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Research Article

Effects of Testosterone Replacement Patients with Moderate to Severe Head Injury and Persistent Hypogonadotropic Hypogonadism: An Open-label Randomized Controlled Trial

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Abstract

Background: Traumatic brain injury (TBI) pertains to the significant potential for brain parenchymal lesions after suffering cranial trauma. Individuals with TBI are at high risk for developing neuroendocrine dysfunction, especially moderate and severe types. This study was conducted to understand relationships between hypogonadism and outcomes at 6 months post-TBI and to study the effect of testosterone supplementation in patients with persistent hypogonadism on the outcome of moderate to severe TBI.

Methods: The study was conducted as an open-label, randomized trial. Males aged 16 - 70 years post-moderate-severe TBI either received injection testosterone 200 mg intramuscularly (IM) every 4 weeks for 3 months in addition to standard care or standard care alone. They were followed up for 6 months. Functional independence measure scoring was used as an outcome measure.

Results: Of 98 patients screened, 62 were initially included. 11 patients expired and 4 did not develop hypogonadism at 3 months and were excluded subsequently from the analysis. Forty-seven patients were randomized to the intervention (n = 24) and control groups (n = 23). There was no significant difference between groups in the improvement on the FIM scores at discharge, 3 and 6 months (p = 0.509, 0.609, and 0.632 respectively). The Treatment group demonstrated the greatest absolute improvement in FIM scores although the results were not significant.

Conclusion: There were no significant differences in functional independence, the intervention group showed greater absolute functional improvement compared to the control group.

Keywords: Testosterone; Traumatic Brain Injury; Persistent Hypogonadotropic Hypogonadism; Functional Outcome

Abbreviations

TBI: Traumatic Brain Injury; RTA: Road Traffic Accident; PHH: Persistent Hypogonadotropic Hypogonadism; FIM: Functional Independence Measure; GCS: Glasgow Coma Scale

Introduction

Traumatic brain injury (TBI) refers to a significant potential for brain parenchyma injury after undergoing cranial trauma [1]. The severity can be classified based on Glasgow Coma Scale scoring (GCS) as severe (GCS 3 - 8), moderate (GCS = 9 - 13) and mild (GCS = 14 - 15) [2]. The vast majority, i.e. around 80% are mild TBI [3]. However, moderate to severe head injuries have a higher propensity to be associated with death and disability [4].

A road traffic accident (RTA) is one of the most common causes of TBI affecting all ages, especially the productive age group [5]. India is a country with a significant burden of fatalities due to RTAs,

with TBI being a large contributor. This places an enormous economic strain on the country as well due to poor functional recoveries [5,6]. Moderate to severe TBI leads to not only neurological dysfunction but neuroendocrine dysfunction as well [7]. Many studies have highlighted hypothalamic-pituitary deficiencies, including persistent hypogonadotropic hypogonadism (PHH) post-TBI as well as the resultant clinical implications [7,7-13].

Hypogonadism can be easily overlooked due to vague symptomatology that may be present with TBI alone. Such cases can go misdiagnosed if there is a lack of awareness and endocrine assessment is not performed [8]. The prevalence of chronic hypogonadism after TBI is reported to be 8-41%. This wide range is attributed to the time of screening, the severity of the injury, and study design [4,9,13]. Recent studies have also shown that anterior pituitary dysfunction is quite common and constitutes around 30-70% of the hormonal abnormalities which occur after TBI [12,14-17]. In a prospective study by Bondanelli., *et al*. patients with hypogonadism exhibited poor functional dependence, disability, and cognitive function at discharge as compared to patients without hypogonadism [18]. In another study by Popovic., *et al.* they found a positive correlation between testosterone and serum gonadotropin levels [19]. Wagner., *et al.* in a small cohort of 38 men with severe TBI with PHH on 6 and 12 months post-injury follow up demonstrated worse disability, cognitive function, and neurological outcomes [10].

The role of serum testosterone in TBI patients is well established now. The relationship between serum testosterone levels with the length of stay, admission, discharge, and changes in functional independence measure (FIM) shows that low serum testosterone levels were associated with longer lengths of stay, lower admission FIM scores, and less improvement in FIM scores [20]. However, a large proportion of the previous studies have used single laboratory measurements to screen for hypogonadotropic hypogonadism. This is in contrast to clinical guidelines which generally recommend that if the initial level of testosterone is found to be low, then, repeat testosterone levels for diagnosis is required especially when symptoms are non-specific [21].

Prospective data characterizing hormone levels across acute, sub-acute, and chronic phases of TBI recovery are limited. The present study builds upon previous work by studying a population of male patients with moderate to severe TBI with persistent hypogonadism and the effect of testosterone replacement.

Methods

Study setting and duration

The study was conducted at a tertiary care hospital in Kochi, India over one year.

Subjects

The study subjects had to meet the following criteria.

Inclusion criteria

- History of TBI (defined as "A form of acquired brain injury, occurs when a sudden trauma causes damage to the brain") [22]
- Moderate to severe TBI, defined as GCS < 13, with radiographic evidence of TBI
- Persistent hypogonadotropic hypogonadism at 3 months, defined as
- Males between ages 16 - 70
- Informed consent was obtained from the patient/relatives.

Exclusion criteria

- Normal testosterone levels at 3-month follow-up
- History of hypothalamic or pituitary tumors
- Orchiectomy
- Luteinizing hormone therapy
- Untreated thyroid disease before the injury
- Testicular trauma.

Study design and sample size

The study was designed to be an open-label, intervention-based trial. Randomization was achieved using a computer-generated sequence. Following consent, hormone levels were measured between 3 - 7 days post-injury and this value was assigned as the week-1 value as it has been reported that acute hypogonadism takes ≥ 2 days to manifest post-TBI [18].

Prospectively, Persistent Hypogonadotropic Hypogonadism (PHH) was defined based on criteria in previous works, which used

hormone measurement at 3 months to determine PHH status [10]. Study participants were designated as having PHH if their samples had testosterone values meeting criteria for hypogonadotropic hypogonadism [testosterone <2.8nmol/ml (minimum normal level)].

The sample size was calculated using nmaster 2.0 software. Based on a previous study it is observed that the P = 12%, absolute precision is 10% and with 95% confidence interval the minimum required sample size is 41 using the formula: N = [z(1-α/2) 2 x P (1-P)]/d2. Here, P: expected proportion = 0.12, d: absolute precision =10%, z(1-α/2) at desired confidence level of 95% = 1.96.

Intervention

Intervention group: This group was supplemented with testosterone [injection testosterone 200 mg IM every 4 weeks] for 3 months [23].

Control group: Received standard care as required.

Study instruments and data collection

- Data was collected as per pre-determined proforma on handwritten sheets Informed Consent was taken from all Patients/Relatives or next-of-kin.
- The outcome was assessed by telephonic/personal interview or OPD follow-up as per feasibility based on FIM.

Outcome measures

The outcome was assessed at 3 and 6 months post-TBI, using the Functional Independence Measure (FIM) and results were compared between the intervention and control groups. The FIM™ assessment can be performed by client observation or interview. Six domains of function are evaluated: self-care, sphincter control, transfers, locomotion, communication, and social cognition. Items are scored on a 7-point ordinal scale, with 7 reflecting complete independence and 1 reflecting total dependence. Scores of 1 to 5 indicate a need for caregiver assistance. Scores in all domains are all added to obtain a total FIM™ score [24].

Data management and statistical analysis

Statistical analysis was performed using IBM SPSS 20.0 software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Categorical variables were described in terms of frequency and proportions. Continuous variables were described as mean ± Standard Deviation (S.D). An independent sample Kruskal-Wallis test was used to test the significance among the non-parametric data. Pearson's Chi-square test was used to find the association between categorical variables. A p-value of <0.05 was considered to be statistically significant.

Ethical concerns

Ethical approval was taken from Institutional Ethics Committee. Written, informed consent was taken from participants' next-of-kin after explaining the study procedure, duration, the role of patients, aim, and objectives of the study to them in their language.

Results

Participant enrollment

The participant CONSORT flow diagram is displayed in figure 1. Of a total of 98 patients screened, 62 patients who fulfilled the inclusion criteria were included in the study. The rest either failed to meet the inclusion criteria or declined to participate. 11 patients expired during treatment and were excluded. 4 patients did not show hypogonadism at 3-month follow-up and hence were also excluded. Hence, a total of 47 patients were randomized, with 24 patients allocated to the intervention group and 23 to the control group.

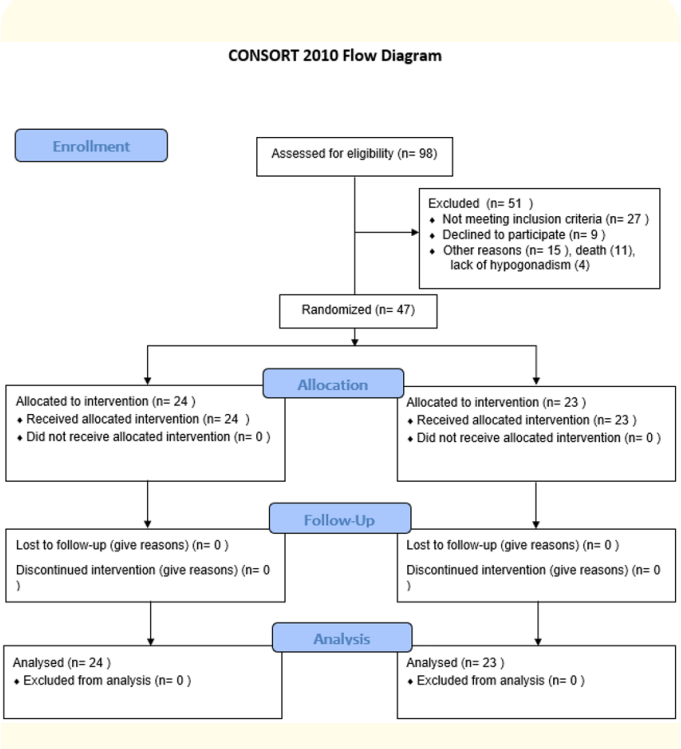

Figure 1: CONSORT flow diagram.

Demographics and baseline characteristics

The overall mean age was 41.23 ± 14.14 years. The average GCS on admission was 4 - 5 for these patients. The mean length of stay for these patients was 6.09 ± 2.87 days. Mean serum testosterone in these patients during week 1 was 0.26 ± 0.18 ng/dl. Four patients, excluded from the main analysis showed no residual PPH at the end of 12 weeks. The mean age of these patients was 38 ± 10.10 years and the mean length of hospital stay was 7.5 ± 1.29 days. The mean serum testosterone at week 1 and week 12 was 2.18 ± 0.26 and 4.31 ± 0.89 ng/dl. All of them belonged to moderate TBI. GCS on admission for all four was 12. Other data has been displayed in table 1.

Variable	Intervention Group (n = 24)	Control group (n = 23)	p-Value
Demographics			
Age	43.13 ± 15.43	39.26 ± 12.704	0.355
TBI severity			
Moderate (GCS 8-12)	7 (14.9%)	9 (19.1%)	0.54
Severe (GCS 3-8)	17 (36.2%)	14 (29.8%)	
Length of hospital stay	25.63 ± 7.85	23.74 ± 11.69	0.518
Serum testosterone levels (ng/ml)			
Week 1	0.99 ± 0.63	1.16 ± 0.85	0.437
Week 12	1.24 ± .594	1.25 ± .771	0.957
FIM scores			
At discharge	54.13 ± 23.87	59.61 ± 26.37	0.509
3 months	68.42 ± 22.15	72.87 ± 24.91	0.609
6 months	77.13 ± 20.87	80.57 ± 24.78	0.632
Absolute change between discharge and 3 month follow-up	14.29 ± 6.925	13.26 ± 6.10	
Absolute change between discharge and 6 month follow-up	23.00 ± 9.61	20.96 ± 7.480	

Table 1: Baseline and outcome data.

Relationship between GCS score at admission and s. Testosterone levels

The GCS scores were positively correlated with serum testosterone levels at week 1 as well as 12 with Pearson Correlation coefficients of 0.735 (Week 1) and 0.817 (Week 12) (Figure 2).

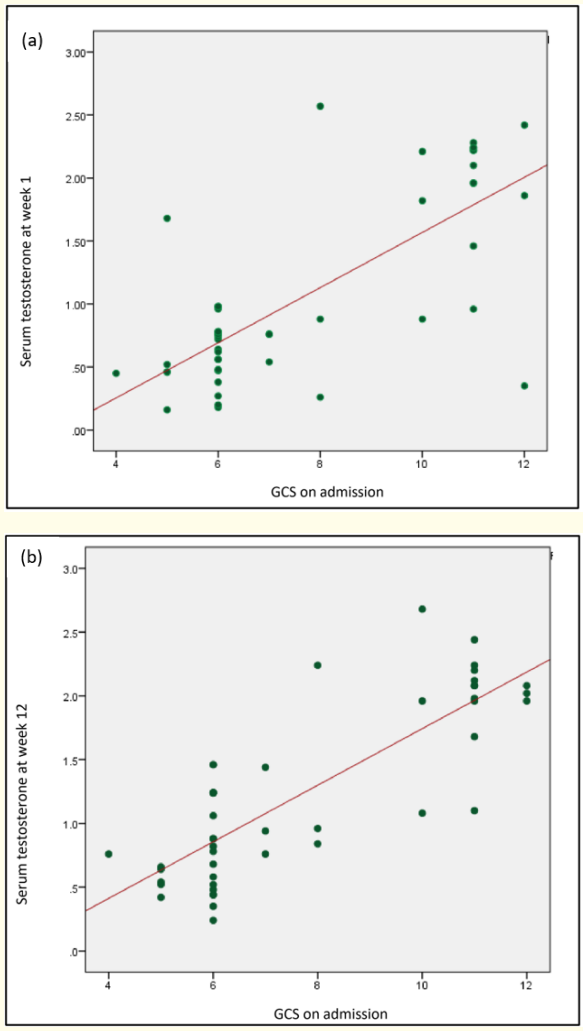

Figure 2: Correlation between GCS score and serum testosterone levels at week 1 (a) and week 12 (b).

Length of hospital stay

The mean length of hospital stay of participants in the intervention group was 25.63 ± 7.85 days and the control group was 23.74 ± 11.69 days. There was no significant difference in length of hospital stay in both groups. (p = 0.518).

Serum testosterone levels

The mean serum testosterone levels at week 1 in the intervention group was 0.99 ± 0.63 ng/dl and the control group was 1.16

± 0.85 ng/dl. No significant difference was noted in mean serum testosterone levels at week 1 in both groups (p = 0.437). At week 12, mean serum testosterone levels in the intervention group were 1.24 ± .594, and the control group was 1.25 ± .771 ng/dl. No significant difference was found in mean serum testosterone levels at week 12 in both groups (p = 0.95).

Functional outcome

On applying the Kruskal-Wallis Test, it was found that there was no significant difference between the FIM scores at discharge, 3 and 6 months follow up in either intervention or control group. However, on applying the one-sample t-test, it was found that there is a significant difference in the FIM scores at discharge, 3 and 6 months follow up within the intervention group as well as control group (p = <0.001 in both the groups).

In comparison, the absolute change in Functional Independence Measures (FIM) scores at discharge, 3 and 6 months follow up was found to be greater in the intervention group than in the control group. However, the difference was not significant.

Discussion

TBI is a significant public health problem and incidence is increasing at an alarming rate. It has become one of the leading causes of morbidity and mortality of young male adults [25-30]. While the majority of the cases (80%) are mild TBI, the moderate to severe cases are the ones causing death and disability [3,4]. Of the 62 patients initially enrolled in our study, 11 patients expired all of whom were admitted with severe traumatic brain injury. RTA is one of the most common causes for TBI affecting all ages, especially the productive age group [5]. This correlated with the etiology in our study, with the cause of TBI in all the enrolled patients being attributed to RTA. The mean age of participants in the intervention group was 43.13 ± 15.43 years and the control group was 39.26 ± 12.70 years. Existing literature also shows that TBI affects mainly the productive age group [3,10-12,16,28,29,31,32].

Hypopituitarism, partial or complete is a known potential complication of head injury and has been described as early as 1918 [4,33]. Individuals with TBI are at high risk for developing neuroendocrine dysfunction especially in the setting of moderate and severe TBI [4]. Many studies are now published highlighting hypothalamic-pituitary deficiencies, including persistent hypogonadotropic hypogonadism (PHH) post TBI and its clinical implications [4,7-13].

In our study, four patients who were initially enrolled had no residual PPH at the end of 12 weeks. All of them belonged to moderate TBI (GCS-12) and were then excluded. The remaining 47 patients had residual PHH. The prevalence of hypogonadism in acute TBI has been reported up to 80% and chronic hypogonadism after TBI is reported to be 8-41% [4,10,13,30].

The mean serum testosterone levels at week 1 in the intervention group was 0.99 ± 0.63 ng/dl and week 12 was 1.24 ± 0.594 ng/dl. We found no significant difference in the mean testosterone levels between the intervention and control groups in the first week as well as week 12. The GCS scores were positively correlated with serum testosterone levels at week 1 as well as 12 (p = <0.001 for both). Existing literature shows that the relationship between the severity of TBI and testosterone levels is discordant. Some studies like Klose., *et al.* and Agha., *et al.* show a positive correlation between testosterone and GCS score and others like Hari., *et al.* and Dalwadi., *et al.* and show no association [34-37]. In a study by Hohl., *et al.* which included only severe TBI patients, testosterone levels did not correlate with GCS [38]. Also, the association between testosterone levels and mortality or morbidity was significant in the study by Olivecrona., *et al.* but not significant in studies by Hohl., *et al.* Dalwadi., *et al.* and Wagner., *et al* [37-40]. The relationship between serum testosterone levels with the length of stay, admission, discharge, and changes in functional independence measure (FIM) shows that low serum testosterone levels were associated with longer lengths of stay, lower on-admission FIM scores, and less improvement in FIM scores [20].

Certain animal studies have already proven the role of Testosterone therapy in TBI by reducing mitochondrial dysfunction and neurodegeneration in the brain [41]. But, there is only one published experimental study among human beings to date [21]. In our study, the intervention group was supplemented with testosterone [injection testosterone 200 mg IM every 4 weeks] for 3 months and the control group received standard care as required. No significant difference between the FIM scores at discharge, 3 and 6 months follow up in intervention or control group was found. A significant difference in the FIM scores at discharge, 3 and 6 months follow up within intervention group as well as control group was seen (p = <0.001 in both the groups). Comparison of the absolute change in FIM scores at discharge, 3 and 6 months was noted to be

greater in the intervention group rather than in the control group. However, the difference was not significant ($p > 0.05$).

The only published study in 2020, a randomized, double-blind, placebo-controlled pilot clinical trial was conducted in the United States [21]. Men between age 18-65 with low Testosterone (T) levels post moderate to severe TBI were included to determine the effects of physiologic testosterone therapy on neurological function and functional independence. They were randomized to receive either physiologic T therapy or a placebo. Hormone levels were assessed at the time of screening for study and at two-week intervals for 12 weeks. Demographics, injury characteristics, concomitant medication usage, and adverse events were documented by medical record review. The intervention given was - Androgel (Testosterone Gel) 2.5-gram stick packs administered with starting dosage of 5g increasing to a max of 10g. Around 498 were screened and 70 were enrolled in the study of which only 22 met all criteria. They were randomized into placebo (10) and intervention (12). There was no significant difference between groups in the rate of improvement on the FIM. The treatment group demonstrated the greatest absolute improvement in FIM scores and grip strength compared to a placebo group. There was no difference in adverse events between groups. They concluded that, although there was no significant difference in rates of recovery, treatment group subjects had greater absolute functional and strength improvement. The results of our study are quite consistent with this study.

The objection to testosterone replacement in hypogonadal men post TBI is due to increased agitation or aggression. Such findings were not reported by Ripley., *et al.* who studied adverse effects [21]. They found an inverse correlation between agitation and serum testosterone levels. Many other studies have reported no increase in agitation or aggression [42-44]. This component was, however, not assessed in our study.

The limitations of our study include the fact that it was an unblinded study with low participant strength at a single center. We also did not study the adverse effects of testosterone supplementation or the effect at longer-term follow-up.

Conclusion

This study has led us to conclude that although there were no significant differences in the FIM scores between the groups, intervention group subjects showed greater absolute improvement in the FIM scores at 3 and 6 months compared to the control group. This means that testosterone replacement may yet show some benefit and is worthy of further study and clinical use in patients with TBI. Further studies with larger study populations are desired.

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