

Evaluation of Thyroid Function Tests and the Effect of Levothyroxine on Traumatic Brain Injury: A Randomized Clinical Trail

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Abstract

Background: Traumatic brain injury (TBI) is one of the causes of death wherein thyroid hormone concentrations are abnormally altered. This study aimed to assess thyroid function tests and the effect of levothyroxine on TBI and its outcome.

Methods: In this randomized clinical trial study, the TBI group Levothyroxine (50 mg) was administered twice daily for three days; the control group received a placebo in a similar pattern. The serum levels of T3, T4, and TSH were evaluated in 100 TBI patients on days 1 and 7. A questionnaire related to Disability was assessed using both Disability Rating Scale (DRS) and Glasgow Outcome Scale (GOS) scores. The obtained data were analyzed by SPSS version 20.

Results: The mean levels of T3 and TSH in both groups were not significantly different. T4 levels of the patients receiving levothyroxine were significantly higher than the control group. The mean DRS scores at the time of discharge were lower in the levothyroxine group compared to the placebo group.

Conclusion: Our results showed that levothyroxine is effective in improving patients suffering moderate head trauma. Furthermore, the T4 serum level can be used as a prognostic factor in these patients.

Keywords: Traumatic Brain Injury, levothyroxine, Glasgow Coma Scale, Glasgow Outcome Scale, Mortality Rate.

Introduction

Traumatic brain injury (TBI) is a vital public and socioeconomic complication worldwide ¹. Moreover, it is known as one of the causes of death and long-term physical disabilities ² and cognitive deficits ³, as well as behavioral and social deficits in high-income countries ⁴. These deficiencies may be due to the reduced nerve input from the cerebral cortex and brainstem areas, which affects the hypothalamic-pituitary (HPA) axis ⁵. ⁶. Some prospective studies have previously reported that alterations in abnormal thyroid hormone concentrations occur in patients with TBI ⁷. The decrease of free T3 and T3 levels is associated with an increase in reverse T3 and normal TSH levels under such conditions ⁸. Despite numerous case reports of long-term disabilities in patients with post-traumatic endocrine disorders, hormonal evaluation performed

after brain injury is not yet considered a part of routine diagnosis in the treatment of the patients ⁹⁻¹¹. Therefore, studying how to reduce and prevent the occurrence of such disabilities is very important because it can help in saving a lot of money for the treatment department. Therefore, this study aimed to evaluate the function of thyroid function tests as well as the effect of levothyroxine on the prognosis of brain trauma patients.

Methods

This randomized clinical trial study was conducted on 100 patients with TBI (60 male and 30 female subjects; age range of 28 to 34 years old) and moderate brain injury admitted to the Neurosurgery Intensive Care Unit of Imam Reza Hospital in Tabriz, Iran, from February 2018 to February 2020.

The protocol of the study was approved by the ethical committee of Tabriz University with (Code: IR.TBZMED.REC.1398.1084). The informed written consent was obtained from the patient's relatives or family before entering the study. The intervention group received levothyroxine 50 mg twice daily at least three days after TBI when it was usually possible to start a diet, and this dose continued for six weeks. Also, a placebo was given to the patients in the control group under similar conditions.

The hormones (TSH, T4, and T3) were measured at the beginning of hospitalization, the next week, and the time of discharge. Data such as age, sex, Glasgow Coma Scale (GCS), Glasgow Scale (GOS), and Disability Rating Scale (DRS) were collected at six months.

The data obtained from the study were evaluated by descriptive statistical methods (mean, standard deviation, frequency, and percentage). Independent-Samples T-Test was used to compare quantitative data. Abnormal data distribution was investigated by the Kolmogorov-Smirnov test. Also, the chi-square test was evaluated to compare qualitative data. Data were analyzed by SPSS 20 software. A P-value less than 0.05 was considered statistically significant.

Result

In this research, 100 patients with brain trauma were studied. Of them, 60 (75%) patients were male, and 20 (25%) cases were female. Male was the predominant gender in both groups. The mean BMI and age in the two groups of patients were similar and did not differ significantly ($p = 0.57$) ($p = 0.68$).

The hospitalization duration in the intensive care unit varied from 12 days to 20 days, and most patients were hospitalized for an average of 15-17 days. Out of 100 patients, 93 cases survived, and seven cases died (Table 1).

In the present study, the mean levels of T3 and TSH in both groups did not differ significantly. Notably, T4 increased in patients receiving levothyroxine compared

to the placebo group and had a significant difference (Table 2).

The TBI patients were evaluated for the effect of levothyroxine on GOS, and a significant difference was observed in the mean scores of GOS performance between the two groups. In other words, the patients receiving levothyroxine had lower scores compared to the placebo group by passing one week from the treatment, at the time of discharge, and in the 6th week (2.7 vs. 3.7) (3.7 vs. 4.2) (3.08 vs. 4.3) ($p = 0.03$) (Table 3).

The mean DRS scores at the time of discharge and bypassing six weeks in the levothyroxine group were lower than in the placebo group. Accordingly, this means that the patients receiving levothyroxine experienced a better recovery period ($p = 0.05$) (Table 3).

Table 1: Patient characteristics and perioperative data.

	placebo group (n = 21)	levothyroxine group (n=21)	p-value
Age (years)	32±6	31±3.30	0.07
Gender (M/F)	34/16	36/14	1.00
Weight (kg)	65.2±12	64.6±15	0.892
BMI (kg/m ²)	32.1±1	26±1.6	0.51
Duration of hospitalization (Day)	15±3	17±40	0.57
patients died /Number of patients	5/50	2/50	0.071

Table 2: Thyroid tests in moderate brain injury.

Parameters	group	beginning of hospitalization	one week after hospitalization	the time of discharge	p-value
TSH (mIU/L)	placebo	1.7±0.8	1.13±0.8	1.24±0.20	0.132
	levothyroxine	1.23±0.4	1.7±0.2	2.3±0.19	
T3 (pmol/dL)	placebo	2.2±0.56	2.8±0.32	3.1±0.46	0.054
	levothyroxine	2.7±0.46	3.8±0.72	4.7±0.56	
T4 (pmol/L)	placebo	15.2±0.5	12.8±0.32	13.3±0.46	0.01
	levothyroxine	14.7±0.43	23.4±0.72	20.6±0.7	

Table 3: Mean DRS and GOS during the study in two groups.

Parameters	Group	beginning of hospitalization	one week after hospitalization	time of discharge	6 months	p-value
Disability Rating Scale (DRS)	placebo	18±4	19±5	15±4	14±4	0.05
	levothyroxine	19±4	18±3	12±2	10±3	
Glasgow Outcome Scale (GOS)	placebo	2.74±0.52	2.78±0.32	3.78±0.82	3.08±0.92	0.03
	levothyroxine	2.58±0.62	3.78±0.42	4.21±0.75	4.31±0.65	

Discussion

Industrialized countries face significant challenges in diagnosing and managing traumatic brain injury and endocrine disorders. Endocrine disorders in patients lead to decreased quality of life, disability, and even death^{12, 13}. So, investigating how to reduce and prevent the development of disabilities following brain damage are of great essence. Therefore, in this study, we evaluated thyroid function tests as well as the effect of levothyroxine on the prognosis of brain trauma patients. Establishing the efficacy of levothyroxine can be considered a crucial step in completing previous similar studies. Also, its widespread use in these patients leads to faster improvement of cognitive disorders and alertness. Therefore, it reduced the length of hospital stay, the rehabilitation period, and the costs imposed on the family and society.

In the present study, both studied groups had a similar situation in terms of demographic characteristics, and there was no significant difference between these two groups (Table 1). Of note, all the patients were under the

same conditions. Our data showed that serum levels of thyroid hormones in patients with traumatic brain injury are not associated with mortality, and there was no significant difference between the two studied groups (Table 1). Previous studies showed high mortality in trauma patients with a significant decrease in T4 levels^{14, 15}. Although, cholera et al. showed that T4 does not affect mortality¹⁶.

The reference range are T4 (12-22 pmol / L), T3 (3.80-6.00 pmol / dL), and TSH (0.4-4.0 mIU / L). Based on this range, the serum T3 concentration of the patients of both groups after trauma was lower than the normal level, and the serum TSH and T4 levels were normal. Lower serum T3 levels in the patients may be due to the effect of various inhibitory factors that are common in acute diseases. The increased glucocorticoids and somatostatin levels showed direct inhibitory effects on TSH secretion. Accordingly, TSH secretion also occurs following the alteration of TRH secretion¹⁷. Previously studies showed that thyroid hormones rapidly are changed within a few hours after injury. Also, the mean

T3 and Serum T4 levels are decreased, and serum rT3 is increased. Several studies showed that T3 and T4 were normal after trauma in the recovered patients¹⁵. Beaver et al. showed a decrease in T3, T4, and TSH levels in brain-damaged patients, with a further decrease in these hormones before their death. These results are also consistent with the observations reported in a study by Rodman et al., which showed changes in thyroid hormones could be a quantitative factor in determining the severity of the injury, such as the prognosis of traumatic brain injury¹³.

The results of this study revealed a significant difference between the two groups of placebo and TBI patients in terms of GOS scores (Table 3). The patients receiving levothyroxine at the time of discharge from the hospital showed significantly higher recovery levels and GOS than the placebo group. Krahulik et al. showed that patients with early hormonal therapy have a higher GOS score, and patients' disability and alertness improved immediately¹⁸. DRS is a sensitive, functional, reliable, and quantitative tool for monitoring patients with head trauma at the recovery moment. In the present study, the average DRS scores at the time of discharge in the levothyroxine group were lower than the placebo group. Likewise, this means that the patients receiving levothyroxine experienced a better recovery. Santarsieri et al. showed a significant relationship between age and DRS, so younger patients had lower DRS scores and better outcomes ($p < 0.01$). They also reported that patients with lower GCS had higher DRS scores^{13, 19, 20}.

Conclusion

The results of this study showed that levothyroxine is effective in improving patients with moderate head trauma. Furthermore, T4 serum level can be used as a prognostic factor in these patients.

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Authors' contributions

FA and FS provided assistance in the design of the study and constructing an idea or hypothesis for research and / or manuscript and planning methodology to reach the conclusion. MP and AM referred patients and assisted in statistical analysis. SB and SG participated in data

collection and manuscript editing. ER and AK carried out the design of study and manuscript and taking responsibility in the construction of the whole or body of the manuscript.

Conflict of interest

The authors stated that they had no conflict of interest.

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Ethical consideration

This study was accepted by the ethical committee of Tabriz University of Medical Sciences.

Ethical code: IR.TBZMED.REC.1398.1084.

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