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A Study to Assess the Association Between Hypocortisolemia and Mortality Among Patients Admitted in Medical Intensive Care Unit in a Tertiary Care Hospital in Central Kerala

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ABSTRACT

Hypocortisolemia is a common complication that we come across in critically ill patients. Hence earlier diagnosis and adequate identification of this complication is warranted for planning early intervention. A cross sectional study was conducted among patients admitted in medical ICU under the Department of General Medicine, Amala Institute of Medical Sciences, Thrissur for a period of one year from March 2021 to February 2022. Consecutive consenting 231 patients were included in the study. Random serum cortisol level was assessed within 24 hours of admission to medical ICU. Patients with random serum cortisol level <15µg/dl were considered to have hypocortisolemia, those with value between 15µg/dl-34µg/dl were considered as normal and those patients with cortisol level >34µg/dl were considered to have hyper cortisolemia. Q-SOFA scoring was performed to assess the severity of illness. The requirement of vasopressors among the study population was noted. Patients were followed until the time of discharge from or death in medical ICU. The proportion of hypocortisolemia in patients admitted to medical intensive care unit was 31.4%. The critically ill patients amongst the study population were found to have a significant association with low cortisol levels. The mean age of mortality was found to be 65.71 years. However, no significant association could be established between hypocortisolemia and mortality among patients admitted to the medical intensive care units. Our study concluded that even though there was a significant association between critically ill patients and those requiring a longer hospital stay with hypocortisolemia, there was no significant association between hypocortisolemia and mortality among patients admitted in ICU.

INTRODUCTION

Cortisol is the main adrenal glucocorticoid and plays a central role in glucose metabolism and in the body's response to stress. Adrenal cortisol production is regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary gland in response to hypothalamic corticotrophin-releasing hormone (CRH)[1-3]. Serum cortisol in turn inhibits the production of both CRH and ACTH (negative feed-back loop) and this system self-regulates to control the proper level of cortisol production. The coordinated stipulatory and inhibitory connections between CRH, ACTH and cortisol are referred to as the hypothalamic- pituitary-adrenal axis. The neuro endocrine response to critical illness consists primarily of activated anterior pituitary function and inactivation of peripheral anabolic pathways. The HPA axis responds differently to both acute and chronic insults. Stimulation of HPA axis, resulting in an elevated plasma level of cortisol, is one of the most important hormonal reactions to severe insults. Cortisol plays a vital role in maintaining the normal vascular tone and in potentiating vasoconstrictor action of catecholamines. Gluco corticoid are both critical felicitations of adaptive response to stress and powerful immunosuppressive agents [4-9]. There is a prompt and sustained rise in both ACTH and cortisol in response to any form of stress. This is accompanied by a loss of circadian variability and ACTH pulsatility. Cortisol concentrations have been found to be elevated in most severe illnesses. Hence plasma cortisol levels seem to reflect severity of illness. Some recent studies suggest that hypocortisolemia is associated with higher mortality. Early literature coats a wide range in incidence of hypocortisolemia in the critically ill. This may be attributed to different types of illnesses encountered from centre to centre. If the proportion of critically ill patients who end up in this state of adrenal exhaustion is large, the result may help in outlining policies for the role of temporary replacement of adrenal function with physiological doses of gluco corticoid.

Aims: To assess the association between hypocortisolemia and mortality among patients admitted in medical intensive unit in Amala Institute of Medical Sciences, Thrissur.

Objectives:

- **Primary Objective:** To determine the association between hypocortisolemia and mortality among patients admitted in medical intensive care unit in Amala Institute of Medical Sciences, Thrissur.

MATERIALS AND METHODS

Study Design: Cross sectional study.

Study Setting: Department of General Medicine, Amala Medical College, Thrissur.

Study Population: Patients admitted to the medical intensive care unit of Amala Medical College, Thrissur.

Duration of Study: 1 year from the date of approval by IRB.

Sample Size:

$n=Z^2p(1-p)/d^2$

Here z=1.96 at 5% type 1 error (P<0.05)., p is the expected prevalence., d is the absolute error of precision. Hence, n=1.968×1.96×0.816(1-0.816)/ 0.05×0.05=230.71

Inclusion Criteria: Adult consenting patients in medical ICU requiring intensive care for >24 hours.

Exclusion Criteria:

- Patients with a known disease of the HPA axis (itself causing adrenal insufficiency).
- Current consumption of drugs interfering with the cortisol assay like glucocorticoid and spironolactone.
- Patients with a known HIV infection.

Procedure: A cross sectional study was conducted among patients admitted in medical ICU under the department of general medicine, Amala Institute of Medical Sciences, Thrissur for a period of one year from March 2021 to February 2022. Consecutive consenting 231 patients were included in the study. On enrolment into the study, a complete history and physical examination was performed and a working primary diagnosis was obtained. Random serum cortisol level was assessed within 24 hours of admission to medical intensive care unit. Patients with random serum cortisol level <15µg/dl were considered to have hypocortisolemia and those patients exhibiting a value between 15µg/dl and 34µg/dl were considered as normal, those patients with cortisol level >34µg/dl were considered to have high cortisol level. Q-SOFA scoring was performed to assess the severity of illness. The requirement of vasopressors among the study population was noted. Patients were followed until the time of discharge from medical intensive care unit or death in medical intensive care unit and the final outcome was noted in all the study patients. Patient data was maintained as confidential and was analyzed using SPSS 23 software[10,11].

RESULTS AND DISCUSSIONS

The mean age of the study population was 64.15 years among which 4.4% were ≤30 years, 12.7% were

between 31-50 years, 47.2% were between 51-70 years and 35.8% were >70 years. Among the 231 patients, 55.5% were males and 44.5% were females.

Table 1: Gender Distribution

Gender	Frequency	Percentage
Male	129	55.5%
Female	102	44.5%

Table 2: Q-SOFA

Q-SOFA	Frequency	Percentage
Low	113	48.5%
High	118	51.5%

Table 3: Random Cortisol

Random cortisol	Frequency	Percentage
Low	74	31.4%
Normal	86	37.6%
High	71	31.0%

Table 4: Use of Vasopressors

Use of vasopressors	Frequency	Percentage
Yes	79	34.5%
No	152	65.5%

Table 5: Days of Stay in Intensive Care Unit

Days of stay in intensive care unit	Frequency	Percentage
1-3 days	173	74.7%
≥4 days	58	25.3%

Table 6: Clinical Outcome

Clinical outcome	Frequency	Percentage
Discharged	197	85.2%
Death	34	14.8%

Table 7: Age Group

Age group	Clinical Outcome		
	Discharged	Death	P-value
≤30 years (n=10)	10 (100%)	0 (0%)	0.212
31-50 years (n=29)	26 (89.7%)	3 (10.3%)	
51-70 years (n=110)	89 (80.6%)	21 (19.4%)	
>70 years (n=82)	72 (87.8%)	10 (12.2%)	

50% of those patients aged ≤30 years were found to have a low random serum cortisol value as against 20% with normal random serum cortisol ad 30% with high random serum cortisol values. Amongst those patients aged between 31-50 years, 34.48% had low random serum cortisol values, 34.48% had normal random serum cortisol values and 31.03% had high random serum cortisol values. 35.05% of patients had low random serum cortisol values among those patients aged between 51-70 years with 34.02% and 30.93% of the remaining patients belonging to that age group having normal and high random serum cortisol levels respectively. Of those patients belonging to age group above 70 years in the study population, 26.32% had low random serum cortisol levels, 43.16% had normal random serum cortisol values and 30.53% had high random serum cortisol values. Amongst the 102 females in the study population, 26.47% of the patients were reported to have a low random serum cortisol value, 39.22% had a normal random serum cortisol value and the rest 34.31% had high random serum cortisol values[12-16]. 36.43% of the male population in the study exhibited low random serum cortisol values whereas 35.66% of them had normal random serum cortisol values and 27.91% had high serum cortisol values. 51.5% patients amongst the 231 were critically ill which was determined using the Q-SOFA scoring system as against 48.5% of the study sample who were not critically ill. In patients who had a high Q-SOFA score in the study population, 36.67% were recorded to have a low serum cortisol value, 30.83% had normal random serum cortisol and the rest 32.5% had a high random serum cortisol value. In a study conducted by Shy-Shin Chang et al which included 30 critically ill patients in a tertiary care hospital in Taiwan, the prevalence of hypocortisolemia was 43%. In comparison to this, our study showed a 36.67% prevalence of hypocortisolemia among critically ill patients. The need for vasopressors was observed in 34.5% of the 231 patients while 65.5% of them did not require the use of vasopressors.40.74% of the subjects requiring vasopressors in the study population expressed a low random serum cortisol value. 25.93% of the same population exhibited normal random serum cortisol values. High random serum cortisol values were observed in 33.33% of those patients requiring vasopressors. Amongst those patients that were not on any vasopressor support, 27.33% had a low random serum cortisol value, 43.33% showed a normal value of random serum cortisol and the rest 29.33% had a high random serum cortisol value. 58.33% of critically ill patients (high Q-SOFA score) required vasopressors whereas only 9.91% of non-critically ill patients (low Q-SOFA score) required vasopressors. In the SHIPS study which looked at patients in intensive care unit on vasopressor support, the prevalence of relative adrenal insufficiency was found to be 81.6%[17-20]. 74.7% of the subjects remained in the intensive care unit for a period ranging between 1 and 3 days whereas 25.3% amongst the 231 patients stayed at least or beyond 4 days. Low random serum cortisol levels were observed in 31.79% of the 173 patients in the study population who required to stay in the intensive care unit from 1-3 days. 37.57% of them had normal random cortisol values whereas the rest 30.64% of the 173 patients who remained in intensive care unit for a duration of 1-3 days had high levels of random serum cortisol. Of the 58 patients who required to be in the intensive care unit for a duration of 4 days and above, 32.76% had low random serum cortisol values, 36.21% had normal random serum cortisol values and high random serum cortisol values were seen in 31.03%[21-24]. 85.2% of the study population were discharged from the intensive care unit while 14.8% expired during stay in the intensive care unit. All patients ≤30 years were discharged from intensive care unit with no death reported amongst them. Among those aged 31-50 years, 89.7 % were discharged from the intensive care unit and 10.3% died

during stay in the intensive unit. 19.4% died during stay in the intensive care unit with 80.6% having been discharged from the intensive care unit among those patients aged 51-70 years Death was observed in 12.2% among patients aged >70 years and 87.8% were discharged from the intensive care unit. However, there was statistically insignificant difference in proportion of clinical outcome according to the age group ($p>0.05$). The mean age of patients being discharged from intensive care unit was 63.88 years and among those who died during stay in intensive care unit, it was 65.71 years. However, there was statistically insignificant mean difference in age between discharged and dead patients ($p>0.05$). 85.8% amongst males in the study population were discharged from intensive care unit and the rest 14.2% expired during stay in the intensive care unit. Amongst females enrolled in the study, 84.3% were discharged from the intensive care unit whereas 15.7% expired. The proportion of hypocortisolemia in patients admitted to medical intensive care unit was 31.4%. Among the various age groups that were included in the study population, the presence of low cortisol levels was observed in those patients between 51-70 years. The critically ill patients amongst the study population were found to have a significant association with low cortisol levels. Mortality was noted more amongst the age group of 51-70 years at 19.4% with mean age being 65.71 years. However an association between hypocortisolemia and mortality could not be established.

CONCLUSION

This study was done to see the association between hypocortisolemia and mortality among patients admitted in intensive care unit of a tertiary care center in central Kerala. This study was conducted among 231 patients admitted to medical intensive care unit over a period of one year. The proportion of hypocortisolemia in patients admitted to medical intensive care unit in our tertiary care center was 31.4%. Among the various age groups that were included in the study population, the presence of low cortisol levels was observed in those patients between 51-70 years along with higher mortality rates in comparison to other age groups. However an association between hypocortisolemia and mortality could not be established.

REFERENCES

1. Ungar, A. and J.H. Phillips, 1983. Regulation of the adrenal medulla. Physiol.l Rev., 63: 787-843.
2. Bateman, A., A. Singh, T. Kral and S. Solomon, 1989. The Immune-Hypothalamic-Pituitary-Adrenal Axis*. Endocr. Rev., 10: 92-112.
3. Dickmeis, T., 2009. Glucocorticoids and the circadian clock. J. Endocrinol., 200: 3-22.
4. Liyanarachchi, K., R. Ross and M. Debono, 2017. Human studies on hypothalamo-pituitary-adrenal (HPA) axis. Best Pract. And Res. Clin. Endocrinol. and Metab., 31: 459-473.
5. Sam, S., T.C. Corbridge, B. Mokhlesi, A.P. Comellas and M.E. Molitch, 2004. Cortisol levels and mortality in severe sepsis. Clin. Endocrinol., 60: 29-35.
6. Jurney, T.H., J.L. Cockrell, T.H. Jurney, J.S. Lindberg, J.M. Lamiell and C.E. Wade, 1987. Spectrum of Serum Cortisol Response to ACTH in ICU Patients. Chest, 92: 292-295.
7. Hamrahian, A.H., T.S. Oseni and B.M. Arafah, 2004. Measurements of Serum Free Cortisol in Critically Ill Patients. New Engl. J. Med., 350: 1629-1638.
8. Amrein, K., G. Martucci and S. Hahner, 2018. Understanding adrenal crisis. Intensive Care Med., 44: 652-655.
9. Burger-Stritt, S. and S. Hahner, 2017. Nebennierenkrise. Der Internist, 58: 1037-1041.
10. Allolio, B., 2015. Extensive expertise in endocrinology: Adrenal crisis. Eur. J. Endocrinol., 172: 115-124.
11. Claessen, K.M.J.A., C.D. Andela, N.R. Biermasz and A.M. Pereira, 2021. Clinical Unmet Needs in the Treatment of Adrenal Crisis: Importance of the Patient's Perspective. Front. Endocrinol., Vol. 12 .10.3389/fendo.2021.701365.
12. Iwasaku, M., M. Shinzawa, S. Tanaka, K. Kimachi and K. Kawakami, 2017. Clinical characteristics of adrenal crisis in adult population with and without predisposing chronic adrenal insufficiency: A retrospective cohort study. BMC Endocr. Disord., Vol. 17 .10.1186/s12902-017-0208-0.
13. Rushworth, R.L., D.J. Torpy and H. Falhammar, 2019. Adrenal Crisis. New Engl. J. Med., 381: 852-861.
14. Hahner, S., 2018. Acute adrenal crisis and mortality in adrenal insufficiency: Still a concern in 2018!. Ann. d'Endocrinologie, 79: 164-166.
15. Dhillo, W., W. Kong, C.L. Roux, J. Alaghband-Zadeh and J. Jones et al., 2002. Cortisol-binding globulin is important in the interpretation of dynamic tests of the hypothalamic--pituitary--adrenal axis. Eur. J. Endocrinol., 146: 231-235.
16. Tsigos, C. and G.P. Chrousos, 2002. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J. Psychosomatic Res., 53: 865-871.
17. Prete, A., A.E. Taylor, I. Bancos, D.J. Smith and M.A. Foster et al., 2020. Prevention of Adrenal Crisis: Cortisol Responses to Major Stress Compared to Stress Dose Hydrocortisone Delivery. The J. Clin. Endocrinol. and Metab., 105: 2262-2274.

18. Spiga, F., J.J. Walker, J.R. Terry and S.L. Lightman, 2014. HPA Axis-Rhythms. Compr. Physiol., 4: 1273-1298.
19. Cooper, M.S. and P.M. Stewart, 2007. Adrenal Insufficiency in Critical Illness. J. Intensive Care Med., 22: 348-362.
20. Keller-Wood, M.E. and M.F. Dallman, 1984. Corticosteroid Inhibition of ACTH Secretion*. Endocr. Rev., 5: 1-24.
21. Ospina, N.S., A.A. Nofal, I. Bancos, A. Javed and K. Benkhadra et al., 2016. ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis. The J. Clin. Endocrinol. and Metab., 101: 427-434.
22. Chan, C.M., A.L. Mitchell and A.F. Shorr, 2012. Etomidate is associated with mortality and adrenal insufficiency in sepsis. Crit. Care Med., Vol. 40 .10.1097/ccm.0b013e31825fec26.
23. Annane, D., S.M. Pastores, B. Rochwerg, W. Arlt and R.A. Balk et al., 2017. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Crit. Care Med., Vol. 45 .10.1097/ccm.0000000000002737.
24. Lipiner-Friedman, D., C.L. Sprung, P.F. Laterre, Y. Weiss and S.V. Goodman et al., 2007. Adrenal function in sepsis: The retrospective Corticus cohort study. Crit. Care Med., Vol. 35 .10.1097/01 .ccm.0000259465.92018.6e.