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Effect of progesterone administration on prognosis of patients with diffuse axonal injury due to severe head trauma

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ABSTRACT

Objective: Severe traumatic brain injury (TBI) has a major role in mortality rate among the other types of trauma. The aim of this clinical study was to assess the effect of progesterone on the improvement of neurologic outcome in patients with acute severe TBI.
Methods: A total of 76 patients who had arrived within 8 h of injury with a Glasgow Coma Score ≤8 were enrolled in the study. In a randomized style 38 received progesterone (1 mg/kg per 12 h for 5 days) and 38 did not.
Results: There was a better recovery rate and GOS score for the patients who were given progesterone than for those in the control group in a 3-months follow-up period (50% vs. 21%); subgroup analysis showed a significant difference in the percentage of favorable outcome between the two groups with GCS of 5–8 ($p = 0.03$).
Conclusion: The use of progesterone may significantly improve neurologic outcome of patients suffering severe TBI up to 3 months after injury, especially those with $5 \leq GCS \leq 8$, providing a potential benefit to the treatment of acute severe TBI patients. Considering this drug had no significant side effects, so progesterone could be used in patients with severe TBI as a neuro-protective drug.

1. Introduction

Nowadays trauma in different regions of the world is the most common cause of death under 35 years of age. Head trauma is responsible for major part of morbidity and mortality in trauma patients. Overall, head trauma or Traumatic brain injury (TBI) is divided into localized and diffuse.

Diffuse brain injury is the most common type of brain damage. Progesterone is a steroid hormone that its neuro-protective effect on ischemia been demonstrated in animal models [1–4]. Progesterone administration after trauma has been shown to have beneficial effect on cerebral edema and secondary neuronal death [5,6].

Laboratory evidence suggests that progesterone in traumatic brain injury decreases brain edema by reducing neural damage and free radicals [5,7–11].

Kumon's et al. [12] created ischemia by obstructing middle cerebral artery and used progesterone within 2 h of ischemia in 48 animals and reported that using progesterone reduces demolition of brain tissue and ameliorate neurologic complications (disorders) [12].

He et al. [13] in a study on mice with traumatic brain injury found that progesterone reduced brain edema, ameliorate brain complications by its anti inflammatory effects and reducing inflammatory cytokines.

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Djebaili et al. [1] traumatized the cortex of frontal lobe in some rats and divided them into case (with progesterone administration) and control groups. They compared these groups after nineteen days and found better cognitive abilities in case group as O'Connor's et al. [14] did. Pan et al. [15] evaluated progesterone injection in rats with brain injury. They confirmed neuroprotective effects of progesterone [15]. Roof et al. [2] compared 2 groups of rats with brain contusion with progesterone administration in first and oil in second group. They found that brain edema decreased significantly in first group and increased in second one [11].

Given that there is no similar study at Tabriz University of Medical Sciences to investigate the neuro-protective effects of progesterone in head injury and Tabriz Imam Reza Teaching Hospital is considered a referral center for all trauma cases in the province and neighboring provinces. We decided to investigate the effect of progesterone as a neuroprotective drug on prognosis of traumatic brain injury in patients with a diagnosis of diffuse axonal injury that underwent non-surgical treatments.

2. Materials and methods

In this single blinded randomized control experiment, samples were male patients with the head trauma and diagnosis of Diffuse Axonal Injury (DAI) whose GCS (Glasgow Coma Scale) was ≤8, which being hospitalized in Trauma ward and Intensive Care Unit (ICU) of Tabriz Imam Reza hospital within less than 8 h of injury during a 17 month period (2010–2011).

$$n = \frac{(z - \alpha/2 + z_1 - \beta)^2 (s_1 + s_2)^2}{(\overline{X_1 - \bar{X}_2})^2}$$

$$\alpha = 0.05 \quad S_1 = 1.3 \quad \bar{X}_1 = 8$$

$$\beta = 0.20 \quad S_2 = 1.8 \quad \bar{X}_2 = 10$$

$$N = 38$$

In above formula α and β are specific values. Other values were collected from similar studies to estimate the sample size in each group. Thirty-eight patients were selected in each case and control group using randomized parallel group design:

BBABABBAABAAABBAAABBBBABBBAAAABAAABBBA
BABBAAABBBAAABBAABABABBBAABBAABAAABBBA
22121221121112211122221222111121112221212211122 2
11122112121222112211211122 21

In this method, 76 male patients over 15 years old who had been admitted in the first 6 h after trauma with a diagnosis of DAI and GCS ≤ 8 were selected, and divided into progesterone group and control group randomly by using table of random numbers (In case group medroxyprogesterone tablets was taken every 12 h, 1 mg/kg gavaged via nasogastric tube for five days & control group that did not receive progesterone). Medroxyprogesterone tablets offered instead of intravenous progesterone due to that tablets are available, with less cost and patients mostly get on PO (per os) regime after operation and oral administration is better in this cases. Given that this drug is not routine treatment protocol of these patients, lack of this drug in control group does not cause any disruption in the treatment of these patients (therapeutic dose is selected based on Xiao et al. 2008) [16] and patients GCS level until discharge and GOS (Glasgow Outcome Scale) three months after discharge were investigated and compared. GOS was categorized as follows:

1-Death, 2-Vegetative state, 3-Severe disability, 4-Moderate disability, 5-Good recovery [17].

For better analysis of data and based on valid articles, patients were divided into two groups with good GOS (good recovery or moderate disability) and unfavorable (death, vegetative state and severe disability). The study was single blinded and only department personnel (nurses in charge of drug administration) was informed of the route of administration but the people who analyzed the level of consciousness and those who analyzed data statistically were unaware of this issue. Being a single blinded was due to that patients should be aware of this action and inform their satisfaction in consent form.

All male patients more than 18 years old with head trauma and diagnosis of DAI and GCS ≤ 8, who were hospitalized in trauma ward or ICU of Tabriz Imam Reza hospital within less than 8 hours of injury, were included in this study.

Female patients due to the progesterone effect on menstrual cycle, patients with a history of hormonal drug use, one month before admission and also male patients under 18 years of old as hormones may have side effect on their normal growth and puberty were excluded.

This project has been approved by the ethics committee of Tabriz University of Medical Sciences with the number of 5/4/5713. Also informed consent was taken from family of all patients. This study has been registered in Iranian Registry of Clinical Trials (www.irct.ir) with the number of N1201011225230.

Obtained data are expressed as mean ± standard deviation, frequency and percentage. Quantitative variables were compared by using Student *T*-test, one way ANOVA and multiple regression and qualitative variables were compared using Chi-Square Test and Fisher's Exact Test. In all investigated cases, the results were considered statistically significant if $P \leq 0.05$.

3. Results

In this study, 76 males over 18 years who were admitted with DAI and GCS ≤ 8 were divided randomly into control and case group each consisting 38 patients.

Mean age of case group was 33.97 ± 12.48 years (19–61) and the control group was 34.68 ± 12.87 years (19–65) and this difference was not statistically significant based on Independent *T*-test ($p = 0.08$). Age criteria in this study had no effect on the rate of patients improvement ($p = 1$). Mean GCS score on admission in case and control groups was 5.74 ± 1.4 and 5.79 ± 1.2, respectively that had no significant difference ($p = 0.86$). GCS score in patients who survived in both groups had a progressive incensement and overall mean GCS score on discharge in case and controls was 12.42 ± 2.67 and 12.04 ± 2.43 respectively that had no significant difference ($p = 0.2$). The highest GCS score in both groups was 15. The data about age, GCS on admission and discharge in two study groups are shown in Table 1.

There were 29 cases of death, 12 (31.6%) out of case group and 17 (44.7%) out of control one. In case group 66.7% of deaths happend within the first week and 33.3% were after then and before one month. All deaths occurred during hospitalization. There were 5 more deaths in control group than case one that was not statistically significant ($p = 0.17$). Of patients with a GCS ≥ 5, four deaths occurred in case group and 10 deaths occurred in the control group that the difference was not statistically significant ($p = 0.08$).

GOS assessment results in patients, 3 months after discharge in both groups of study have been summarized in Table 2. Recovery rate in patients with GCS ≤ 8 in the case group was more than control one and favorable GOS score in case group was 50% that was higher than control one (29%). Unfavorable scores in case and control group were observed in 50% and 71% respectively, but this difference was not statistically significant ($p = 0.059$).

To increase the accuracy of the investigation, patients were divided into and analyzed as two subgroups: patients with