

Role of Sertraline in insomnia associated with post traumatic brain injury (TBI) depression

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Abstract: Traumatic brain injury (TBI) is a major cause of disability (1, 2). Sleep disturbances, such as insomnia, are very common following traumatic brain injury and have been reported in frequencies from 40% (3) to as high as 84% (4). Sleep disruption can be related to the TBI itself but may also be secondary to neuropsychiatric (e.g., depression) or neuromuscular (e.g., pain) conditions associated with TBI or to the pharmacological management of the injury and its consequences. Post-TBI insomnia has been associated with numerous negative outcomes including daytime fatigue, tiredness, difficulty functioning: impaired performance at work, memory problems, mood problems, greater functional disability, reduced participation in activities of daily living, less social and recreational activity, less employment potential, increased caregiver burden, greater sexual dysfunction, and also lower ratings of health, poor subjective wellbeing. These negative consequences can hamper the person's reintegration into the community, adjustment after injury, and overall QOL. (5) The connection between depression and insomnia has not been investigated within the post TBI population to a great extent. For the general population, clinically significant insomnia is often associated with the presence of an emotional disorder (6). Fichtenberg et al. (2002) (7), in his study established that the strongest relationship with the diagnosis of insomnia belonged to depression. Given the high prevalence of depression during the first 2 years following TBI (8), a link between depression and insomnia among TBI patients makes innate sense. The present study aims at assessing role of sertraline in post TBI insomnia associated with depression.

Introduction

Traumatic brain injury (TBI) is a major cause of disability (1, 2). Sleep disturbances, such as insomnia, are very common following

traumatic brain injury and have been reported in frequencies from 40% (3) to as high as 84% (4). Sleep disruption can be related to the TBI itself but may also be secondary to

neuropsychiatric (e.g., depression) or neuromuscular (e.g., pain) conditions associated with TBI or to the pharmacological management of the injury and its consequences.

Post-TBI insomnia has been associated with numerous negative outcomes including daytime fatigue, tiredness, difficulty functioning: impaired performance at work, memory problems, mood problems, greater functional disability, reduced participation in activities of daily living, less social and recreational activity, less employment potential, increased caregiver burden, greater sexual dysfunction, and also lower ratings of health, poor subjective wellbeing. These negative consequences can hamper the person's reintegration into the community, adjustment after injury, and overall QOL. (5)

The connection between depression and insomnia has not been investigated within the post TBI population to a great extent. For the general population, clinically significant insomnia is often associated with the presence of an emotional disorder⁶. Fichtenberg et al. (2002) (7), in his study established that the strongest relationship with the diagnosis of insomnia belonged to depression. Given the high prevalence of depression during the first 2 years following TBI (8), a link between depression and insomnia among TBI patients makes innate sense.

The present study aims at assessing role of sertraline in post TBI insomnia associated with depression.

Materials and methods

The study was carried out in Neurosurgery ward and OPD of SMS Medical

College and group of hospitals, Rajasthan, a 3000 bedded superspeciality tertiary care centre. Sample was recruited through the follow up in neurosurgery OPD and Indoor. Being the largest medical institute in the state of Rajasthan, it caters the health needs of entire state as well as neighboring states.

A total of 250 male traumatic brain injury patients with mild to moderate severity were screened initially. Eighty patients were found to have depression on assessment with PHQ-9 and subsequent interview with psychiatrist. Out of these eighty patients, fifty- six were found to have insomnia, who finally constituted the study sample size. The study was further divided randomly in to two groups, consisting of twenty eight patients in each group. One group designated as intervention group (cases) was given 50 mg sertraline daily PO. The other group was not given any medication and served as control group.

The nature and purpose of the study was explained to the participants and written informed consent was obtained either by the participant himself or his next of kin. The study was limited to male participants only to ensure the homogeneity of the group with regard to the interactions of demographic variables, disease characteristics, and social stresses. The study protocol was approved by the institution's ethical committee.

All the participants were evaluated initially after two week interval for first 4 weeks and at the end of 6 months.

To be eligible to participate in study, the patients had to be 18 years or older, should have had at least two weeks old injury, have a

history of TBI with a documented loss of consciousness or other evidence of a TBI (i.e., pathology on neuroimaging), and be able to comprehend or answer verbal or written questionnaires.

Participants were excluded from the study if they were known 1. To have a serious medical illness, 2. To have a current substance abuse disorder using DSM-IV criteria, 3. To have mass brain lesions or other neurologic diagnoses other than TBI, 4. To have a history of current or past psychosis or mania, MDD or any other mental disorder except current depression using DSM-IV criteria, or 6. To have a history of clinically significant liver or renal disease.

At the initial assessment, demographic characteristics of the cases and controls were assessed on a self-designed semi structured proforma by interviewing the participants with additional information on injury characteristics of the cases by exploring the medical records and neuroradiological investigations.

Severity of TBI was assessed by GCS. Initially cases and controls were assessed on Insomnia Severity Scale for insomnia.

At the end of six months, both cases and controls were assessed on ISI to measure improvement in sleep.

Measures

In this study, the interview was focused on assessment of severity of TBI, depression and insomnia using GCS, PHQ-9 and Insomnia severity scale (ISS).

GCS (9), an extensively used clinical scale for assessing the depth and duration of

impaired consciousness and coma. Three aspects of behavior are independently measured—motor responsiveness, verbal performance, and eye opening. These can be evaluated consistently by doctors and nurses and recorded on a simple chart which has proved practical both in a neurosurgical unit and in a general hospital. The scale facilitates consultations between general and special units in cases of recent brain damage, and is useful also in defining the duration of prolonged coma.

Depression was assessed by administering the nine-item PHQ-9, a self-report version of PRIME-MD11 which assesses the presence of major depressive disorder using modified Diagnostic and Statistical Manual, Fourth edition (DSM-IV) criteria. There is good agreement reported between the PHQ diagnosis and those of independent psychiatry health professionals (for the diagnosis of any one or more PHQ disorder, kappa = 0.65; overall accuracy, 85%; sensitivity, 75%; specificity, 90%) (17, 18). In this study Hindi version of PHQ-9 was used. It has been validated in Indian population and is considered to be reliable tool for diagnosis of depression. The PHQ-9 is a dual instrument that is used to establish a provisional depressive disorder as well as it provides a symptoms severity score. For the diagnosis of depression, we define clinical significant depression as: a PHQ-9 score of 8–9 as minor depression, a PHQ-9 score of 10 or greater as moderate depression; a score of 15 or more and one of the two cardinal symptoms (either depressed mood or anhedonia) as definite major depression (10, 11). We considered

PHQ 9 score of 10 or more as depression in this study.

Insomnia was assessed on Insomnia Severity Index (ISI) (12). ISI is one of the most commonly used disease-specific measures for self-perceived insomnia severity.

The ISI has 7 items describing insomnia-related health impairments. Each item is rated on a 5-point Likert scale with scores ranging from 0 to 4, indicating “none”, “mild”, “moderate”, “severe” and “very severe” sleep problems, respectively. The total ISI score is calculated by summing the scores from the 7 items, and range from a minimum of 0 to a maximum of 28, with higher scores reflecting more severe sleep problems. In clinical assessments, the ISI total summary score falls into 1 of 4 ISI categories; with scores 0–7, 8–14, 15–21, and 22–28 indicating no clinically significant insomnia, sub-threshold insomnia, moderate insomnia and, clinically severe insomnia, respectively. The psychometric properties of the ISI have been evaluated in earlier studies and have been reported to have sound measurement quality for measuring perceived insomnia severity and the impact of insomnia in different populations (13, 14).

We used Hindi version of the Insomnia Severity Index (15) which has a reliability of 0.91 and a corrected item correlation range of 0.56–0.87. Hindi version of the Insomnia Severity Index is a valid and reliable tool for the measurement of severity of insomnia.

Lesion localization was done on the basis of CT scan, conducted as part of the initial work up of the patient. The results were characterized as presence or absence of contusions, intracerebral bleed, subarachnoid,

epidural or subdural bleed in various regions, namely, frontal, temporal, parietal and occipital.

Statistical analysis

Data were checked for normality, outliers, and missing data. No imputation of missing data was performed. Statistical analyses were performed by correlation analyses (Pearson and Spearman), paired t test and Chi-square tests analyses.

Results

A total of 250 male patients of TBI were recruited in this study. 35.6% of the 250 patients were found to have depression (n=89). 9 out of 89 depressive patients dropped out from the study (10.11%). 80 patients (32%) of TBI with depression were evaluated for insomnia. 56 patients (70%) of post TBI depression with insomnia finally constituted the study sample.

Maximum number (30.4%) of patients with insomnia were found in the age group of 18-24 years (n=17), followed by 26.7% in the age group 25-34 years (n=15). However it was found to be statistically insignificant (p=0.938).

Insomnia as measured on ISI was statistically more common (p=0.04) in mild TBI cases (58.9%) than the moderate TBI (41.1%) patients with depression. Majority of the patients (46.43%) who had insomnia sustained injury more than 6 months back (n=26), followed by 23.2% of injury being less than 3 months duration (n=13). Although this observation was found to be statistically insignificant (p=0.934).

Neuroanatomical localization was also correlated with insomnia in post TBI depression among TBI patients. Left side of brain injury was present in the majority (55.35%) of patients. This was followed by right side injury in 39.28% of patients (n=22) and diffuse axonal injury in 5.35% of patients (n=3). It was found insignificant on statistical analysis ($p=0.761$) [Table 1].

Cerebral contusion was the most common (32.14%) finding of injury (n=18), followed by multiple injury including contusion in 30.35% (n=17) of the cases. Out of these 17 cases, 14 patients had contusion. Thus, overall patients with contusion constituted 57.14% (n=32) of the study sample. Other findings, like extradural, subdural, subarachnoid hemorrhage and even fractures were also found to be implicated in lesser frequency. We further tried to explore the distribution of cerebral contusion in these patients, and found 14 (57.1%) among 32 contused patients had multiple contusions, although single lobe contusion were also associated with insomnia, but in lesser numbers [Table 2].

Mean score of ISI at the beginning of the treatment was 18.821 with SD 2.091 and 18.643 with SD 3.129 in intervention and control group respectively, and this was found to be statistically insignificant ($p=0.802$). At the end of the study, significant improvement was observed in ISI scores in intervention group (mean=8.464, SD=2.202), as compared to control group (mean=10.786, SD=2.114). This effect was statistically significant ($p=0.00018$) [Table 3].

TABLE 1
Demographic characteristics of TBI depressive insomniac patients

age in years	Cases	Control	Total	
18-24	10	7	17	
25-34	7	8	15	$X^2=0.798$
35-44	5	6	11	($p=0.938$)
45-54	4	5	9	
55-64	2	1	3	
65 or more	0	1	1	
type of injury				
RTA	22	24	46	$X^2=0.563$
FFH	4	3	7	($p=0.754$)
ASSAULT	2	1	3	
OTHERS	0	0	0	
GCS				
MILD	16	17	33	$X^2=0.074$
MODERATE	12	11	23	($p=0.786$)
DURATION OF HEAD INJURY				
<3 MONTHS	8	9	17	$X^2=0.136$
3-6 MTHS	7	6	13	($p=0.934$)
>6 MONTHS	13	13	26	
LOCALIZATION				
RIGHT SIDE	10	12	22	$X^2=0.547$
LEFT SIDE	16	15	31	($p=0.761$)
DIFFUSE AXONAL INJURY	2	1	3	

TABLE 2
Lesion type based on CT scan

CT SCAN FINDINGS-	Case	Control	Total
contusion	8	10	18
multiple injury	9	8	17
EDH	1	3	4
SDH	3	2	5
SAH	2	0	2
NAD/DAI	5	4	9
OTHERS/FOREIGN BODY	0	1	1
SITE OF CONTUSIONS IN BRAIN-			
RIGHT FRONTAL	1	2	3
LEFT FRONTAL	2	2	4
RIGHT PARIETAL	1	0	1
LEFT PARIETAL	0	0	0
RIGHT TEMPORAL	1	0	1
LEFT TEMPORAL	1	2	3
MULTIPLE CONTUSIONS	8	6	14

TABLE 3
Statistical analysis of insomnia among TBI depressive patients

		MEAN	SD	SE	P value
ISS (AT 0 MTH)	CASES	18.821	2.091	0.395	0.802
	CONTROL	18.643	3.129	0.591	
ISS(AT 6 MTH)	CASES	8.464	2.202	0.416	0.00018
	CONTROL	10.786	2.114	0.399	

Discussion

Our study population was almost close to the age of distribution of TBI in general adult male population. The age range was 18-86

years with a mean age of 31.83 years in the intervention group and 32.95 years in the control group. Jain et al. (2) and Verma et al. (2007) (16) have also reported similar findings with regard to age and sex distribution in their study on chronic TBI patients evaluated for sleep disorders.

Insomnia was reported in 70% of post TBI depressive patients. This finding is supported by earlier studies, wherein insomnia has been reported between 15% and 77% in post TBI patients shortly after or well into the future (2-4). This finding was considerably less than the 77% reported by Varney et al. (16), who used DSM-III criteria. Conversely, these findings were considerably more than the 14% reported by Deb et al. (18) who relied on ICD-10 diagnostic criteria. The correlation between occurrence of insomnia and duration in TBI was found insignificant. Insomnia has been reported between 29% and 50% in post TBI patients during one year after the trauma (19, 20, 21). Population-based studies indicate that insomnia occurs in approximately 40% of individuals with a TBI of any severity and is often the most prevalent somatic complaint in this population (27).

Insomnia in depression was more common in mild TBI patients than those with moderate severity. The reason for this common occurrence in mild TBI could have been that mild TBI patients are more likely to retain their cognitive functions intact, thus are capable of acknowledging their deficits caused by trauma.

Clinchot et al. (1998) (17) and Fichtenberg et al. (2002) (22) showed an inverse relationship and Cohen et al. (1992) (23) noted

increased prevalence with increasing severity of TBI. Some researchers have postulated the reason for this paradoxical finding to the fact that the people with severe brain injury are likely to under report and those with milder injury are more aware of their problem and therefore more likely to report about insomnia. Verma et al. (2007) (16) looked at the more objective data that can be collected with polysomnography and multiple sleep latency test. Their work noted that there was a relationship between severity of TBI and some but not all of the measures of the sleep disorders. In particular more severe TBI was associated with higher percentage of stage I sleep, number of awakening per night and the night spent awake each night.

This study has also tried to explore the neuroanatomical localization of injury in respect to insomnia. Cerebral contusion was the most commonly implicated area involving multiple lobes, however single lobe involvement was also seen. Brain injury secondarily caused by extradural, subdural or intraparenchymal hematoma or involvement of brainstem (with contusion, distortion and hemorrhage) can compromise neurotransmitter release. The raised intracranial pressure during the acute or subacute stages of TBI, either secondarily to cerebral edema or cerebral hyperaemia may contribute indirectly (24).

Our finding that sertraline is associated with decrease in insomnia symptoms after TBI is consistent with evidence about the neuropathological mechanism that may contribute to the development of major depression following TBI. Human post

mortem pathologic (25), cerebrospinal fluid (26), and imaging (27) evidence supports a role for serotonin in the depressions of TBI patients. Patients who are depressed following mild TBI have blunted prolactin response to buspirone, suggesting altered serotonin function in these patients compared with patients not depressed after mild TBI. Hence, it may be argued that the occurrence of insomnia may have been associated with coexisting depression in these patients and improvement in mood symptoms with sertraline may have led to improvement in insomnia as well.

Fava Maurizio et al (28), 2002, conducted a study to assess whether fluoxetine, sertraline, and paroxetine differ in efficacy and tolerability in depressed patients and the impact of baseline insomnia on outcomes. Patients (N = 284) with DSM-IV major depressive disorder were randomly assigned in a double-blind fashion to fluoxetine, paroxetine, or sertraline for 10 to 16 weeks of treatment. Using the Hamilton Rating Scale for Depression (HAM-D) sleep disturbance factor score, patients were categorized into low (<4) or high (≥ 4) baseline insomnia subgroups. Changes in depression and insomnia were assessed. Safety assessments included treatment-emergent adverse events (AEs), reasons for discontinuation, and AEs leading to discontinuation. In addition, AEs were evaluated within insomnia subgroups to determine emergence of activation or sedation. Depression improvement, assessed with the HAM-D-17 total score, was similar among treatments in all patients ($p = 0.365$) and the high ($p = 0.853$) and low insomnia (p

= 0.415) subgroups. Insomnia improvement, assessed with the HAM-D sleep disturbance factor score, was similar among treatments in all patients ($p = 0.868$) and in the high ($p = 0.852$) and low insomnia ($p = 0.982$) subgroups. Analyses revealed no significant differences between treatments in the percentages of patients with substantial worsening, any worsening, worsening at endpoint, or improvement at endpoint in the HAM-D sleep disturbance factor in either insomnia subgroup. Treatments were well tolerated in most patients. No significant differences between treatments in the incidence of AEs suggestive of activation or sedation were seen in the insomnia subgroups. Improvement in overall depression and in associated insomnia was achieved by most patients regardless of baseline insomnia.

Kathleen Brady et al (29), 2000, conducted a twelve-week, double-blind, placebo-controlled trial preceded by a 2-week, single-blind placebo lead-in period. Sertraline treatment yielded significantly greater improvement than placebo on 3 of the 4 primary outcome measures including insomnia. Sertraline was well tolerated, with insomnia the only adverse effect reported significantly more often than placebo (16.0% vs 4.3%; $P=0.01$).

Since the ISI values also improved in controls over time although less than cases, it is possible that patients get adjusted over a period of time. Hence, it may be argued that the drug may not be as effective beyond initial few months after development of insomnia as in the beginning. However, it does not rule out the importance of intervention as compliance

to treatment gets affected because of associated insomnia and depression.

Conclusion

There has been an understanding that the psychological consequences especially depression are likely to affect insomnia independently, as it may also lead to poor participation in productive and healthy living, decreased social and leisure activities, reduced sexual interest, poor drug compliance further deteriorating the existing problem. The overall improvement in insomnia in these patients may be explained by the improvement in depression with sertraline treatment.

Limitations

The present study has not taken patients with severely low GCS into consideration. Moreover, ISI scale used is more of a subjective index which takes into consideration patient's verbatim.

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