Effect of Posttraumatic Serum Thyroid Hormone Levels on Severity and Mortality of Patients with Severe Traumatic Brain Injury

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Abstract- Traumatic brain injury (TBI) is an important cause of death and disability in young adults ,and may lead to physical disabilities and long-term cognitive, behavioral psychological and social defects. There is a lack of definite result about the effect of thyroid hormones after traumatic brain injury in the severity and no data about their effect on mortality of the injury. The aim of this study is to evaluate the effect of thyroid hormones after traumatic brain injury in the severity and mortality and gain a clue in brain injury prognosis. In a longitudinal prospective study from February 2010 until February 2011, we checked serum levels of T3, T4, TSH and TBG of severely brain injured patients and compared the relationship of them with primary Glasgow Coma Scale (GCS) score and mortality of patients. Statistical analysis used SPSS 11.5 software with using chi-square and Fisher exact test. Serum levels of T3 and T4 were decreased after brain trauma but not TSH and TBG. Mortality rates were higher in patients with lower T4 serum levels. The head injury was more severe in whom with low T3 and T4. Follow a severe brain injury a secondary hypothyroidism is happened due to pituitary dysfunction. Also, serum level of T3 and T4 on the first day admission affect on primary GCS score of patients which is an indicator of severity of brain injury. In addition, mortality rates of severely brain injured patients have a high correlation with the serum level of T4 in the first day admission.

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Introduction

Traumatic brain injury (TBI) is an important cause of death and disability in young adults ,and may lead to physical disabilities and long-term cognitive, behavioral psychological and social defects. The post-resuscitation Glasgow Coma Scale (GCS) is the most widely used clinical classification of TBI Severity (Table 1). GCS is based on the patient's response (eye opening, verbal and motor function) to various stimuli. A score of 13-15 is considered mild, 9-12 moderate, and <8 severe TBI (1-3). Substantial changes in serum levels of thyroid hormones have been described following many non-thyroidal illnesses, in particular after major Surgery (4), burns (5) most critical illness (6) and drug therapy (7). Decreased levels of T3 and free T3 associated with increases in reverse T3 and normal TSH levels have been observed in such conditions (8). This pattern is suggestive of a decrease in thyroid function of hypothalamic or pituitary origin as TSH levels remain normal despite low thyroid hormone levels. In addition, low T4 levels are usually present in critically ill patients and a relation between T4 levels and both severity and outcome has been observed in intensive care medical patients (6,9). Also, low T3 and low T4 syndrome is present after severe trauma in patients with multiple injuries as well as with head injury (3).

Lack of a definite result about the effect of thyroid hormones after traumatic brain injury on severity (according to post resuscitation GCS score) of traumatic brain damaged patients, no data about their effect on mortality of traumatic brain damaged patients and many controversies in this field motivate us to do this large study. This study also is the largest research in this topic

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Table 1. GCS scores chart.

	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli	Abnormal flexion to painful stimuli	Flexion / Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

till now. Our aim is to evaluate the pattern of thyroid function changes after traumatic brain injury and its effects on prognosis.

Patients and Methods

This study is a longitudinal prospective study on 72 patients with severe traumatic brain injury admitted in neurosurgery intensive care unit of Rajaee Hospital, Shiraz, Iran, since February 2010 till February 2011.

The severity of head injury was graded using the GCS (Table 1). GCS≤8 considered as severe brain injury. This score is determined from the assessment of the patient's best ocular, motor, and verbal response to verbal and painful stimuli; the score ranges from 3 to 15 (C7). Inclusion criteria were GCS≤8 during at least 6 hours following admission, use of mechanical ventilation for 24 hours or more, age, 60 years, no evidence of infection and no history of thyroidal disease or thyroid hormone therapy before. All patients were admitted via the emergency department where initial evaluation, resuscitation and emergency surgery consult were performed to rule out the major surgical problems. Blood, colloid and crystalloid solution were administered according to clinical needs. The usual clinical management of patients was not modified by the study. No steroid, beta-blocker nor amiodarone were administered during the study. T3, T4, thyroid stimulating hormone (TSH) and tyrosine binding globulin (TBG) were measured during the first 24 hours of admission. Blood samples were taken via an arterial catheter, and the serum was stored at -20°C until hormones assay. T3 and T4 were determined by radioimmunoassay (RIA), using ARIA II autoanalyser (Becton Dickinson, Orangeburg, NY). TSH was determined by a sensitive immunoradiometric assay (limit of detection 0.03 mu/l) (RIA-gnost hTSH, Behring Diagnostica, Marburg, FRG). Reference normal range of T3, T4, TSH and TBG were 80 -200 ng/dl, 4.5-12.5 µg/dl, 0.5-4.70 mIU/l and 16-34 mg/L respectively.

Statistical analyses were done by SPSS 11.5 software with using chi-square and Fisher exact test. The results are reported as mean±SD. A *P* value of less than 0.05 was considered as significant.

All patients' relatives signed the written informed consent and the study was approved in the local committee of medical ethics in Shiraz University of Medical Sciences, ethics department.

Results

According to inclusion and exclusion criteria 72 patients were included in this study. In 48 patients (66.7%) T3 was reduced and 24 patients (33%) T3 was not changed. TBG level of all 72 patients was not changed after brain injury. T4 levels of 16 patients (22%) are decreased, but in 56 patients (77.8%) T4 levels did not change. Serum levels of TSH in 7 patients (9.7%) were reduced. TSH levels of 64 patients (88.9%) were not changed, and in one patient (1.4%) TSH levels were increased. Mean (SD) of primary GCS score of patients was 6.1 (1.4). 14 patients (19.4%) of ones with severe brain injury were expired and 58 patients (80.6%) were survived and discharged from hospital after treatment.

From 48 patients with reduced T3, ten patients (20.8%) expired and from 24 patients without T3 reduction, 4 patients (16%) expired. It means that T3 reduction has not effect on mortality (*P*=0.76). From 16 patients with reduced T4, 6 patients expired but from 56 patients without T4 reduction, 8 patients expired. It means that T4 reduction influence on patient's mortality (*P*=0.038). All expired patients did not have any changes in serum TSH and TBG, so they did not influence on mortality (*P*=0.46). Primary GCS score of patients with reduced T3 was 5.89±1.4 and primary GCS score of patients without T3 reduction was 6.6±1.3.

It means that primary GCS score of the patients has a correlation with serum T3 level of the first day admission (*P*=0.045).

Table 2. Mortality of head injured patients according to changes in thyroid function tests.

	T4 total/mortality (%)	T3 total/mortality (%)	TSH total/mortality (%)
decreased	16/6 (37.5)	48/10 (20.8)	7/0 (0)
No change	56/8 (14)	24/4 (16)	64/14 (21)
increased	0/0 (0)	0/0 (0)	1/0 (0)

Primary GCS score of patients with reduced T4 was 5.5±0.96, and primary GCS score of patients without T4 reduction was 6.27±1.5. It means that serum level of T4 in the first day admission influence on primary GCS of patients (P=0.031). Primary GCs score of patients with reduced TSH was 5.9±1.1, and primary GCS score of the patients without TSH reduction was 6.1±1.2. It means that serum level of TSH did not have any correlation with primary score of the patients (Table 2).

Discussion

Influence of traumatic brain damage on thyroid hormones

In our study serum level of T3 was reduced significantly (P=0.002) and serum level of T4 was reduced, as well (P=0.03). Reduction in T3 was more than reduction in T4 (P=0.01). But TSH and TBG was not changed significantly (P>0.05) after head injury. Chiolero *et al*., also showed that T3 and T4 were both significantly low after brain injury also TSH, as well (3). Hypothalamic and pituitary disturbances have been demonstrated following severe head injury (2,10-13,21-24), but inconsistent data have been published on thyroid hormones. Normal T3 level and T3 resin uptake were observed after the 4th day post-injury by Haider *et al.,* (14) who concluded that the secretion of thyroid hormones is uninfluenced by head injury, but these authors mention neither the state of consciousness of their patients nor whether steroid has been administered. In contrast, Rudman *et al.,* (11) and Fleisher *et al.,* (12) observed decreased levels of T3 and T4 and TSH in severely comatose head injured patients receiving steroids 6 to 32 days following injury. The decrease in T4 serum levels can be attributed to both a reduction in thyroid hormone secretion and to the presence of inhibitors of thyroid hormone-binding, which have been demonstrated in patients with nonthyroidal illnesses (15-19).

In addition, it has been shown that a reduction in 5'-deiodinase activity is also present in nonthyroidal illnesses, which is responsible for the low T3 level and explains the opposite changes in rT3 level (7,18). Recent studies showed that both severe traumatic brain injury and prolonged mechanical ventilation result in hormonal disturbances early after injury, suggesting a pathophysiological response to brain injury and subsequent intensive care treatment rather than morphological damage (2,21-24). Normal TSH levels were observed in our patients, which can be considered as inappropriately low in the face of decreased thyroid hormone levels. Thus, severely traumatized brain injured patients developed a low T3, lowT4 and inappropriately normal TSH level due to a varying degree of hypothalamic-pituitary-thyroid axis dysfunction, and secondary hypothyroidism due to hypothalamic damage in head trauma.

Relationship between severity and mortality of head injury and thyroid hormone levels

Our data suggest that serum level of T3 and T4 on the first day admission effect on the severity of brain damage (P=0.045 & 0.031, respectively) that was evaluated with GCS score of the patients. But the level of TSH did not influence on the severity of head injury. Also, our data showed that serum level of T4 in the first day admission of severely brain injured patients correlate with the mortality of them. However, level of T3 and TSH did not affect on the patient's mortality. Chilero *et al.,* (3) showed that T3 level was correlated with the severity of injury, but T4 level were not. Previous studies have also indicated that the decrease in T4 level is related to the severity of illness and to the outcome (6,9,16,17). A high mortality has been observed in critically ill patients with markedly decreased T4 level 6, but Chiolero *et al.*, showed that T4 did not affect on mortality (3). T_4 is involved in controlling the rate of metabolic processes in the body and influencing physical development. Administration of thyroxin can significantly increase the concentration of nerve growth factor in the brains of adult mice (20). Our study, which is the largest one in this topic, showed Reduction of T4 increase mortality of brain injured patients. In conclusion, our study showed that severely traumatized brain injured patients developed a low T3, low T4 and inappropriately normal TSH level due to a varying degree of hypothalamic-pituitary axis dysfunction. It means that follow a severe brain injury a secondary hypothyroidism is happened due to pituitary dysfunction. Also, we showed that serum level of T3

and T4 on the first day admission affect on primary GCS score of patients, which is an indicator of severity of brain injury. In addition, mortality of severely brain injured patients has a high correlation with the serum level of T4 in the first day admission.

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