

Baseline Blood Cortisol Level and the Risk of Delirium Development in Adult Intensive Care Unit

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ABSTRACT

Introduction: A biomarker predicting further development risk of delirium would be of interest. Cortisol, as a lipid base blood hormone playing role in hypothalamo-pituitary-adrenal axis, might be a good indicator. However, relationship between baseline blood cortisol level and delirium formation has not been yet investigated in ICU.

Methods: Patients >18 years followed >48 hours in Hacettepe University Anesthesiology ICU from January 2017 to 2020 were included. Delirium was diagnosed according to CAM-ICU scale (D[+] vs D[-]). Primary outcome was whether baseline (at admission) blood cortisol level differs between groups and secondary one was to detect predictive factors associated with delirium.

Results: 125 out of 562 patients were included in which 38 (30%) were diagnosed with delirium. Mean age was 52±25 years in D [+] group [Female (F): 17 (45%)] while it was 64±21 years in D [-] group [F: 39 (45%)] (p=0.11 and p=0.57 for age and gender, respectively). Groups did not differ regarding laboratory parameters including baseline serum cortisol level, LOS, and mortality. Only rates of previous alcohol use and steroid administered in ICU, unlike pneumonia as a cause of admission, were higher in D [+] groups while compared to D [-]. However, no parameter has persisted as an independent factor for predicting delirium while adjusted for age (>50 years), gender, and blood cortisol level in binary backward logistic regression analysis.

Discussion: It seems baseline blood cortisol level may not be a good predictor regarding further delirium formation in mixed medical and surgical ICU patients.

Keywords: delirium, cortisol, intensive care unit

Introduction

Delirium is a frequently encountered pathology in intensive care unit (ICU) and it is of importance regarding its relation with ICU/hospital length of stay (LOS) and mortality (1). Numerous risk factors have already been reported with respect to development of delirium. Nonetheless some studies indicating conflicting results with respect to the relationship between blood cortisol level and delirium development in patients followed in non-ICU, there is no knowledge regarding the issue in patients admitted to ICU (1). Due to the fact that blood cortisol is the output mediator of hypothalamo-pituitary-adrenal axis, it has a major role on stress response which is also a driving pathway for delirium development (2), thus it might be a good indicator regarding prediction of delirium. In current study, the effect of baseline serum cortisol level on the risk of delirium development in ICU was retrospectively evaluated in mixed medical and surgical patients followed in Anesthesiology ICU.

Methods

Patients: Data from patients >18 years old admitted to Hacettepe University Anesthesiology ICU and followed >48 hours between January 2017 to January 2020 were retrospectively evaluated. Anesthesiology ICU is a mixed, closed, and tertiary level ICU that drains patients from pre-surgical, post-surgical, neurological, cardiological, internal medicine, or emergency departments. All data regarding socio-demographic, additional diseases, baseline (at admission) laboratory values, follow-up notes with respect to formation of delirium and its treatment choice, LOS, and outcome status (alive or dead) at ICU discharge were gathered from our hospital's electronic records. Patients in whom a cortisol level not studied within 24 hours after admission to ICU and patients on a steroid treatment prior to ICU admission were excluded. The study was approved with a registration number of GO/162-2020 by Hacettepe University Ethical Board, Ankara, Turkey.

Description-Measures: Patients were evaluated from admission to discharge (alive or dead) with respect to delirium development three times a day with Confusion Assessment Method for the ICU (CAM-ICU) scale¹ adapted and validated in Turkish language in 2005 (3) by nurses who had a minimum experience of five years in ICU. Patients were separated into two groups as delirium positive (D [+]) and negative (D [-]). Serum cortisol samples were obtained into an EDTA biochemistry tube with a minimum blood draw volume of 0.6 ml according to our routine rules regarding blood analysis in Anesthesiology ICU. Cortisol level was studied with chemiluminescent microparticle immunoassay method (4) that had a normal range between 4.3 to 21 mcg/dl in humans >18 years old.

Outcomes: Primary outcome was to detect whether baseline blood cortisol level differs between D [+]and D [-] groups. Secondary outcome was to describe predictive risk factors with respect to delirium development.

Statistical Analysis: All values are represented as mean \pm standard deviation (SD), 95% confidence intervals [95% CI], percentages, medians with interquartile ranges [IQR] as appropriate. Distribution normality was analyzed with the Kolmogorov-Smirnov and Shapiro-Wilk tests properly. Differences were tested with Mann-Whitney *U* / Student's *t*, paired *t* and Chi-square / exact tests appropriately. Extrapolatory analysis regarding effect of baseline cortisol level on delirium was evaluated by these basic univariate tests. While risk factors regarding delirium was being analysed, factors with a *p* value of <0.05 in univariate model were included into the multivariate steps. A backward conditional logistic regression analysis was performed for detecting independent risk factors predicting delirium development. A *p* value of <0.05 was accepted as significant. All analyzes were calculated with SPSS 23 IBM® statistics program provided by Hacettepe University Faculty of Medicine, Turkey.

Results

125 out of 562 patients were included in which 38 (30%) were diagnosed with delirium. Mean age was 52 \pm 25 years in D[+] group [Female (F): 17 (45%)] while it was 64 \pm 21 years in D [-] group [F: 39 (45%)] (*p*=0.11 and *p*=0.57 for age and gender, respectively). Groups were similar regarding demographics and comorbidities (Table 1.). Only pneumonia was found to be lower in D [+] group than in D [-] as a cause of admission (10 (26%) vs 43 (49%), *p*=0.01). Steroid administration rate in ICU and previous alcohol consumption were higher in D [+] group than in D [-] one (27 (71%) vs 45 (52%), *p*=0.04; 4 (11%) vs 1 (1%), *p*=0.03, respectively).

Median [IQR] baseline cortisol level, as primary outcome, was not different between groups as 15 [7-29] mcg/dl and 18 [11-29] mcg/dl in D [+] and D [-] groups, respectively (*p*=0.49). Remaining laboratory parameters, LOS, and mortality did not differ between groups (Table 1). Although neither cut-off was found to be associated with further delirium development, it has to be mentioned that 62 (50%) patients were diagnosed to have subclinical hypercortisolism (5), whereas 16 (13%) to have relative adrenal insufficiency (6) according to baseline blood cortisol levels.

Table 1. Differences Between Groups with and without Delirium

	Delirium Positive n= 38 (30%)	Delirium Negative n= 87 (70%)	<i>p</i>
Age* (years)	52 \pm 25	64 \pm 21	0.11
Gender (F), n(%)	17(45)	39(45)	0.57
APACHE-II**	15 [11-22]	17 [11-27]	0.58
SOFA**	4 [3-6]	6 [3-9]	0.66
Smoking, n(%)	12 (32)	31 (36)	0.66
Alcohol, n(%)	4 (11)	1 (1)	0.03
Central Catheter Access, n(%)	21 (55)	55 (63)	0.40
IMV, n(%)	27 (71)	58 (67)	0.62
Additional Diseases			
HT, n(%)	18 (47)	49 (56)	0.35
DM, n(%)	11 (29)	32 (37)	0.39
COPD, n(%)	8 (21)	23 (26)	0.52
Astma, n(%)	3 (8)	4 (5)	0.43
CKD, n(%)	5 (13)	13 (15)	0.79
CAD, n(%)	9 (24)	19 (22)	0.84
CHF, n(%)	9 (24)	27 (31)	0.40
Stroke, n(%)	4 (11)	11 (13)	0.73
Dementia, n(%)	1 (3)	4 (5)	0.51
Malignancy, n(%)	8 (21)	19 (22)	0.92
Causes of Admission			
Fracture, n(%)	3 (8)	6 (7)	0.84
ARDS, n(%)	1 (3)	6 (7)	0.34
Pneumonia, n(%)	10 (26)	43 (49)	0.01
COPD Exacerbation, n(%)	6 (16)	12 (14)	0.77
GIS hemorrhage, n(%)	0 (0)	7 (8)	0.10
Post-surgery, n(%)	10 (26)	14 (16)	0.18
Sepsis, n(%)	5 (13)	21 (24)	0.16
Post-CA, n(%)	6 (16)	19 (22)	0.43
Drug Used			
Steroid, n(%)	27 (71)	45 (52)	0.04
Immunosuppressive, n(%)	3 (8)	4 (5)	0.43
CCB, n(%)	12 (32)	15 (17)	0.07
B-blocker, n(%)	15 (40)	42 (48)	0.36
ACE-I, n(%)	7 (18)	15 (17)	0.87
Anti-biotics, n(%)	32 (84)	81 (93)	0.12
Laboratory Values			
Cortisol** (mcg/dl) †	15 [7-29]	18 [11-29]	0.49
Hb** (g/dl) †	9.9 [8.9-13.9]	10.2 [9.4-12.4]	0.74
Leukocyte** (x10 ³ mm ³) †	11 [7-14]	11 [8-14]	0.91
Creatine** (mg/dl) †	1.2 [0.7-2.1]	1 [0.7-2.4]	0.65
BUN** (mg/dl) †	36 [16-52]	24 [16-50]	0.36
Albumin** (g/l) †	2.9 [2.5-3.4]	2.7 [2.4-3.2]	0.34
Sodium** (mEq/l) †	136 [134-140]	137 [133-140]	0.90
PaO ₂ /FiO ₂ ** †	274 [180-301]	205 [158-316]	0.71
Outcomes			
LOS* (days)	9 [5-19]	11 [5-21]	0.71
Mortality, n(%)	11 (29)	32 (37)	0.39

ACE-I: Angiotensin Converting Enzyme Inhibitor, APACHE-II: Acute Physiology and Chronic Health Evaluation-2 score, ARDS: Acute Respiratory Distress Syndrome, BUN: Blood Urea Nitrogen, CA: Cardiac Arrest, CAD: Coronary Artery Disease, CCB: Calcium Channel Blocker, CHF: Congestive Heart Failure, CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, DM: Diabetes Mellitus, F: Female, GIS: Gastrointestinal System, Hb: Hemoglobin, HT: Hypertension, IMV: Invasive Mechanical Ventilation, LOS: Length of Stay, SOFA: Sequential Organ Failure Assessment
*mean \pm SD, **median[IQR], † Values obtained at admission
Text in bold means statistical significance

Table 2. Factors Predicting Delirium in Backward Conditional Logistic Regression Analysis

	B	OR	LL CI 95%	UL CI 95%	p
Age†	-0.74	0.47	0.19	1.15	0.101
Pneumonia*	-0.86	0.42	0.17	1.03	0.059
Steroid Administration §	0.63	1.89	0.80	4.46	0.146
Cortisol Level**	-0.31	0.72	0.27	1.92	0.521
Alcohol	1.99	7.38	0.72	75	0.091

Hosmer and Lemeshow Test: 0.06

* Pneumonia diagnosis as an admission cause to ICU increases the risk of delirium development, § Steroid administered in ICU, **A blood cortisol level of < 9 mcg/dl.

† Age>50 years

Table 3. Studies Investigating Cortisol & Delirium Association in Patients Undergone Surgery

Article	Patient/Way Cortisol Obtained	Result
Sun L, Jia P, Zhang J, et al. Production of inflammatory cytokines, cortisol, and Abeta1-40 in elderly oral cancer patients with postoperative delirium. <i>Neuropsychiatr Dis Treat</i> 2016; 12: 2789-95.	257 patients with tumor surgery (oral cancer) Blood cortisol ‡	No differences in pre-operative cortisol levels Higher cortisol levels in patients with delirium at post operative phases.
Eshmaey M, Arlt S, Ledschbor-Frahnert C, Guenther U, Popp J. Preoperative Depression and Plasma Cortisol Levels as Predictors of Delirium after Cardiac Surgery. <i>Dement Geriatr Cogn Disord</i> 2019; 48(3-4): 207-14.	183 patients undergoing elective cardiac surgery Blood cortisol †	No association between pre-operative cortisol levels and delirium formation.
Guo Y, Sun L, Li L, et al. Impact of multicomponent, nonpharmacologic interventions on perioperative cortisol and melatonin levels and postoperative delirium in elderly oral cancer patients. <i>Arch Gerontol Geriatr</i> 2016; 62: 112-7.	160 patients with tumor surgery (oral cancer) Urine cortisol ‡	Higher postoperative, but not pre-operative, urine cortisol levels in patients who developed delirium.
Kazmierski J, Banys A, Latek J, Bourke J, Jaszewski R. Cortisol levels and neuropsychiatric diagnosis as markers of postoperative delirium: a prospective cohort study. <i>Crit Care</i> 2013; 17(2): R38.	113 patients undergoing cardiac surgery Blood cortisol ‡	Both pre and post-operative higher cortisol levels associated with delirium formation.
Mu DL, Wang DX, Li LH, et al. High serum cortisol level is associated with increased risk of delirium after coronary artery bypass graft surgery: a prospective cohort study. <i>Crit Care</i> 2010; 14(6): R238.	243 patients undergoing CABG* Blood cortisol §	Higher cortisol levels associated with delirium.
Plaschke K, Fichtenkamm P, Schramm C, et al. Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6. <i>Intensive Care Med</i> 2010; 36(12): 2081-9.	114 patients with cardiac surgery Blood cortisol §	Higher cortisol levels in delirium patients.
Shi CM, Wang DX, Chen KS, Gu XE. Incidence and risk factors of delirium in critically ill patients after non-cardiac surgery. <i>Chin Med J (Engl)</i> 2010; 123(8): 993-9.	164 patients undergoing non-cardiac surgery Blood cortisol §	Higher cortisol levels in delirium patients.
Hauer D, Weis F, Campolongo P, et al. Glucocorticoid-endocannabinoid interaction in cardiac surgical patients: relationship to early cognitive dysfunction and late depression. <i>Rev Neurosci</i> 2012; 23(5-6): 681-90.	111 patients undergoing cardiac surgery 56 induced with oral hydrocortisone for supporting stress response No cortisol measuring	No association between given glucocorticoid support and delirium.

† Cortisol level obtained prior to surgery

§ Cortisol level obtained after surgery

‡ Cortisol level obtained prior to and after surgery

*Coronary Artery By-pass Graft Surgery

No parameter, found significant in univariate analysis, persisted as an independent factor in terms of secondary outcome while adjusted for age (>50 years), gender, and blood cortisol level in binary backward logistic regression analysis (Table 2).

Discussion

Biomarkers accurately predicting delirium before its development would be crucial in terms of providing pathways for brand therapeutic drugs. Cortisol, an endogenous hypothalamic-

pituitary-adrenal axis hormone, has already been investigated in this perspective in surgical patients mostly at peri-operative phases (7-15) with vague results (Table 3). Probably, owing to the fact that both surgery's own stress and anesthesia given had affected the renowned 'circadian clock' that might cause different individual blood cortisol responses (16).

Importance of serum cortisol level for further delirium development has been studied not only in patients solely undergoing surgery but

also in patients with sepsis and septic shock in which cortisol level was found to be higher at first three consecutive days in patients with brain dysfunction while compared to those without (17). In that study, it is important to emphasize that cortisol levels had been obtained at admission to ICU and during next four consecutive days (17). Restricting factor in mentioned article was that its results were not able to be generalizable for cortisol effects on delirium. Because brain dysfunction had been defined as a combination of a Glasgow Coma Scale (GCS) of <13 and delirium positivity according to CAM-ICU criteria (17). Another study achieved with 100 medical ICU patients has showed higher blood cortisol level obtained after development of delirium to be correlated with delirium diagnosis in inflamed patients described according to systemic inflammatory response syndrome (18). Even though the latter study does not provide knowledge regarding predicting effect of baseline blood cortisol in terms of delirium formation, it highlights a crucial point regarding the importance of a study design while evaluating efficacy of a biomarker on delirium development. Lacking of a stratification among patients with respect to inflammatory-infectious circumstances while studying the predicting effect of serum cortisol, a mediator having role in systemic inflammation-infection pathways, probably the driving factor giving rise to these ambiguous results including the current study.

Our study has some limitations. First one is the retrospective nature of the research which causes data loss and a possible

selection bias. Secondly, heterogeneity of data gathered from a mixed ICU draining patients from multiple sources has reduced the generalizability of our results. Thirdly, not a standardized sedo-analgesia protocol to be provided is another limitation of our study.

In conclusion, baseline serum cortisol levels were retrospectively evaluated with respect to its value detecting further delirium development in patients followed in Anesthesiology ICU. We have detected baseline serum cortisol level not to predict further delirium formation in mixed medical and surgical ICU patients, as most of the other previous studies performed in patients followed in non-ICU (7-15). To our best knowledge there is not a study investigating the predicting effect of baseline serum cortisol level on further delirium development in mixed medical and surgical ICU patients. We consider our study is important regarding its brand new perspective on this issue. Further prospective studies those stratificate patients in terms of inflammation might give abundant knowledge and trigger new treatment facilities against delirium.

Conclusion

According to our study, blood cortisol level obtained at the admission to ICU may not be a good predictor for further delirium formation in patients followed in ICU.

AUTHOR CONTRIBUTIONS:

Concept: MYP, BK, SBA; **Design:** MYP, NDBY,SBA; **Supervision:** MYP, BK, SBA; **Fundings:** MYP, BK, SBA; **Materials:** MYP, NDBY, SBA; **Data Collection and/or Processing:** MYP, NDBY; **Analysis and/or Interpretation:** MYP, BK, SBA; **Literature Search:** MYP, SBA; **Writing Manuscript:** MYP, NDBY SBA; **Critical Review:** MYP, BK,SBA.

Ethics Committee Approval: The study was approved with a registration number of GO/162-2020 by Hacettepe University Ethical Board, Ankara, Turkey

Informed Consent: Due to retrospective nature of our study only a local ethical board approval was gathered.

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors have no conflicts of interest to declare.

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