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ORIGINAL ARTICLE

Patients Who Fainted Whilst Giving a Blood Sample in the Blood Collectıon Unit and a Stress Mediator: Cortisol

Kan Alma Ünitesinde Kan Örneği Verirken Bayılan Hastalar ve Bir Stress Medyatörü: Kortizol

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ABSTRACT

Objective: Serum cortisol is a glucocorticoid and can be used as a stress mediator in association with adrenal insufficiency. A diagnosis of adrenal insufficiency is made when the episodically released serum cortisol levels are below 3 mcg/dl by making a single measurement at any time of the day. In this study, we aimed to define the presence of underlying adrenal insufficiency by measuring serum cortisol levels in patients who fainted while giving blood samples in the blood collection unit and brought to the emergency room by the hospital code blue team after receiving critical care.
Materials and Methods: Observational, prospective study; It consists of 28 patients brought to emergency department by Code Blue Team between 2017 and 2020. After physical examination and electrocardiogram(ECG) evaluation, samples were taken for complete blood count, biochemical parameters, venous blood gas, cardiac biomarkers and serum cortisol measurement. Blood samples taken at the time of application were studied in the emergency laboratory on the same day. Obtained results were analyzed with SPSS 22 and MATLAB programs.
Results: The lowest serum serum cortisol level was 9 mcg/dL, and the highest serum cortisol level was 40,4 mcg/dL. Serum cortisol levels were higher in females than males. To evaluate statistically difference between serum cortisol values of male and female, t-test was applied. The test results revealed that gender is not a determining factor in serum cortisol levels (p=0,26). Moreover, correlation analysis was performed to determine strength of the relationship and Pearson correlation was calculated (r=0.314). Statistical analysis indicated that the correlation coefficient is not statistically significant at the 95% confidence level. The patient diagnosed with adrenal insufficiency with a single measurement was not defined in the study population.
Conclusions: Patients with acute adrenal insufficiency may come to the emergency department with orthostatic hypotension, agitation, syncope, abdominal pain and fever, and may result in death if it is left untreated. When the serum cortisol levels of the patients who experienced intense stress during blood sampling and had syncope were examined within the scope of the study, a critical value that would make the diagnosis of adrenal insufficiency was not found. Although emotional stress is 20% among the precipitating factors of adrenal crisis, no significant relationship was found between stress and serum cortisol in our study . The limitations of our study are that it can only be carried out during working hours 08:00 -16:00, and advanced diagnostic tests for primary and/or secondary adrenal insufficiency can not be performed in the emergency room.

Keywords: Syncope, Adrenal Insufficiency, cortisol

ÖZ

Amaç: Kortizol bir glukokortikoiddir ve adrenal yetmezlikle ilişkili olarak stres mediatörü olarak kullanılabilir. Epizodik olarak salınan serum kortizol seviyelerinin tek ölçümle 3 mcg/dl nin altında olması ile adrenal yetmezlik tanısı konur. Çalışmamızda kan verme ünitesinde kan verme aşamasında bayılan ve ilk müdahalesi hastane mavi kod ekibi tarafından yapıldıktan sonra aynı ekiple acile gelen hastaların serum kortizol seviyelerini görüntüleyerek altta yatan adrenal yetmezlik varlığını tespit etmek amaçlanmıştır.
Gereç ve Yöntem: Gözlemsel, prospektif çalışma; 2017 ve 2020 yılları arasında acil servise senkop ön tanısıyla mavi kod tarafından getirilen 28 hastadan oluşmaktadır. Fizik muayene ve elektrokardiyogram(EKG) ile hasta değerlendirildikten sonra hastadan tam kan sayımı, biyokimyasal paramatreler, venöz kan gazı, kardiyak biyobelirteçler ve serum kortizol ölçümü için örnekler alındı. Başvuru anında alınan kanlar; acil laboratuvarında aynı gün çalışıldı. Elde edilen sonuçlar SPSS 22 ve MATLAB programları ile analiz edildi.
Bulgular: En düşük serum kortizol düzeyi 9 mcg/dl, en yüksek serum kortizol düzeyi 40,4 olarak ölçüldü. Serum kortizol düzeyleri erkeklere nazaran kadınlarda daha yüksek olarak ölçüldü. T testi analizi ile erkekler ve kadınların serum kortizol düzeyleri arasındaki farkın istatistiki açıdan anlamlı olup olmadığı araştırıldı. Test sonucu; cinsiyetin, kortizol düzeylerinde belirleyici faktör olmadığını ortaya koydu(p=0,26). Buna ek olarak, kan alma zamanıyla serum kortizol değerleri arasındaki ilişkinin gücünü belirlemek amacıyla korelasyon analizi yapıldı ve bu amaç için Pearson korelasyon katsayısı hesaplandı (r=0.314). Yapılan istatistiksel analizler sonucunda bu korelasyonun %95 güven aralığında anlamlı olmadığı sonucuna varıldı. Tek ölçümle adrenal yetmezlik tanısı alan hasta, çalışma popülasyonunda tanımlanmadı.
Sonuç: Akut adrenal yetmezlik tanılı hastalar, acil servise ortostatik hipotansiyon, ajitasyon, senkop, karın ağrısı ve ateş ile gelebilir, tedavi edilmezse ölümle sonuçlanabilir. Çalışma kapsamında kan verme esnasında yoğun stres yaşayan ve senkop geçiren hastaların serum kortizol düzeylerine bakıldığında adrenal yetmezlik tanısı koyduracak kritik bir değer saptanmadı. Adrenal krizin presipitan faktörleri arasında %20 oranla emosyonel stres olmasına rağmen bizim çalışmamızda stres ve serum kortizol arasında anlamlı bir ilişki bulunamamıştır. Çalışmamızın kısıtlılıkları sadece mesai saatleri (08:00-16:00) içerisinde yürütülebilmesi, primer ve/veya sekonder adrenal yetmezlik için ileri tanı tetkiklerinin acilde uygulanamıyor olmasıdır.

Anahtar Kelimeler: Senkop, Adrenal Yetmezlik, Kortizol

Introduction

Adrenocorticotropic hormone (ACTH) is a polypeptide hormone; synthetized in pituitary gland and hypothalamus. It modulates to production of mineralocorticoids, glucocorticoids and androgens in adrenal cortex. Serum cortisol, a glucocorticoid, is a homeostatic mediator of stress and it has been shown in recent studies that it can be used as a biomarker of stress associated with primary or secondary adrenal insufficiency[1]. The measurement of serum cortisol is made after waking up in the morning. Serum cortisol levels are 10 to 20 mcg/dL higher in the morning than at other times of the day. Low serum serum cortisol level (<3 mcg/dL) measured in the early morning (approximately at 06:00) strongly suggests adrenal insufficiency[2, 3]. Values greater than 19 µcg/dL almost exclude the diagnosis of adrenal insufficiency. Clinic of adrenal insufficiency varies depending on whether it is acute causing adrenal crisis or chronic with inexplicable symptoms. Therefore, the diagnosis of adrenal insufficiency requires critical clinical suspicion. More importantly, adrenal crisis should be considered in every patient with or without a diagnosis of adrenal insufficiency presenting with vascular collapse. In this study, we aimed to monitor the serum cortisol levels measured at any time of the day in patients who applied to the blood tests centre for examination and had syncope during the procedure and then brought them to the emergency room after the first intervention by the code blue. In the present study, impact of gender on serum cortisol levels is evaluated and the relationship between blood collection time and serum cortisol. To the best knowledge of the authors, this is the first study that evaluate adrenal insufficiency by measuring serum cortisol levels in patients who fainted while giving blood samples in the blood collection unit and brought to the emergency room by the hospital code blue team after receiving critical care. This provides an impetus for the our study.

Material and Methods

This observational, prospective study was performed in tertiary care centre, Health Sciences University, X Faculty of Medicine, Regional Training and Research Hospital (X/Turkey). The patient group consists of patients who felt faint while giving samples for blood tests at blood collection centre, and brought to the emergency room by the code blue team with a pre-diagnosis of pre-syncope or syncope between 2017 and 2020. Total 28 patients were included in the study. The sample size can be considered as statistically valid as it is larger than 25. Patients without cardiac, neurological and bleeding-related syncope were included in the study. Patients who refused to participate in the study were excluded from the study. Blood samples were taken from only patients who were young (28 years old avaregely) and did not have any known chronic disease.

In order to measure the levels of serum cortisol, blood samples were taken into BD SST tube with silica clot activator, polymer gel, silicone-coated interior. These samples were centrifuged for 10 min at 3000 rpm at +4°C. At the obtained plasma, serum cortisol levels were assayed with Siemens Atellica IM Analyzer (Siemens Healthcare Diagnostics GmbH, Erlangen, Germany).

Ethics Approval

Ethics committee approval of the study was obtained with Y University Clinical Research Ethics Committee Decision (2021/09)

Results

Basic statistical characteristics (mean, median, standard deviation etc.) of the serum cortisol data series are also summarized in Table 1.

In the first part of the study, we evaluated the presence of underlying adrenal insufficiency in the patients. To this end, we compared the serum cortisol levels of all patients (minimum, maximum and mean; 9, 40.4 and 19.35 µcg/dL) with 3 µcg/dL, which is known as critical level of adrenal insufficiency. As the serum cortisol levels were higher than the critical value, no adrenal insufficiency was diagnosed for our study group. Before the analysis, assumptions such as the normal distribution of the data was checked by using Anderson Darling (AD) test. The AD test results indicated that the considered data series were normal distributed as the computed p values were higher than critical value 0.05 (see Table 2 for the AD test results).

To evaluate statistically difference between serum cortisol values of male and female, a sample t-test was used. Descriptive data showed that 10 males and 18 females took part in the study, and the average/ mean serum cortisol level in males were 18.09 and in females 20.88. T-test analysis revealed that there was no statistically significant difference in the mean serum cortisol level in terms of gender ($t(26) = 1.134$, $p=0.267$). Based on this findings, it can be said that gender is not a determinant of serum cortisol level, although the serum cortisol level of female is higher than that of male. Moreover, correlation analysis was conducted to check if there was a relationship between blood collection time and serum cortisol levels. According to descriptive data, blood collection times vary between 8:43 and 15:04, while serum cortisol levels vary between 9 and 40,4 with an average of 19.88 (table 2). Pearson correlation coefficient was computed between blood collection time and serum cortisol levels and it was found as 0.310. The statistical significance of the Pearson correlation was checked by Student's t test at the significance level of 0.05. No statistically significant relationship was found between the variables, although there was a moderate positive linkage (table 2). As a result, it can be concluded that blood collection time does not affect serum cortisol levels (Figure 1). All statistical analysis was carried out using the software SPSS software version 22 (SPSS, Inc., Chicago, Illinois) and commercial software MATLAB[4].

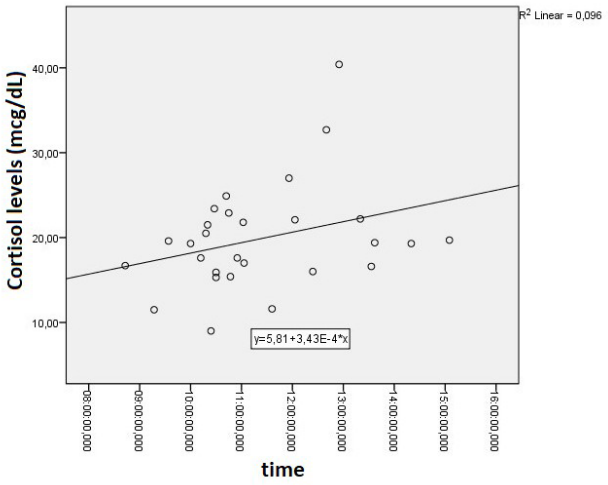

Figure 1: Scatter plot of blood collection time and serum cortisol levels

Table 1. Basic statistical characteristics of Gender-related serum cortisol values and t-test analysis results

Variable	*Gender*	*N (age range, years)*	*Mean*	*Median*	*Min*	*Max*	*Standard deviation*
Serum cortisol value	Male	10(14-32)	18.09	18.50	11.5	22.2	3.56
	Female	18(18-40)	20.89	19.50	9	40.4	7.30
	All	28(14-40)	19.90	19.35	9	40.4	6.29

*p>0,05

Table 2. Anderson Darling Test results for the Serum cortisol data series

Gender	Anderson Darling test statistic	the computed p value	Ho Hypothesis	*t test statistic/ p-value*
Male	0.3168	0.500*	Accept	1.134/0.267*
Female	0.572	0.121*	Accept	

*p>0.05

Table 3. Relationship between blood collection time and serum cortisol level

	Minimum	*Maximum*	*Median (range)*	*Pearson R (p)*	*R^2*
Blood coll. time	8:43	15:04	10:51 (6:21)	0.310 (0.24)	0.09
Serum cortisol	9	40.40	19.35 (3.40)		

*p>0.05

Discussion

Adrenal insufficiency (AI) constitutes the group of diseases caused by the insufficiency of serum cortisol synthesis and/or secretion in the adrenal cortex[5]. Adrenal insufficiency may occur as a result of adrenal gland pathology itself (primary), hypothalamic or pituitary axis pathology (secondary), or as a result of suppression of the hypothalamic-pituitary-adrenal axis (tertiary) resulting from recent escalation of oral, nasal, topical, inhaled, and intra-articular exogenous glucocorticoid treatment[6]. In fact, in recent studies, a significant proportion of patients treated with inhaled steroids have been shown to have tertiary adrenal insufficiency, but it has been reported that they received treatment outside of endocrine clinics because they could not get a correct diagnosis. Therefore, tertiary insufficiency, rather than primary and secondary adrenal insufficiency, is more common in recent times[7]. Adrenal insufficiency may present as a spectrum of clinical features ranging from malaise, fatigue, and decreased quality of life to adrenal crisis. Undiagnosed or misdiagnosed failure can cause significant morbidity and mortality. In addition, the publications emphasizing the relationship of dysfunction in any step of the hypothalamo-pituitary-adrenal axis with mortality show the necessity of accurate and timely diagnosis and appropriate treatment[8, 9]. Diagnosis of adrenal insufficiency, regardless of its cause, is based on demonstration of low serum cortisol production[10]. The normal reference range for serum cortisol levels is wide, although different values in the morning and afternoon. As such, it can keep basal corticotropin (ACTH) and/or cortisol secretion within the normal range even if a patient has pituitary or adrenal insufficiency. If the serum serum cortisol concentration is low and the concomitant plasma ACTH concentration is too high, the patient is considered to have primary adrenal insufficiency. If plasma ACTH concentrations are low along with the serum cortisol level, the patient should be considered for secondary (pituitary) and/or tertiary (hypothalamic) insufficiency[11]. In emergency situations, the ACTH value is not usually measured to determine the level of the disorder. If the diagnosis of adrenal insufficiency is suspected due to randomly measured low serum cortisol concentration, as in our study; dynamic stimulus tests should be performed to diagnose after ACTH measurement[12]. Additionally, dynamic function tests should be performed when the function of the hypothalamic-pituitary-adrenal axis is suspected[13]. As in our study, the reason for the inadequacy of diagnosis in outpatients admitted at any time of the day is the episodic serum cortisol secretion[14]. Serum cortisol values are higher in the morning hours compared to other time periods of the day. Serum cortisol levels below 3 mcg/dL measured at these hours strongly support adrenal insufficiency even with a single measurement. In critically ill patients with bilateral adrenal hemorrhage, traumatic brain injury or sub-arachnoid hemorrhage in the emergency department, adrenal crisis should be suspected in patients with hemodynamic instability who remain in shock despite adequate fluid resuscitation and vasopressor support and hydrocortisone therapy at a dose of 200mg/24 hours should be initiated[15]. It is essential that the treatment of patients presenting with possible acute adrenal insufficiency with/without adrenal crisis accompanied by hypoglycemia and hyponatremia should not be delayed whilst performing diagnostic tests.

Conclusion

Patients with acute adrenal insufficiency may

be admitted to the emergency department with orthostatic hypotension, agitation, syncope, abdominal pain and fever, and may result in death if it is left untreated.[16]. In the present study, we investigated the presence of underlying adrenal insufficiency by serum cortisol levels in patients who fainted while giving blood samples in the blood collection unit and brought to the emergency room by the hospital code blue team after receiving critical care. The main findings of this study can be summarized as follows: No critical value was found in the serum cortisol levels of patients who had syncope under intense stress, which would make the diagnosis of adrenal insufficiency. Although emotional stress is 20% among the precipitating factors of adrenal crisis, no significant relationship was found between stress and serum cortisol in our study[17]. Although there was a difference in the serum cortisol levels of males and females, this difference was not statistically significant at a=0.05 significance level. No statistically significant relationship was observed between blood collection time serum cortisol levels.

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