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ORIGINAL ARTICLE

Role of sertraline in posttraumatic brain injury depression and quality-of-life in TBI

Ahmed Ansari, Akhilesh Jain[1], Achal Sharma, R. S. Mittal, I. D. Gupta[2]

Department of Neurosurgery, S.M.S. Medical College, [1]Department of Psychiatry, ESIC Model Hospital, [2]Department of Psychiatry, S.M.S Medical College, Jaipur, Rajasthan, India

ABSTRACT

Introduction: Traumatic brain injury (TBI) is a major cause of disability. Depression is one of the major squeal of TBI in both in-patient and out-patient populations. Depression is associated with numerous negative outcomes, thus affecting quality-of-life (QOL) adversely in these patients. Addressing depression in treatment regimen of TBI may improve QOL of these patients.

Objective: The present study is designed to evaluate the role of sertraline in post TBI depression and its impact on QOL.

Materials and Methods: Eighty male patients with post TBI depression were included in the study among the 250 male patients of mild to moderate TBI recruited for the evaluation. Half of the patients were given sertraline 50 mg PO, whereas other half served as control without sertraline treatment. Participants were assessed on Glasgow Coma scale, Patient Health Questionnaire-9 (PHQ-9) and World Health Organization QOL (WHOQOL) at regular interval till the end of 6 months.

Result: Depression was found in 35.6% of total patients recruited. Most of the patients (63.1%) were below 35 years of age. Depression was more common in mild TBI cases than those with moderate TBI (53.7% vs. 46.25%, $P = 0.04$). Left side brain injury (56.25%) with cerebral contusions was more commonly associated with depression ($P = 0.04$). Patients in sertraline group responded well to treatment with significant improvement in mod symptoms (PHQ-9 score 14.88 ± 3.603 vs. 5.33 ± 2.98, $P = 0.04$)). All the four domains of QOL improved significantly in sertraline group than the control group with sertraline treatment.

Conclusion: Management of TBI should also focus on treatment of associated mood symptoms, which is likely to be associated with poor QOL in these patients. Sertraline has been found to be effective in the treatment of depression with significant improvement in QOL in TBI patients.

Key words: Depression, quality of life, traumatic brain injury

Introduction

Traumatic brain injury (TBI) is a major cause of disability.[1] One of the major sequelae of TBI is depression in both inpatient and outpatient populations.[2] Most studies in this regard have included a majority of patients with moderate to severe injuries, though patients with mild injuries also have increased the risk of depression after TBI.[3,4] TBI patients with co-morbidities, such as depression subsequently, have greater functional disability and post-concussive symptoms and perceive their injury more severe than do those without depression.[5]

Post-TBI depression has been associated with numerous negative outcomes including 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 lower ratings of health, poor subjective well-being, and poorer QOL.[2,6,7]

Prior estimates of depression among individuals with TBI range widely, from 15% to 77%.[4,6,8] Depression with TBI can manifest shortly after injury or well into the future.[7,9]

Quality-of-life has gained importance as a primary objective of health care system intervention,[10] and for assessment and

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Address for correspondence:
Dr. Ahmed Ansari, SMS Medical College, Jaipur, Rajasthan, India.
E-mail: ahmed.ansari2@gmail.com,

treatment of TBI. QOL can be broadly defined as an indicator of the injury, treatment and level of recovery that a person subjectively expresses after experiencing an injury/disease and it includes a person`s perceived wellness, subjective well-being and needs satisfaction.[11,12] It is a multidimensional construct comprising physical, psychological, and social factors.[13] Berger *et al*., 1999,[14] noted four functioning domains-physical, psychological, social (especially vocational status and relationship with family and friends), and cognition.

Studies in various populations have shown that treating depression can be effective and can decrease functional impairment, somatic symptoms, and perception of impairment. A few studies have examined the efficacy of antidepressants in the treatment of depression following TBI.[15-17] However, few have focused on examining whether treatment decreases functional disability and brings out changes in overall QOL.[18,19]

More elaborative studies may prove more informative and credible in recognition of this important secondary condition. Hence, the present study is designed to evaluate the role of sertraline (selective serotonin reuptake inhibitor) in post TBI depressive patients and its impact on QOL.

Materials and Methods

The study was carried out in the neurosurgery ward and OPD of SMS Medical College and group of hospitals, Rajasthan, a 3000 bedded superspecialty tertiary care center. 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 the entire state as well as neighboring states.

A total of 250 male TBI patients with mild to moderate severity were screened initially. Eighty patients who were found to have to have depression on assessment with Patient Health Questionnaire-9 (PHQ-9) and subsequent interview with a psychiatrist finally constituted the study sample size. The nature and purpose of the study were 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 about 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 2-week interval for first 4 weeks and monthly interval subsequently till 6 months.

To be eligible to participate in study, the patients had to be 18 years or older, should have had at least 2-week 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 Diagnostic and Statistical Manual, Fourth edition (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, major depressive disorder (MDD) or any other mental disorder except current depression using DSM-IV criteria, or (5) to have a history of clinically significant liver or renal disease.

The study sample comprising of TBI patients with depression was further divided randomly into two groups, consisting of forty patients in each group. One group designated as intervention group (cases) was given 50 mg sertraline daily PO. The group was not given any medication and served as a control group.

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 cases was assessed by Glasgow Coma scale (GCS). Cases and controls were assessed on PHQ-9, World Health Organization QOL (WHOQOL)-BREF for depression and quality-of-life (QOL), respectively.

The follow-up of cases and control was done as scheduled till the end of 24 weeks. At each followup cases were assessed on GCS, PHQ-9 and WHOQOL-BREF to observe the severity of TBI, depression, and QOL respectively in response to the treatment.

Measures

In this study, the interview was focused on assessment of severity of TBI, depression and QOL using GCS, PHQ-9 and WHOQOL-BREF.

Glasgow Coma scale,[20] 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 9-item PHQ-9, a self-report version of PRIME-MD11 which assesses the presence of MDD using modified 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, κ =0.65; overall accuracy, 85%; sensitivity, 75%; specificity, 90%).[21,22] In this study, Hindi version of PHQ-9 was used. It has been validated in Indian population and is considered to be a 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.[21,22] We considered PHQ 9 score of 10 or more as depression in this study.

The WHOQOL-BREF, was developed by the World Health Organization QOL Group, in 15 international field centers.[23] It is a self-report questionnaire that contains 26 items, and each item represents one facet. The facets are defined as those aspects of life that are considered to have contributed to a person's QOL. Among the 26 items, 24 of them make up the 4 domains of physical health (7 items), psychological health (6 items), social relationships (3 items), and environment (8 items). The other 2 items measure the overall QOL and general health. It can be conveniently used in studies that assess QOL as one of the several variables longitudinally at several time intervals and has been used in studies focused on TBI. In this study, Hindi version was used.[24] The scale has been shown to have good discriminant validity, sound content validity and good test-retest reliability at several international WHOQOL centers. Despite the heterogeneity of facets included within domains, all domains display excellent internal consistency. QOL can be additional outcome variable giving information about an individual's life that other variables cannot.

Lesion localization was done on the basis of computed tomography 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) and Chi-square tests analyses.

Results

A total of 250 male patients of TBI were recruited in this study. About 35.6% of the 250 patients were found to have depression ($n = 89$). Nine out of 89 depressive patients dropped out from the study (10.11%). Finally, 80 patients (32%) of TBI with depression constituted the study sample.

Maximum number (35.6%) of patients were found in the age group of 18–24 years ($n = 28$), followed by 27.5% in the age group 25–34 years ($n = 22$). This was found to be statistically insignificant ($P = 0.06$).

Motor vehicle accidents were the most common cause 87.5% ($n = 70$) of post TBI depressive patients, followed by falls, assaults and foreign body injury, each accounting for 7.5% ($n = 6$), 3.75% ($n = 3$) and 1.25% ($n = 1$), respectively.

Depression as measured on PHQ-9 was statistically more common ($P = 0.04$) in mild TBI cases (53.7%) than the moderate TBI (46.25%). Majority of the patients (46.25%) who had depression sustained injury more than 6 months back ($n = 37$), followed by 30% of depressed patients sustaining TBI 3-6 months back ($n = 24$). This was found to be statistically insignificant ($P = 0.96$).

Neuroanatomical localization was also correlated with depression among TBI patients. Left side of brain injury was present in the majority (56.25%) of patients. This was followed by right side injury in 33.75% of patients ($n = 27$) and diffuse axonal injury in 10% of patients ($n = 8$). It was found significant on statistical analysis ($P = 0.04$) [Table 1].

Cerebral contusion was the most common (31.25%) finding of injury ($n = 25$), followed by multiple injuries including the contusion in 28.75% ($n = 23$) of the cases. Out of these 23 cases, 12 patients had a contusion. Thus, overall patients with contusion constituted 46.25% ($n = 37$) of the study sample. Other findings, such as 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 depressed patients, and found 18 (48.65%) among 37 contused patients to have multiple contusions, although single lobe contusion were also associated with depression, but in lesser numbers [Table 2].

Mean score of PHQ-9 at the beginning of the treatment was 14.88 with a standard deviation (SD) =3.603 and 13.2 with SD = 3.107 in intervention and control group respectively. At the end of the study, significant improvement was observed in PHQ-9 scores in the intervention group (5.33, SD 2.98) when compared to the control group (6.29, SD = 3.221). This effect was statistically significant ($P = 0.04$) [Table 3].

The QOL of study population was measured on WHOQOL at the beginning of the study and again at the end of the study. Table 4 shows mean value and standard deviations in all four domains in cases and controls, as measured on WHOQOL BREF.

At the start of study domain 1 (physical) score in intervention group (38.88 ± 11.882) versus control group (40 ± 10.997) was statistically insignificant ($P = 0.66$). Domain 2 (psychological) score at the start of study in intervention

Table 1: Demographic characteristics of TBI depressive patients

	Cases	Control	Total	*P*
Age in years				
18-24	16	12	28	0.06
25-34	8	14	22	
35-44	7	6	13	
45-54	7	5	12	
55-64	2	2	4	
65 or more	0	1	1	
Type of injury				
RTA	34	46	70	0.19
FFH	3	3	6	
Assault	3	0	3	
Others	0	1	1	
GCS				
Mild	17	26	43	0.04
Moderate	23	14	37	
Duration of head injury				
<3 months	12	12	24	0.96
3-6 months	10	9	19	
>6 months	18	19	37	
Localization				
Right side	11	16	27	0.4
Left side	24	21	45	
DAI	5	3	8	

TBI – Traumatic brain injury; FFH – Fall from height; RTA – Road traffic accident; GCS – Glasgow coma scale; DAI – Diffuse axonal injury

Table 2: Lesion type based on CT scan

CT scan findings	Case	Control	Total
Contusion	11	14	25
Multiple injury	13	10	23
EDH	1	5	6
SDH	4	3	7
SAH	3	0	3
NAD/DAI	5	3	8
Others/foreign body I	0	1	1
Site of contusions in brain			
Right frontal	2	2	4
Left frontal	4	4	8
Right parietal	1	0	1
Left parietal	0	0	0
Right temporal	1	0	1
Left temporal	2	3	5
Multiple contusions I	11	7	18

CT – Computed tomography; SDH – Subdural hematoma; EDH – Epidural hematoma; DAI – Diffuse axonal injury; SAH – Subarachnoid hemorrhage; NAD – No abormalities detected

group (39.50 ± 14.338) versus control group (45.30 ± 14.848) with *P* value of 0.07 was also statistically insignificant. Similarly, domain 3 (social) score in intervention (47.60 ± 15.751) versus control (45.95 ± 14.789) was found statistically insignificant ($P = 0.6$). Domain 4 (environmental) score was also statistically insignificant ($P = 0.08$) between intervention

Table 3: Statistical analysis of depression among TBI patients

PHQ-9	Mean	SD	*P*
At start of study			
Cases	14.88	3.603	0.22
Control	13.2	3.107	
At end of study			
Cases	5.33	2.987	0.04
Control	6.29	3.221	

TBI – Traumatic brain injury; SD – Standard deviation; PHQ – Patient health questionnaire

Table 4: WHOQOL statistical analysis at the start and end of the study

WHOQOL	Mean	SD	*P*
At the start of study			
D1			
Cases	38.88	11.882	0.66
Control	40	10.997	
D2			
Cases	39.5	14.338	0.07
Control	45.3	14.848	
D3			
Cases	47.6	15.751	0.6
Control	45.95	14.789	
D4			
Cases	37.43	12.683	0.08
Control	44.45	10.261	
At the end of study			
D1			
Cases	45.38	11.816	0.001
Control	33.5	12.635	
D2			
Cases	47.23	16.623	0.01
Control	39.13	13.354	
D3			
Cases	58.15	18.565	0.001
Control	40.65	20.202	
D4			
Cases	43.55	13.027	0.16
Control	39.6	11.845	

SD – Standard deviation; WHOQOL – World Health Organization Quality of Life

group (37.43 ± 12.683) and control group (44.45 ± 10.261) at the base line.

At the end of 6 months, domain 1 score was improved significantly ($P = 0.001$) in intervention group (45.38 ± 11.816) as compared to control group (33.50 ± 12.635) which showed further decline. Likewise, domain 2 score at the end of 6 months, in intervention (47.23 ± 16.623) versus control (39.13 ± 13.354) was found statistically significant ($P = 0.01$) in terms of improvement in intervention group and further deterioration in control group. Similar was the observation with domain 3 score

in the intervention group (58.15 ± 18.565) versus control group (40.65 ± 20.202) as it was again statistically significant ($P = 0.001$) with improvement in intervention group and downfall in control group. Intervention group also showed improvement in domain 4 score (43.55 ± 13.027) whereas control group had additional drop in domain 4 score (39.60 ± 11.845), however it was statistically insignificant ($P = 0.16$).

Discussion

Our study population was implicitly closed 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. Similar age distribution have been reported in earlier studies by Verma *et al*.[25] and Jain *et al*.[4]

Out of 250 TBI patients, 35.6% patients developed depression. This finding is supported by earlier studies, wherein depression has been reported between 15% and 77% in post TBI patients shortly after or well into the future.[4,6-9] 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*.[26] who relied on ICD-10 diagnostic criteria. This variation in prevalence rates may have been caused by methodological issues including differences in depression assessment tools used in the research, the time course of depression assessment, and differences in injury severity of persons with TBI (mild vs. severe injuries). This finding gets the robust support from the study by Jorge *et al*.,[8] who reported that mood disorders were significantly more frequent in patients who sustained TBIs than in patients with similar background characteristics who underwent similar level of stress but who did not sustain brain injury. TBI has been consistently associated with damage to the prefrontal cortex, basal ganglia, and the white matter tract that connect these structures. Depression may be related to the same physiologic mechanism.

Depression was more common in mild TBI patients than those with moderate severity. This may be explained by the fact that mild TBI patients are more likely to retain their cognitive functions intact, thus are capable of acknowledging their deficits caused by trauma. They may also explain their mood symptoms explicitly as they experience it which may not be the case with moderate or severe trauma.

The study data also support the relationship between duration of head injury and depression. Incidence of depression was higher (46.25%) in patients sustaining injury more than 6 months back. This was supported by Varney *et al*., 1987[16] who interviewed 120 patients following TBI and found half of the TBI patients not manifesting depression until at least 6 months after injury. The notion supporting this fact is that as the patient regains his cognitive function over a period, he is able to better delineate his mental condition. The average time since injury was longer, however, this ruled out the recovery of emotional function as playing a role in the findings.

This study has also tried to explore the neuroanatomical localization of injury in respect to depression. 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 intra-cranial pressure during the acute or subacute stages of TBI, either secondarily to cerebral edema or cerebral hyperemia may contribute indirectly.[25]

Our finding that sertraline is associated with decreased depressive symptoms after TBI is consistent with evidence about the neuropathological mechanism that may contribute to the development of major depression following TBI. Human postmortem pathologic,[27] cerebrospinal fluid,[28] and imaging[29] evidence supports a role for serotonin in the depressions of neurologic 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.[30] Ashman *et al*., 2009[31] conducted a double-blind placebo controlled trial with block randomization, sertraline was administered for 10 weeks. Participants were at least 6 months post-TBI, and TBI included documented loss of consciousness or other evidence, such as pathology or imaging. Diagnosis of depression was established by DSM-IV criteria and a Hamilton Rating Scale for Depression (HAM-D) score higher than 18. Dosage of sertraline was not fixed and could be adjusted at 2-week intervals, with a maximum dosage of 200 mg/d. The primary outcome of interest was a change in depression status measured with the HAM-D. A positive response was considered to be a decrease of 50%, or a drop below 10 on the HAM-D. Of those who completed the study, 59% of the treated group and 32% of the control group had a positive response. Honn Lee *et al*., 2005[32] also found sertralline to have significant effects on depressive symptoms compared to placebo. Since the PHQ 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 depression as in the beginning. However, it does not rule out the importance of intervention as compliance to treatment and overall QOL may get affected because of associated depression.

We divided equal number of patients in intervention and control group to assess the impact of sertraline on QOL in TBI patients. The controls were recruited amongst the depressive patients

who were not given sertraline. The objective of this study was the participant perspective, which is the normal perspective in QOL studies. This perspective, however relies upon participants having sufficient cognitive awareness to provide insight into their own condition for meaningful assessments.[26]

Our study shows that the intervention group with sertraline treatment improved significantly in terms of QOL in all the four domains, whereas control group without sertraline treatment further deteriorated in all the domains of QOL. Fann *et al*., 2000[33] conducted an 8-week, nonrandomized, single-blind, placebo run-in trial of sertraline on 15 patients diagnosed with major depression between 3 and 24 months after a mild TBI. On the Hamilton Rating Scale for Depression, 13 (87%) had a decrease in score of ≥ 50% ("response"), and 10 (67%) achieved a score of ≤ 7 ("remission") by week 8 of sertraline. There was statistically significant improvement in psychological distress, anger and aggression, functioning and post concussive symptoms with treatment. However, Ashmann *et al*.,2009,[31] found no statistically significant differences at baseline between sertralline group and placebo groups on baseline measures of depression (24.8 ± 7.3 vs. 27.7 ± 7.0) or QOL (2.96 ± 1.0 vs. 2.9 ± 0.9). There has been an understanding that the psychological consequences especially depression are likely to affect different aspects of QOL independently as it may 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 QOL in these patients may be explained by the improvement in depression with sertraline treatment.

Conclusion

Depression is common than a chance occurrence and may lead to poor QOL in already compromised post TBI patients. Antidepressant like sertraline has been found effective in treating associated mood symptoms in this population. Treatment of depression following TBI may significantly improve functioning in different domains of QOL including physical, psychological, social and environmental domains. Given the myriad stressors that can affect a patient's physical, social, work, and family functioning, the finding that pharmacological treatment of depression can improve functioning in these areas is especially salient.

Limitations

There were several limitations in the present study. Assessment of depression and its effect with sertraline was based upon subjective experience that may have resulted in under-reporting or over-reporting of symptoms. It is recognized; however that subjective experience provides only partial and sometimes inaccurate information regarding the disease. Severe TBI cases were not included, due to their inability to comprehend the directions. Hence the present study does not give an overall picture of TBI patients. Since females were not included in this study, it is not appropriate to generalize the results.

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