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Correlation between Catecholamine Levels and Outcome in Patients with Severe Head Trauma

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Abstract: Some studies have shown that catecholamines and the changes in their levels during and after head trauma can be useful in predicting the outcome in head trauma patients. The goal of this study is to search for a probable relation between urine levels of catecholamines and prognosis in patients with severe head trauma. Fifty four patients with severe head trauma Glasgow Coma Scale (GCS≤8) on admission time were recruited in Imam Reza Hospital within one. These patients were included when having no major accompanying trauma in other organs. Twenty four hour urine was collected after admission and levels of metanephrine and nor-metanephrine were measured. The relation between urine levels of these metabolites with final outcome and also with GCS at admission, 24, 48 h and 1 week after admission and discharge time and Glasgow Outcome Scale (GOS) were studied. Fifty two patients, 48 males and 4 females with a mean age of 32.3±14.7 (3-72) years were included. The main underlying etiologies were motorcycle (46.2%) and car accidents (25%). Diffuse axonal injury, brain contusion and subdural hematoma were three main diagnoses (28.8, 17.3 and 15.4% of the cases, respectively). 19 (36.5%) of the patients expired within the study period. The mean level of metanephrine and normetanephrine in urine were 207.9±200.5 and 330.2±218.4 μg in 24 h, respectively. There was no meaningful relation between urine levels of these metabolites and any of GCS and GOS. There was also no meaningful relation between these parameters and final prognosis in patients.

Key words: Urine catecholamine, brain contusion, subdural hematoma, glasgow coma scale, glasgow outcome scale

INTRODUCTION

Trauma is one of the major causes of death in all societies and only one of its sub classifications, head trauma, has a prevalence of 200 to 300 cases in 100.000 people a year. In head trauma patients, the trauma is categorized into two types. Primary brain injury that takes place in accident time and secondary injury that develops following primary trauma so that cellular processes leading to cellular death in brain and deterioration of clinical status of the patients begin (Winn, 2003). By now, different prognostic factors have been proposed in regard to the mortality and final prognosis of patients with head trauma (Lingsma *et al.*, 2010; Steyerberg *et al.*, 2008; Menon and Zahed, 2009; Oh *et al.*, 2006; Murray *et al.*, 2007). Catecholamine levels are one of the suggested items in trauma patients prognoses. Trauma initiates a cascade of physiological procedures. Fear accompanied by trauma provokes sympathetic system. On the other hand, pain is a powerful provoker of sympathoadrenal axis which increases sympathetic tone and catecholamine release. Sympathetic system activation can occur following injury, bleeding and hypovolemia. Sympathetic effect and Catecholamines release, including epinephrine and nor-epinephrine, have numerous effects such as increase in blood pressure, heart rate, heart contractibility and ventilation per minute. Although these effects of catecholamines after severe injuries increase survival probability in short term, sympathoadrenal axis excitation in long term can lead to reverse physiological effects. High catecholamine levels can cause arteriolar contraction and therefore decrease oxygen and metabolic substrates delivery to the tissues and also catabolic metabolic state which is seen in severe trauma (Fink *et al.*, 2005). To the best of knowledge there is only one study on catecholamine metabolites in urine so for with no significant results (Kearney *et al.*, 1992). This study is to evaluate the relation between urine catecholamine metabolites levels with GCS and prognosis in patients with severe head trauma for the first time. Any significant finding would influence the routine workup and management in these patients.

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MATERIALS AND METHODS

Fifty four patient with severe head trauma were studied in a cross sectional, descriptive-analytic study. Follow up was not possible for two patients; therefore the study was carried out on 52 patients. Urine catecholamine metabolites levels in first 24 h of admission were measured and their relation with prognoses of patients was evaluated. The study was carried out in Tabriz Imam Reza Hospital and primary data collection and analysis lasted for 12 months starting from Jan 2009 to Jan 2010. Patients were entered the study immediately after being examined by resident of neurosurgery in emergency ward if that they had GCS≤8 and surgical approval and did not have severe chest and/or abdomen traumas. Urine catheters were inserted in all patients and 24 h urine was collected after primary medical measurements and patient transfer to the ward. Urine samples were collected and pH was adjusted to 1-3 with HCl. Urine samples were collected by wringing the compresses, centrifuged at 4°C and acidified. All acidified samples were kept at -20°C until analysis. The routine analysis of free catecholamines (metanephrine and normetanephrine) was made by HPLC-EC (M515 pump, Wisp 740 autosampler and a M460 amperometric detector; Waters, Saint Quentin, France) after extraction from urine by ion exchange. Urinary 24 h creatinine concentrations were determined using a compensated rate-blanked Jaffé based method on a Modular P900 (Roche Diagnostics) (Pussard *et al*., 2009). Routine serum laboratory tests including determining the serum levels of glucose, hematocrit, creatinine, Blood Urea Nitrogen (BUN), Na and K were performed on admission, too (Fink *et al*., 2005). Clinical examination and GCS estimation were performed by resident of neurosurgery 24 and 48 h and one week after trauma. The GOS was also determined when patients were discharged. The relation between the urinary levels of catecholamines with the GCS and GOS scores, as well as the short-term outcome (discharge, expire) was determined. Informed consents were signed by the first degree relatives of the patients. This study is approved by the Ethics Committee of Tabriz University of Medical Sciences. Obtained data are presented as Mean±SD and frequency and percentage. SPSS™ Ver. 15 statistical software was used. Quantitative variables were compared using student t-test (Independent samples), Mann Whitney U-Test. Qualitative variables were compared using contingency tables and chi-square test and or Fisher's Exact test considering the conditions. Correlation was evaluated defining Spearman coefficient (rho). Results with $p \le 0.05$ were considered statistically meaningful in all studied items.

RESULTS

Fifty two cases with severe head trauma were studied. The mean age of the patients was 32.3±14.7 (13-72, median 28) years including 10 (19.2%) cases ≤20 years, 27 (51.9%) cases between 21 and 40 years and 15 (28.8%) cases ≤41 years. Forty eight (92.3%) patients were male and 4(7.2%) were female. Thirty three (63.5%) patients were hospitalized in trauma ward and 19 (36.5%) in the Intensive Care Unit (ICU). Accompanied traumas existed in 8(15.4%) patients which were all bone fractures. Thirteen (46.2%) patients were traumatized in car, 9(17.3%) as pedestrians, 4(7.7%) with fall accidents and 2 (3.8%) in quarrel. The hospitalization time was 16.1±10.8 (2-45) days. Regarding lab findings; the mean hemoglobin level was 12.7±2.3 (8.4-19.2 median 12.9) mg dL^{-1} (15 decreased, 3 increased, 34 normal), mean hematocrit level was 34.2±6.6 (22-43 median 37) percent (8 decreased, 2 increased, 42 normal), mean blood sugar level was 108.3±73.3 (94-444 median 163) mg dL^{-1} (18 increased, 34 normal), mean sodium level was 143.8±4.1 (128-151 median 144) meq dL^{-1} (2 decreased, 4 increased, 46 normal), mean potassium level was 4.0±0.8(0.8-6.3 median 4) meq dL^{-1} (5 decreased, 2 increased, 45 normal), mean BUN level was 33.5±11.8 (12-82 median 33) mg dL^{-1} (5 increased, 47 normal), mean serum creatinine level was 1.0±0.3 (0.6-1.7 median 0.9) mg dL^{-1} (2 increased, 50 normal), mean 24 h urine creatinine level was 1.6±0.9 (0.2-3.5 median 1.6) mg dL^{-1} (all normal), mean urine metanephrine level was 207.9±200.5 (30.5-1219 median 187.5) microg/24 h (14 increase, 38 normal), mean urine normetanephrine level was 330.2±218.4 (54.1-1 median 282.9) microg/24 h (5 increased, 47 normal), mean GCS at admission time, 24 h after admission, 48 h after admission, 1 week after admission and at discharge time were respectively 6.4±1.5(median 7, 3-8), 6.8±1.7 (median 7, 3-11), 6.7±2.5 (median 7, 0-14), 6.4±5.1 (median 71, 0-15), 8.1±6.1 (median 10.5, 0-15) and the mean GOS was 2.6±1.4 (median 3, 1-5). Finally 33 patients (63.5%) were discharged and 19 (36.5%) were expired. The final diagnoses are summarized in Table 1. Accordingly, the diffuse axonal injury, brain contusion and subdural hematoma were the three leading underlying causes. The correlation between urine catecholamine levels and GCS and GOS in different age-groups and in all patients is summarized in Table 2. Accordingly, there was no meaningful correlation between urine metanephrine and normetanephrine and GCS on admission, 24, 48 h and 1 week after discharge. There was no meaningful correlation between urine metanephrine and normetanephrine and GOS. The relations between studied criteria and urine catecholamine

Table 1: Final diagnosis percentage among patients

Diagnosis	Percentage
Diffuse axonal injury	28.8
Brain contusion	17.3
Subdural hematoma	15.4
Subarachnoid hemorrhage	7.7
Subarachnoid hemorrhage and diffuse axonal injury	7.7
diffuse axonal injury + brain edema	7.7
Subarachnoid hemorrhage and brain contusion	3.8
Epidural hemorrhage	1.9
Subarachnoid hemorrhage and brain edema	1.9
Diffuse axonal injury + brain contusion	1.9
Subarachnoid hemorrhage and intraventricular hemorrhage	1.9
intraventricular hemorrhage and brain contusion	1.9
Subarachnoid hemorrhage and subdural hematoma	1.9

Table 2: The relation between urine catecholamine levels and GCS and GOS in different age groups

Age groups	Catecholamine	Statistical analysis	Base GCS	24 h GCS	48 h GCS	GCS after a week	GCS at discharge	GOS
Overall	Normetanephrine	rho	0.240	0.092	0.231	0.078	0.112	0.091
		p-value	0.086	0.515	0.099	0.580	0.427	0.520
	Metanephrine	rho	0.057	-0.051	0.064	-0.082	-0.057	0.002
		p-value	0.687	0.720	0.651	0.592	0.960	0.989
≤20 years	Normetanephrine	rho	0.122	0.023	0.118	0.040	0.167	0.043
		p-value	0.098	0.203	0.068	0.430	0.203	0.430
	Metanephrine	rho	0.023	-0.078	0.043	-0.123	-0.076	0.011
		p-value	0.187	0.901	0.781	0.503	0.998	0.902
21-40 years	Normetanephrine	rho	0.203	0.104	0.320	0.102	0.092	0.177
		p-value	0.112	0.313	0.102	0.222	0.502	0.650
	Metanephrine	rho	0.043	-0.077	0.187	-0.065	-0.092	0.001
		p-value	0.201	0.304	0.501	0.443	0.801	0.781
41 years≤	Normetanephrine	rho	0.198	0.020	0.188	0.091	0.010	0.100
		p-value	0.202	0.456	0.232	0.302	0.400	0.201
	Metanephrine	rho	0.043	-0.046	0.021	-0.022	0.001	0.014
		p-value	0.088	0.465	0.402	0.693	0.982	0.902

Table 3: The relation between basic variables and urine catecholamine levels with prognosis in different age groups.

Age groups	Variables	Discharged (n = 33)	Expired (n = 19)	p-value
Overall	Gender (male/female)	30/3	18/1	0.534
	Hospitalization word (ICU/trauma)	13/20	6/13	0.573
	Accompanying fracture	7	1	0.126
	Metanephrine (μg)	(188.2)211.6±199.3	(184.6)201.4±207.8	0.862
	Normetanephrine (μg)	(283.1)340.5±215.6	(264.2)312.3±227.9	0.658
≤20 years	Gender (male/female)	8/1	1/0	0.900
	Hospitalization word (ICU/trauma)	6/3	0/1	0.400
	Accompanying fracture	2	0	0.800
	Metanephrine (μg)	(282.7)299.1±141.0	(758.9)758.9±0.0	0.200
	Normetanephrine (μg)	(205.7)199.3±80.0	(947.2)947.2±0.0	0.200
21-40 years	Gender (male/female)	15/0	11/1	0.444
	Hospitalization word (ICU/trauma)	6/9	3/9	0.683
	Accompanying fracture	2	1	0.586
	Metanephrine (μg)	(286.3)341.9±239.6	(222.1)235.9±160.4	0.217
	Normetanephrine (μg)	(185.0)168.9±84.8	(166.5)167.4±125.5	0.829
41 years ≤	Gender (male/female)	7/2	6/0	0.486
	Hospitalization word (ICU/trauma)	1/8	3/3	0.235
	Accompanying fracture	3	0	0.229
	Metanephrine (μg)	(302.8)379.5±248.6	(184.6)390.5±260.3	0.998
	Normetanephrine (μg)	(193.7)295.2±358.4	(145.9)145.3±154.2	0.388

Data are shown as Mean±SD (median)

levels with patients' outcome in different age-groups and in all patients are summarized in Table 3. Accordingly, there was no significant difference between the two groups regarding gender, hospitalization ward, accompanying fractures in other parts of body and the mean urine levels of metanephrine or normetanephrine.

DISCUSSION

Trauma initiates a cascade of physiological events and one of them is the catecholamines release. Sympathoadrenal axis excitation in long term can lead to reverse physiological effects such as decreased oxygen and metabolic substrates delivery to the tissues and catabolic state in severe trauma (Fink *et al*., 2005). Hamill *et al*. (1987) studied the plasma levels of epinephrine, nor-epinephrine and dopamine in 33 patients with head trauma and discovered that the levels of these indicators have reverse relation with the level of consciousness and GCS of the patients and patients with lower GCS had higher levels of these chemicals. Plasma catecholamine levels of patients with very low GCS (Hamill *et al*., 1987; Koiv *et al*., 1997) were 4 to 5 times more than normal people. They also could predict the probability of recovery of patients measuring serum catecholamines (Hamill *et al*., 1987). The relation between venous epinephrine and norepinephrine levels in patients with head trauma with level of consciousness were studied by Koiv *et al*. (1997) and a reverse relation between serum epinephrine and norepinephrine levels with GCS and consciousness levels was observed. They suggested that the evaluation of these markers could be a useful method for early determination of prognosis in patients with head trauma (Koiv *et al*., 1997). In other studies, Clifton *et al*. (1981) and Woolf *et al*. (1991) reported similar results. On the other hand, rapid metabolism of epinephrine and norepinephrine, their very low concentrations in plasma and also changes in their serum levels in different hours of day can lower the validity and prognostic accuracy of measuring these chemicals in plasma. Rapid catabolism of these materials and their turning into more stable metabolites urges measuring the materials resulting from their catabolism (i.e. metanephrine, nor-metanephrine and VMA) rather than direct measurement of epinephrine and norepinephrine (Burtis *et al*., 2005; Defour *et al*., 2001). Based on these facts and as the studies on plasma catecholamine levels in patients with head trauma are not recent, we were to study the probable relation between urine catecholamine metabolites levels 24 h after severe head trauma with patients' GCS in different stages, GOS and final outcome of the patients. There was no meaningful relation between urine levels of these metabolites and level of consciousness or final outcome of the patients. A similar study has been carried out in this regard: Kearney *et al*. (1992) studied 36 patients with severe head trauma (26 blunt and 10 penetrating traumas, all having GCS lower than 9). Twenty four hour urine metabolites after admission such as VMA, metanephrine and nor-metanephrine were measured in this study. Half of the patients expired during the study. Five candidates for elective neurosurgery were selected as the controls. There was no meaningful relation between levels of catecholamine metabolites in urine and patients' outcome. However, the levels of these chemicals were meaningfully higher in patients with severe head trauma than the control group. As it is seen, the results of our study are in accordance with this study. Feldman *et al*. (1993) in a study carried out on 15 patients with severe head trauma, showed that urine levels of catecholamine metabolites increase gradually and reach their maximum level on day 7 to 10. Therefore, it is suggested that urine levels of these metabolites can be measured in this period and their relation with patient outcome can be evaluated.

CONCLUSION

There was no meaningful statistical relation between urine catecholamine levels (metanephrine and normetanephrine) in first 24 h of hospitalization and GCS at admission time and 24 and 48 h and 1 week after admission and GOS at discharge time. There was no meaningful statistical relation between level of catecholamine metabolites in urine and outcome in patients with severe head trauma. Based on the current study, measuring urine catecholamine metabolites 24 h after admission in patients with severe head trauma cannot predict their prognoses therefore is not suggested. Further studies in this regard on patients with different degrees of head trauma and are required. In future studies, urine metabolite levels should be measured continuously in hospitalization period until discharge or expiration of the patients.

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