Original Article / Özgün Araştırma

Evaluation of the Relationship of Intracranial Pressure with the Levels of Hypothalamic-Pituitary-Gonadal Axis Hormones on Prognosis in Severe Brain Injury

Kafa Travmasında Kafa İçi Basınç ve Hipotalamo-Hipofizer-Gonadal Aks Arasındaki İlişkinin Değerlendirilmesi

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Abstract

Objective: Head traumas have an important place among all traumatic injuries and it is an important public health problem worldwide. Novel methods predicting prognosis may contribute to a decrease in the mortality and morbidity rates.

Materials and Methods: Continuous intracranial pressure (ICP) measurements, initial cerebral computed tomography (CT) and measurement of the hypothalamic-pituitary-gonadal (HPG) axis hormones between the 0^{th} and 4^{th} days were performed in 15 adult male patients with severe head trauma. The relationship of these parameters with the short-term results of the patients on the 15^{th} day was evaluated. Additionally, provocation tests were carried out to evaluate the HPG axis function.

Results: High ICP and compression of basal cisterna increased mortality and they were found to affect prognosis (p=0.009 and p=0.033, respectively) No statistically significant association was found between midline shift and prognosis. No relationship was found between mortality and mean basal hormone values on the 0^{th} day and between the 1^{st} and 4^{th} days.

Conclusion: ICP measurement values and the presence of compression of basal cistern on the initial brain CT can be used to predict the prognosis in severe head injury but there is no significant relationship between hypophyseal hormone values and prognosis.

Öz

Amaç: Kafa travmaları tüm travmatik yaralanmalar içinde önemli bir yer tutar ve ülkeler için önemli bir sağlık problemidir. Prognozu tahmin edici öngören yöntemlerin artması mortalite ve morbidite oranlarının azalmasını sağlayabilir.

Gereç ve Yöntemler: Çalışmada 15 ağır kafa travmalı yetişkin erkek olguda sürekli intrakraniyal basınç (İKB) ölçümleri, ilk bilgisayarlı beyin tomografisi (BT), 0-4. günlerde büyüme hormonu, tiroid uyarıcı hormon, lüteinleştirici hormon, folikül uyarıcı hormon, prolaktin T3, T4 ve Te hormon düzeyleri ölçümü yapıldı. Bu

parametrelerin, olguların 15. gündeki kısa dönem sonuçları ile ilişkisi değerlendirildi. Ayrıca 4. gün olgularda hipotalamo-hipofizer aksı değerlendirmek amacıyla tirotropin salıcı hormon (TRH) ve lüteinizasyon hormonu salan hormone (LHRH) ile provokasyon testleri yapıldı.

Bulgular: Yüksek İKB'nin ve bazal sisternaların kompresyonunun mortaliteyi artırdığı, bunların prognoz üzerine etkin olduğu bulundu (sırası ile p=0,009; p=0,033). Orta hat şifti ile prognoz arasındaki istatistiksel olarak anlamlı birliktelik saptanmadı. Sıfırıncı gün ve 1-4. günlük ortalama bazal hormon değerleri ile mortalite arasında ilişki bulunamadı. TRH ve LHRH ile provakasyon testi sonrası yeterli yanıt elde edilen olgularda hipotalamo-hipofizer aksın sağlam olduğu kabul edildi.

Sonuç: Bulgularımıza göre, İKB ölçüm değerleri ve ilk beyin BT'de bazal sisternaların kompresyonunun varlığı ağır kafa travmalarında prognozu tahmin etmek için kullanılabilir fakat hipofizer hormon değerleri ile prognoz arasında anlamlı bir ilişki yoktur.

Introduction

Head trauma has reached epidemic levels because of increasing traffic acciedents and violence especially among people with low socioeconomic status. The types of head trauma and their severity vary significantly from one population to the another (1-4). Against the severe head traumas, complex pathophysiological changes are observed in patients with head trauma as the response of the brain and its surrounding structures.

Along with the structural changes, changes in hypothalamic-pituitary function also occur in patients with head trauma. Studies have shown that hormonal responses towards trauma reflect the severity of the injury. While some hormone levels increase, others decrease. These results support the involvement of hypothalamic-pituitary-gonadal (HPG) axis after trauma and it is thought that it can be used as a prognostic marker after a severe head trauma (5,6).

In this study, it was planned to investigate the relationship of prognosis with intracranial pressure (ICP) values, brain computed tomography (CT) findings and hormonal changes in patients with severe head trauma.

Materials and Methods

In this study, we included 15 male patients who were admitted to the emergency department at Pamukkale University Medical Faculty Hospital with the diagnosis of traumatic brain injury and treated in the Department of Neurosurgery between January 2002 and October 2002. All medical records of included 48 patients were analyzed. The mean age of the patients was 43.13±18.17 years (range: 19-73). Among 48 (31.25%) cases hospitalized for the treatment of head trauma, 15 patients were selected who met the inclusion citeria of the study. In order to avoid the influence of age and gender on hormone profile, women, children and patients younger than 16 years or older than 75 years of age were excluded from the study. Patients, who were admitted within 24 hours after trauma, whose Glasgow Coma Scale (GCS) score was 8 or less, and who had a non-endocrine disease, were included in this study (Table 1). This study was designed as a neurosurgeon thesis as a part of medical assistant programme which is approved by Pamukkale University Faculty of Medicine and informed consent was approved by the relatives of all patients.

After the initial evaluation of the patients admitted to the emergency department, neurological examinations were performed, GCS scores were reported, cerebral computed tomography (CCT) and blood samples were taken.

After admission to the intensive care unit, the following standard neurosurgical treatment protocol was used:

a) All patients were intubated and mechanically ventilated (PaO_2 >100 mmHg and $PaCO_2$ 25-35 mmHg by the lowest FiO_2 as possible),

b) Multimodal monitoring was applied in all patients,

c) In patients who needed surgical intervention, craniotomy and hematoma drainage were performed,

d) For sedation, propofol was administered at a dose of 1-3 mg/kg/h by continuous infusion,

Table 1. Glasgow Outcome Scale	
Good recovery	5
Moderate disability	4
Severe risability	3
Persistent vegetative state	2
Death	1

e) For monitoring central venous pressure, subclavian venous catheterization was done,

f) Mannitol was administered as a fast loading dose of 1-2 g/kg and infusion of 4x0.5-1 g/kg as a maintenance dose together with furosemide with a maintenance dose of 3x0.5 mg/kg. In addition, when the ICP rised above 25 mmHg, mannitol was administered at a dose of 0.25 g/kg,

g) Treated with 3x100 mg of phenytoin,

h) In patients with hypotension, excluding surgical etiology, 5-20 µ/kg/min dopamine and, if necessary, dobutamine was started at a dose of 4-10 ug/kg/min; the goal of this treatment was to keep average arterial pressure at the range of 80-100 mmHg,

i) Intraparenchymal ICP was monitored using an intraparenchymal neurosensory kit (Codman ICP Express monitor),

j) Parenteral nutrition was started after achieving hemodynamic stability and enteral nutrition was started gradually.

The cases were divided into three groups according to the presence of the shift on the first CCT:

1) No shift,

2) Shift ≤1 cm, and

3) Shift >1 cm.

Furthermore, into two groups as: group 1 (normal) and group 2 (compressed by the appearance of basal cistern and third ventricle on the first CCT.

In order to determine the baseline values of growth hormone (GH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicule stimulating hormone (FSH), prolactin (PRL) and their end-organ responses, free triiodothyronine (fT3), free thyroxine (fT4) and total testosterone (tTe), blood samples were taken on the first day, and between 7:00 a.m and 9:00 a.m. from the 1st through the 4th days, and on the 15th day. Prolactin levels were evaluated on the first day only to avoid the effect of sympathomimetic agents on prolactin levels. Usually, the first blood sample was taken in the emergency department on the first day and the time elapsed from the injury ranged from 2 to 6 hours. Thyrotropin-releasing hormone (TRH) and gonadotropin-releasing hormone (GnRH) provocation tests were administered in patients who lived up to day 4, in order to evaluate the HPG axis on the 4th day. For this, 200 µg TRH and 100 µg GnRH were given intravenously and then blood samples were taken at 0th, 15th, 30th, 60th, 90th and 120th minutes and were centrifuged, and stored until biochemical examination.

GH measurement was performed by the chemiluminescence method, and measurement of the other hormones was performed by the fluorescence polarization immunoassay method. The normal values of our laboratory for men are: FSH: 2.4-14.9 mIU/mL, LH: 1.7-8.6 9 mIU/mL; TSH: 0.41-4.01 mIU/mL; GH: 0.06-5.0 ng/mL; PRL: 3.6-16:3 ng/mL; fT3: 2.1-3.8 pg/mL; fT4: 0.75-1.65 ng/dL; and tTE: 300-1000 ng/dL. After the GnRH and TRH challenge tests, an increase of a hormone level at the rate of 150-200% was evaluated as light, and an increase of more than 200% was evaluated as normal response. The results were evaluated at the end of the 15th day by the GCS and then, were divided into two groups for statistical analysis (Table 1, 2).

Statistical Analysis

Statistical analysis was performed by SPSS 10.0 for Windows. Biochemical parameters were grouped into high, low, and normal, and ICP parameter was used for quantitative analysis of the values; the differences between the living cases and those who died were evaluated by the Mann-Whitney U test; the relationships between the biochemical parameters and mortality, between the CCT findings and mortality were analyzed by chi-square test (Pearson's chi-square test, Fisher's exact test), the differences between the baseline and peak values of pre- and post-provacation tests were evaluated using the Wilcoxon test; A p value of less than 0.005 was considered statistically significant whereas a p value of less than 0.001 was considered very significant. We found the same results when analyzing biochemical findings by the Mann-Whitney U test and chi-square tests.

Results

Fifteen patients with a severe brain injury were included in the study. All patients had a GCS score of 8 or less in the initial evaluation (median GCS score: 4.00-3.00). Seven patients (46%) were with multiple

Table 2. Groups evaluating by Glasgow Outcome Scale score

Group 1	The cases with GOS score 1
Group 2	The cases with GOS score 2-5

GOS: Glasgow Outcome Scale

trauma, six patients (40%) had thoracic trauma, four patients (26%) had abdominal trauma, four patients (26%) had bone fractures, one case had urological trauma (6%), and four patients (26.6%) underwent neurosurgical surgery (Table 3).

The patients were divided into two groups for statistical examination at the end of 15 days according to the findings of the Glasgow Outcome Scale (GOS): patients in group 1 were with a GOS score of 1, (11 patients; 73.3%), those in group 2 had a GOS score of 2-5 (four patients; 26.7%).

Shift on the first CCT: One patient was with a shift ≤1 cm (6.7%), three were with >1 cm (20.0%) and 11 patients (73.7%) had no shift on the first CCT. One patient with a shift ≤1 cm (100%), three of three cases with a shift >1 cm (100%) and seven of 11 cases with no shift (63%) died. There was no shift on the first CCT in the living patients. There was no statistically significant relationship between prognosis and presence or absence of shift on the first CCT.

Table 3. Clinical data of patients

Case	Age (year)	CT	TT	AT	BF	UT	GCS	GOS	NSI	Ethiology
1	37	+	-	-	-	-	8	3	+	TA
2	22	+	+	-	-	-	4	1	-	TA
3	60	+	+	+	+	-	4	1	-	TA
4	22	+	-	-	-	-	4	1	-	GW
5	29	+	-	-	-	-	7	1	-	F
6	45	+	-	-	-	-	7	3	-	TA
7	54	+	+	-	+	-	8	2	-	TA
8	35	+	+	+	-	-	3	1	-	TA
9	19	+	+	+	-	-	6	1	+	TA
10	20	+	-	-	-	-	3	1	+	F
11	65	+	+	-	+	-	6	1	-	TA
12	73	+	-	-	-	-	3	2	-	TA
13	49	+	-	+	+	+	4	1	-	TA
14	62	+	-	-	-	-	4	1	-	TA
15	55	+	-	-	-	-	5	1	+	TA

CT: Cranial trauma, TT: Thorax trauma, AT: Abdominal trauma, BF: Bone fracture, UT: Urological trauma, GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale, NSI: Neurosurgical intervention, TA: Traffic accident, GW: Gunshot wounds, F: Fall

Basal cisterns on the first CCT: Four patients (26.7%) were reported to be with normal basal cisterns and 11 patients (73.3%) were with compressed basal cistern. One of four patients with normal basal cistern (25%) and 10 of 11 patients with compressed basal cistern (90.9%) died. One of the living cases was found to be with compressed basal cistern. There was a statistically significant relationship between compression of the basal cisterns and prognosis in both living and dead patients. Compression of the basal cistern increased mortality (Table 4).

ICP: The mean duration of ICP monitoring was 3.8±2.7 days. There was no statistically significant difference between the living and dead cases (p=0.009 and p=0.006, respectively). ICP values in dead patients were higher then in living patients (Table 5). ICP values on the first day in all cases were higher than 25 mmHg. The mean ICP values in the three cases were below 25 mmHg.

Biochemical parameters: There was no statistically significant difference between the first day and the 1-4 days average basal values of GH, TSH, PRL, FSH, LH, T3, T4, and tTE in living and died patients. There was a statistically significant difference between the basal and peak values of FSH, LH, and TSH in patients who were administered the provocation test on the 4th day (p=0.018, p=0.018, and p=0.028, respectively) (Table 6). Median values of hormon levels are also given in Table 6.

Table 4. Living or dead patients rates according to the findings of the first cerebral computed tomography

Parameters		Living patients		Dead patients		p
		S	%	S	%	
Basal cisterns	Compressed	1	9.1	10	90.9	0.033
	Normal	3	75	1	25	
Midline shift	>1 cm	0	0	3	100	0.371
	≤1 cm	0	0	1	100	
	None	4	36.4	7	63.6	

The GH values on the first day were normal in nine cases (60%), and high in six cases (40%). There was no low level of GH in any cases. Mortality was observed in five patients (55.6%) with normal GH values, and in six patients with high GH values (100%). The GH levels were within normal limits in all living patients on the 15th day. All patients who had high GH levels on the first day and high mean GH values between 1st and 4th days died, but there was no statistically significant difference. The GH levels in six dead patiens were found to be very high on the day of dying.

On the first day, the PRL values were normal in seven patients (46.7%) and high in eight patients (53.3%). There was no low level of PRL in any cases. There was observed mortality in six patients (85.7%) with normal PRL values, and five patients (62.5%) with high PRL values. The PRL levels were found to be high in all living patients on the 15th day.

Table 5. Results of living and dead cases

Parameters	Living cases (median-IQR)	Dead cases (median-IQR)	p
ICP (first day) (mmHg)	28.00-4.25	48.00-4.00	0.009
Mean ICP (1-4 days) (mmHg)	3.75-2.23	47.50-6.60	0.006
LH (first day) (mIU/mL)	7.55-23.28	4.50-7.80	0.296
Mean LH (1-4 days) (mIU/mL)	5.16-3.06	5.90-2.25	0.395
FSH (first day) (mIU/mL)	4.40-26.15	3.50-3.40	0.557
Mean FSH (1-4 days) (mIU/mL)	2.49-6.08	3.40-2.77	0.433
TSH (first day) (µIU/mL)	0.79-0.82	1.26-1.40	0.296
Mean TSH (1-4 days) (µIU/mL)	0.75-1.59	0.70-1.21	0.794
GH (first day) (ng/mL)	3.75-3.17	5.90-7.20	0.214
Mean GH (1-4 days) (ng/mL)	0.57-0.35	11.92-14.68	0.151
PRL (first day) (ng/mL)	21.35-22.80	13.20-7.60	0.151
fT3 (first day) (pg/dL)	1.64-1.96	1.85-0.79	0.695
Mean fT3 (1-4 days) (pg/mL)	1.09-1.09	1.12-0.49	1.000
fT4 (first day) (ng/dL)	0.62-0.14	0.71-0.34	0.214
Mean fT4 (1-4 days) (ng/dL)	0.54-0.29	0.57-0.18	0.601
tTe (first day) (ng/dL)	211.83-377.82	193.61-76.67	0.695
Mean tTe (1-4 days) (ng/dL)	99.32-142.89	117.40-55.81	0.695

IQR: Interquartile range, GH: Growth hormone, ICP: Intracranial pressure, LH: Luteinizing hormone, FSH: Follicule stimulating hormone, TSH: Thyroid stimulating hormone, PRL: Prolactin, fT3: Free triiodothyronine, fT4: Free thyroxine, tTe: Total testosterone

Discussion

In this study, we investigated the relationship of ICP values with CT findings, anterior pituitary hormone, GH, TSH, PRL, FSH, LH, and T3, T4, tTE, values in patients with severe head injury.

As well known, high ICP is associated with poor prognosis. In our study, we also showed that high ICP levels increased mortality significantly (1-7). In our study, there were no complications reported in the literature, such as infection, hemorrhage and cerebrospinal fluid leak due to ICP monitoring.

The relationship of poor prognosis with the presence of the midline shift and compression of the basal cistern especially in initial CCT have been reported by various researchers in the literature (1-10). In our study, we found that compression of basal cisterns increased overall mortality, and this finding was found to be associated with poor prognosis. All patients with a shift on initial CCT died. However, there was no relationship between the midline shift and poor prognosis. We assume that the reason for this finding was the limited number of patients.

Different results have been reported in various studies on the effects of head traumas on hormonal changes (11,12). King et al. (11) measured the serum

Table 6. The median values before and after the provocation test

Parameters	Basal (medianIQR)	Peak (median-IQR)	p
LH (mIU/mL)	2.90-3.40	34.80-19.90	0.018
FSH (mIU/mL)	2.20-0.60	4.20-1.40	0.018
TSH (µIU/mL)	1.64-3.43	2.35-4.02	0.028

LH: Luteinizing hormone, FSH: Follicule stimulating hormone, TSH: Thyroid stimulating hormone, IQR: Interquartile range

levels of pituitary hormones in six patients with uncomplicated head injury. They showed that only three patients had a trend of elevated of serum PRL values (11). In another study conducted by Matsuura et al. (12), the authors performed TRH test in 30 patients soon after trauma to evaluate the effects of acute head injury on hypothalamohypophyseal functions. The basal level of the PRL was increased in patients with severe head injuries compared to those without. The patients with severe head injuries exhibited a lower PRL response to TRH (12). In our study, PRL values of the first day were normal or high. There were no low PRL values in any subject in our study. We could not measure PRL levels except for the first day due dopamine use for the treatment of hypotension, since dopamine inhibits the release of PRL. The TSH levels were found to be normal in most of the cases on the first day and on 1-4 days, and low values of TSH were found in the remaining cases.

In our study, the frequency and the amplitude of the pulse was not investigated. The blood samples were collected between 7:00 a.m. and 9:00 a.m. on the basis of the available information in the literature. The LH and FSH levels on the first day and mean results on the 1-4 days were normal in the majority of cases, only the higher values were obtained for the LH levels in the remaining cases. For FSH, we couldn't detect an obvious change to make a comment on. The mean fT3, fT4, and tTE levels on the first day and 1st to 4th days were low in majority of the patients.

In this study, the first day GH levels and the mean GH levels on the 1-4 days were normal in the majority of patients and higher in the remaining subjects. All patients who had higher levels of GH died, but there was no statistically significant relationship between higher levels of GH and mortality. Additionally, GH levels in the half of dead patients on the day of dying were immeasurably high.

In our study GH, LH, and PRL levels tended to be normal or high; and TSH, fT3, fT4, and tTe levels tended to be normal or low. FSH levels were within the normal range in majority of subjects. We evaluated HPG axis by the provocation tests with TRH and luteinizing hormone-releasing hormone (LHRH). If there were an adequate response after the provocation tests, we considered that HPG axis were intact. There was no association between mortality and first day's basal levels and 1-4 days mean levels of GH, TSH, PRL, FSH, LH, fT3, fT4, and tTe hormones. We could not measure adrenocorticotropic hormone and cortisol levels due to some technical problems. There was no change in hormone profile in patients who underwent surgery.

These results indicate that the pituitary response to head trauma is quite variable. Many factors may explain these differences:

a) The severity of head trauma,

b) The time of receipt of the blood samples,

c) Administered drugs,

d) Pulsatile secretion of the pituitary hormones, and

e) Heterogenity of the working groups and the cases.

The results of the studies have been interpreted in itself because of these factors were not standard for each study. The operating results with similar characteristics should be compared with each other.

Conclusion

High levels of ICP and compression of the basal cistern on CCT increase the mortality in severe head trauma patients. We have not found a relationship between mortality and the presence of midline shift on the CCT and hormonal parameters. Presence of the high levels of ICP and compression of the basal cistern on CCT are associated with mortality and provide us an opportunity to anticipate the results. However, hormonal parameters are not associated with mortality and they are not used in evaluating prognosis. Therefore, we have searched the relationship of high levels of ICP and presence of the compression of the basal cistern on CCT in estimating mortality. This allows us to reverse the adverse events or change, so that we get better results in reducing mortality and morbidity.

Ethics

Ethics Committee Approval: The study was approved by the Pamukkale Local Ethics Committee, Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.K., Concept: B.Ç., Design: B.Ç., Data Collection or Processing: Z.K., Analysis or Interpretation: A.Y., Literature Search: M.A., K.M.Ö., K.T., Writing: M.A.

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