induced response in patients with SAH and a lower GCS score during treatment in the ICU [4]. The aim of our study was to establish the relationship between the level of cortisol measured in the saliva of patients with aSAH, the Glasgow Coma Scale (GCS) score, and the rate of mortality in the intensive care unit (ICU).

Materials and methods. Study design. This was a prospective observational cohort study of patients with aSAH who were treated between January 2019 and September 2021 in the Intensive Care Unit (ICU) of the Department of Anesthesiology and Intensive Care at “St. Ivan Rilski” Hospital, Sofia. The trial was approved by the ethical committee of University Hospital “St. Ivan Rilski”. We chose a non-invasive method for collecting samples for economic reasons and for the purpose of our study.

Inclusion and exclusion criteria. Our study included patients with aSAH treated with endovascular embolization for cerebral aneurysm with daily examination of the level of cortisol in saliva at 08.00 AM and 08.00 PM until ICU discharge or death. Saliva samples were collected from each patient using a salivette (Sarstedt). A salivary ELISA kit was used for quantitative measurement of cortisol levels in the saliva samples. One hundred and forty-four consecutive patients were treated for aSAH with endovascular embolization between January 2019 and September 2021. Endovascular embolization was performed within 24 h of admission. Six patients were excluded because of problems with the numbers or timing

of saliva collection and ten were also excluded because of long-term 42 days (± 7 days) treatment in the ICU and complications associated with acute respiratory failure, lung infection, acute renal failure, and sepsis. None of the investigated patients were sedated during the treatment.

A total of 128 patients were included in this study. All patients with SAH were treated in the intensive care unit (ICU) according to the same hospital treatment protocol: 1. Nimodipine i.v.; 2. Euvolemia (normal CVP and Hct range); 3. Prophylactic hypertension (maintain MAP around or above 90 mmHg); 4. Vasopressor-induced elevation of mean arterial pressure; 5. Normal blood oxygenation and saturation. Observed parameters: Daily salivary cortisol levels, haemodynamic parameters (mean arterial pressure), neurological status, and the level of consciousness (GCS) were monitored. Data were collected daily until ICU discharge (average 12.2 days, 7–14 days) or death.

Statistical analysis. Statistical analyses were performed using the SPSS version 23 software (IBM Corp., Armonk, NY, USA). A descriptive analysis of consecutive time-point measurements of mean salivary cortisol levels, Glasgow Coma Scale score, and mean arterial pressure was performed. Data are presented as mean $\pm$ standard deviation (SD). The associations between mean salivary cortisol levels and the Glasgow Coma Scale were analyzed using Pearson's correlation coefficient r . The statistical significance was set at $p < 0.05$.

Results. This study included 53 women and 75 men. The mean patient age was 64.2 years (range: 42–77 years). Eighteen (14.06%) patients died. All patients had a Fisher score of first or second grade and Hunt and Hess grade first or second. We found no direct relationship between mortality rate and the degree of Fisher or Hunt and Hess scale. Aneurysm location in observed patients were: ICA right 39, ICA left 35, MCA right 25, MCA left 17, a. basilaris 2. All surviving patients in this study had GCS 14 and 15 p. Patients who died showed poor levels of consciousness (GCS 13–3 p.), which progressively decreased in direct proportion to increased salivary cortisol levels. Salivary cortisol levels were significantly higher in deceased patients, both in the morning (31.8 nmol/l for deceased patients vs. 16.8 nmol/l for patients discharged alive; $p < 0.001$) and in the evening during the follow-up period (5.2 nmol/l for deceased patients vs. 3.6 nmol/l for patients discharged alive; $p < 0.001$). There was no difference in mean arterial pressure (Table 1).

Salivary cortisol levels remained significantly higher in the morning and evening in deceased patients than in those discharged alive during the entire follow-up period (Table 1, Fig. 1).

The median survival time among the deceased patients was 10 days, with a minimum of 6 days and maximum of 12 days. The dynamics of salivary cortisol levels differed in the morning and evening in deceased patients (Fig. 2).

We found a statistically significant correlation between the increase in morning salivary cortisol levels and the decrease in GCS scores in 11 of 18 deceased

T a b l e 1

Mean salivary cortisol levels (nmol/l) at 8 h and 20 h and mean arterial pressure (mmHg) among alive and deceased patients

Day	Discharged alive patients				Deceased patients		
	Mean salivary cortisol levels nmol/l – 8 h	Mean salivary cortisol levels nmol/l – 20 h	MAP – mean arterial pressure mmHg		Mean salivary cortisol levels nmol/l – 8 h	Mean salivary cortisol levels nmol/l – 20 h	MAP – mean arterial pressure mmHg
1 day	15.2	3.5	89		26.7	5.5	91
2 day	16.5	3.6	88.0		28.2	5.7	92
3 day	15.7	3.2	91.0		27.1	6.1	88
4 day	17.5	2.8	85.0		27.7	4.8	87
5 day	17.9	3.8	93.0		25.5	4.7	85
6 day	18.1	4.2	94.0		30.3	5.1	89
7 day	16.2	4.1	84.0		31.4	4.5	94
8 day	17.3	3.7	87.0		39.1	4.7	91
9 day	16.9	3.6	88.0		36.5	4.8	90
10 day	15.8	3.1	88.0		35.1	4.7	92
11 day	18.1	4.4	92.0		37.7	5.9	91
12 day	16.7	3.3	94.0		36	6.1	87
Mean values	16.8	3.6	89.4		31.8	5.2	89.8

patients (Table 2). The same correlation for evening salivary cortisol levels was found in only 5 patients (Table 2).

Discussion. Salivary cortisol. The idea of assessing salivary cortisol as a reflection of free biologically active cortisol in plasma was introduced in the 80s [5]. This method has been used to study physiological stress responses and pathological syndromes [6–11]. Our experience confirms the findings of different centres that salivary cortisol using ELISA is a cheap, fast, and reliable method for obtaining information on plasma cortisol levels and assessing the hypothalamic-pituitary-adrenal response. We excluded less than 10% of our consecutive patients with aSAH because of problems with the number or timing of saliva collections. The saliva sampling method was tested even in free-living environments, and the feasibility of home-based sampling was proven [12].

Effects of increased cortisol. Severe illnesses, such as aSAH, usually trigger a stress response with activation of the hypothalamic-pituitary-adrenal and sympathetic systems. Studies have linked high serum cortisol levels to high mortality, especially in patients with Cushing's syndrome and acute coronary syndrome [7–11]. Experimental and clinical studies have found significant acute and late

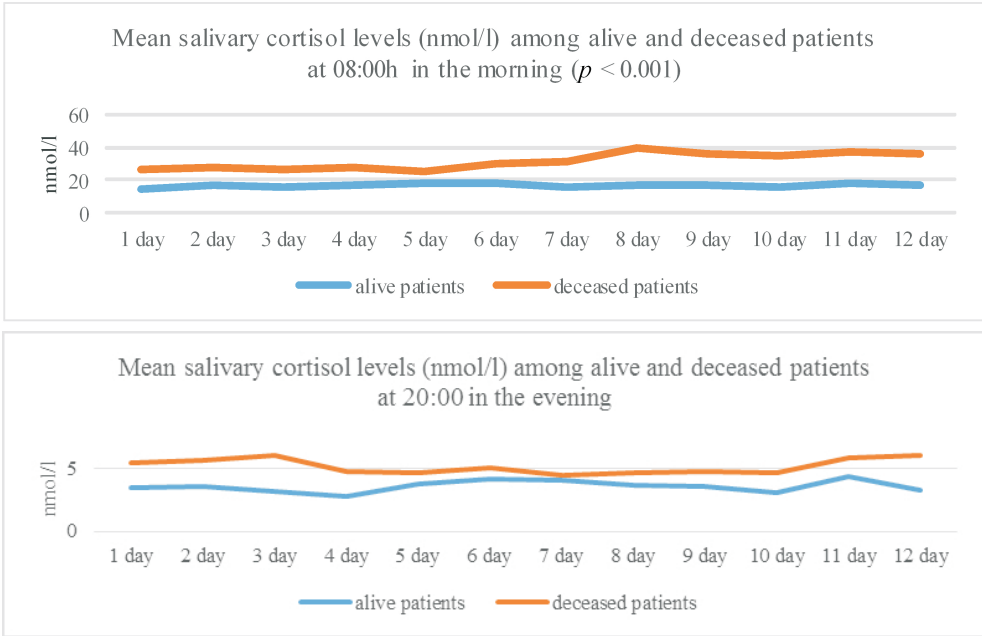


Fig. 1. Mean salivary cortisol levels (nmol/l) among alive and deceased patients at 08:00 h in the morning and at 20:00 in the evening ($p < 0.001$)

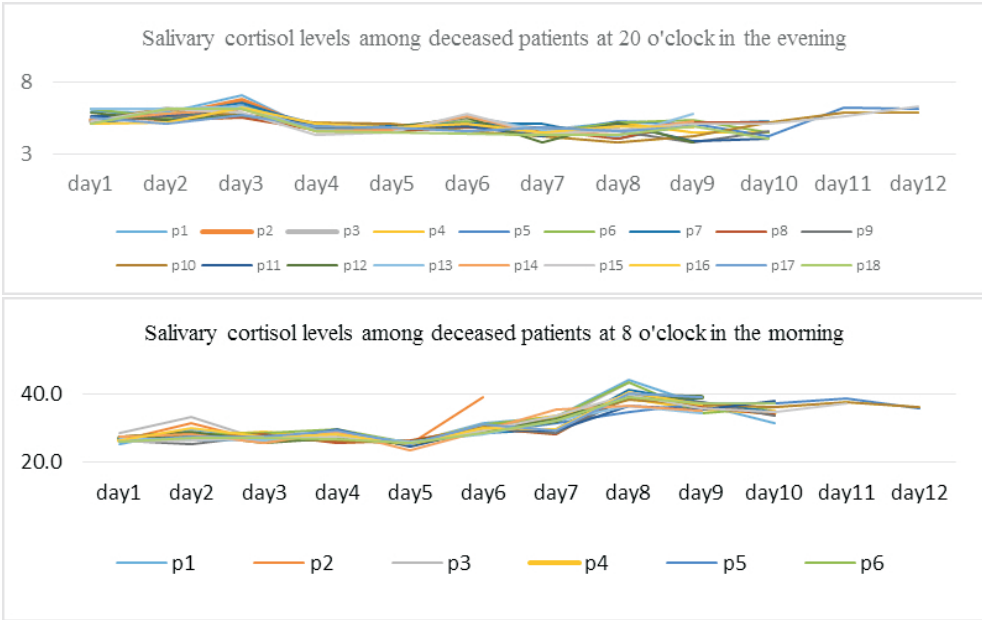
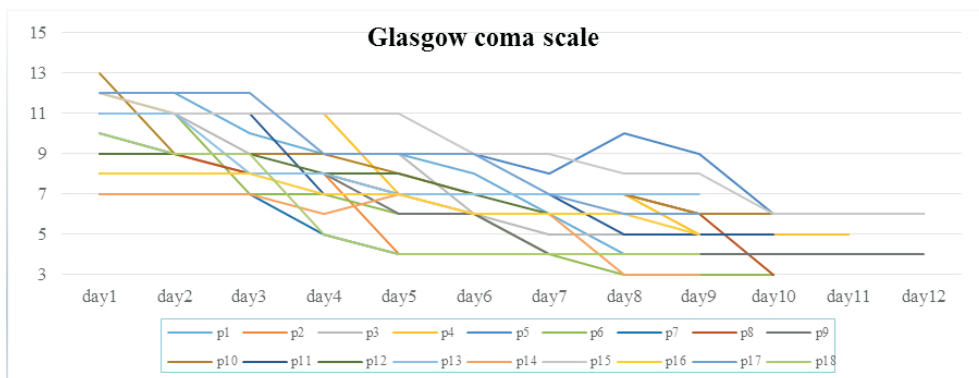


Fig. 2. Salivary cortisol levels among deceased patients at 8 and 20 o'clock

Table 2

Correlation between salivary cortisol levels (in the morning and in the evening) and Glasgow Coma Scale



Patients	Pearson correlation	Significance (2-tailed) <i>p</i> -value	Pearson correlation	Significance (2-tailed) <i>p</i> -value
	8 o'clock in the morning		20 o'clock in the evening	
Patient 1	−0.768	0.009*	0.470	0.171
Patient 2	−0.393	0.441	0.474	0.342
Patient 3	−0.557	0.151	0.510	0.197
Patient 4	−0.688	0.028*	0.775	0.008*
Patient 5	−0.662	0.019*	0.037	0.909
Patient 6	−0.726	0.018*	0.578	0.080
Patient 7	−0.521	0.122	0.634	0.049
Patient 8	−0.556	0.120	0.164	0.673
Patient 9	−0.755	0.012*	0.688	0.028
Patient 10	−0.663	0.037*	0.560	0.093
Patient 11	−0.767	0.010*	0.845	0.02*
Patient 12	−0.823	0.006*	0.723	0.028*
Patient 13	−0.498	0.173	0.593	0.093
Patient 14	−0.863	0.001*	0.329	0.388
Patient 15	−0.662	0.052	0.197	0.540
Patient 16	−0.788	0.012*	0.617	0.077
Patient 17	−0.515	0.156	0.769	0.015*
Patient 18	−0.423	0.000*	0.831	0.006*

increases in serum cortisol levels during aSAH [13, 14]. Elevated morning total cortisol levels in the acute phase of SAH have been found to be associated with a higher risk of fatal outcomes and a higher rate of delayed ischemic neurological deficits [14–16]. Salivary cortisol was investigated only in SAH survivors one year after the acute event to investigate long-term endocrinological sequelae. Salivary cortisol concentrations during waking were significantly higher in patients with SAH than in the controls [17]. To the best of our knowledge, this is the first study to investigate the prognostic value of salivary cortisol levels during the acute phase of aSAH. Our results confirm the negative prognostic value of elevated salivary cortisol levels both in the morning at 8.00 AM and in the evening at 8.00 PM. Moreover, we found a statistically significant correlation between the increase in morning salivary cortisol and the decrease in GCS score in most patients who died of aSAH (Table 2). The need for morning and evening cortisol measurements has also been demonstrated in serum cortisol measurements [15].

Salivary cortisol and stress treatment. Our data confirmed a correlation between salivary cortisol levels and poor outcomes in patients with aSAH. The value of diurnal salivary control measurements in neurosurgical ICUs has been demonstrated in acute trauma patients [18]. In contrast, sedation may diminish serum cortisol in the serum [19]. The possibility of stress treatment and serum cortisol control in patients with aSAH may be a goal of future studies. Salivary cortisol measurement appears to be a fast, easy, and reliable method for controlling this treatment.

Conclusion. Measurement of salivary cortisol levels in patients with aSAH provides additional information about prognosis. Patients who die during the acute phase of aSAH have higher morning and evening salivary cortisol levels than those who survive. Patients who died demonstrated a progressive increase in salivary cortisol levels in the morning.

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