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Original Research Article

A Hospital-Based Study Assessing the Efficacy of Amantadine in Improving Cognitive Dysfunction in Patients with Severe Traumatic Brain Injury

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Abstract

Aim: The aim of the present study was to study the efficacy of amantadine in improving cognitive dysfunction in patients with severe traumatic brain injury.

Methods: We conducted a single institution‑based observational study at Department of Neurosurgery. We obtained informed consent from the legal representative or next of kin/relative for each patient to be enrolled and have their data published. 70 patients were included in the study. The patients who survived severe TBI were observed for 2 months with Full Outline of Unresponsiveness (FOUR) score.

Results: The cognitive function improved progressively during the 4‑week treatment interval as shown by significant improvement on FOUR score, DRS, and GOS. The adverse effects included spasticity, agitation, vomiting, rash, restlessness, diarrhoea, elevated liver function tests, generalised tonic-clonic seizures (GTCS), constipation, focal convulsions, and nausea.

Conclusion: Administration of amantadine is safe and associated with rapid cognitive improvement in patients with static or declining cognitive function occurring after severe TBI, which is the foundation for functional independence.

Keywords: Amantadine, Cognitive Dysfunction, Severe Traumatic Brain Injury.

Introduction

Traumatic brain injury (TBI) is a major cause of mortality and morbidity [1] and even immediate survivors have significant risk of morbidity and mortality due to subsequent secondary pulmonary complications. [2] Moreover, brain injuries are considered one of the leading causes of disability worldwide [3] as about half of survivors of TBI especially those who developed severe sequel [4] will continue to suffer chronic severe disability despite of receiving an appropriate rehabilitation program [5] and so, represent socioeconomic burden. [6] Consciousness includes two main components; the alertness or arousal and conscious perception or awareness. [7] Anatomically, the level of arousal is mainly supported by the brainstem and the thalami and awareness is underpinned by cerebral cortex and through the fronto-parietal network. [8] Clinically, alertness can be observed as the presence of eye opening and awareness is mostly inferred by command and can be further divided into awareness of self and environment. [9]

Amantadine hydrochloride is an FDA-approved medication for the treatment of dyskinesia in Parkinson's disease [10] and influenza prophylaxis. [11] It acts as a N-Methyl-D-aspartate (NMDA) receptor antagonist and dopamine agonist via dopamine release and dopamine reuptake inhibition. Its mechanism of action seems to support the current hypothesis that disruption in the dopaminergic and glutamatergic pathways are responsible for cognitive deficits in TBI. [12] Therefore, there has been growing interest in exploring the potential use of amantadine for cognitive recovery in this clinical condition. Despite promising results in animal models [13-15], the effect of amantadine in treating cognitive deficits after TBI remains controversial. In 2018,

the AAN recommended the use of amantadine to hasten the rate of cognitive recovery in disorders of consciousness. [16]

Kraus and colleagues [17] found a positive effect of amantadine on executive function, but not attention and memory, in an open-label, prospective study of 22 individuals with chronic TBI receiving 400mg of amantadine daily over 12 weeks. A retrospective study by Reddy and colleagues [18] studied amantadine use in 25 adolescents whose cognitive function failed to return to baseline after 21 days of rest after sports-related concussion. This cohort who received amantadine 100mg twice-daily was compared to a cohort (matched on age, sex, and concussion history) who were not treated with pharmacological agents. This comparison found superior pre- to post-test improvements in concussion symptoms (total score on 22- item self-report symptom inventory), verbal memory, and reaction time for the amantadine group, but no between-group differences for visual memory and visual motor processing speed.

The aim of the present study was to study the efficacy of amantadine in improving cognitive dysfunction in patients with severe traumatic brain injury.

Materials and Methods

We conducted a single institution‑based observational study at department of neurosurgery, Govt. T.D. Medical College & Hospital, Alappuzha, Kerala, India for one year. We obtained informed consent from the legal representative or next of kin/relative for each patient to be enrolled and have their data published. 70 patients were included in the study. The patients who survived severe TBI were observed for 2 months with Full Outline of Unresponsiveness (FOUR) score. We used the FOUR score as it has an advantage over Glasgow Coma Scale (GCS) to assess nonverbal signs of consciousness in intubated patients and in whom all components of GCS cannot be performed. Furthermore, FOUR score can be performed in later course to compare the cognitive and functional status of the patient. Those patients, who either did not improve from the day of trauma or those patients who had stopped improving after a certain number of days and were fulfilling the inclusion/exclusion criteria were considered and enrolled for the study. We enrolled a total of fifty patients who received amantadine 200 mg/day (100 mg twice a day) orally or through enteral feeding tube for duration of 4 weeks.

While recruiting, we excluded patients with known comorbid conditions as previous studies have reported occurrence and exacerbation of adverse effects in patients with preexisting disease. During the study, we monitored the patients for occurrence of any adverse effects. The functional assessment done using FOUR score, Disability Rating Scale (DRS), and Glasgow Outcome Scale (GOS) at enrollment, 1 and 4 weeks of treatment, and 2 weeks posttreatment was compared.

Results

Table 1: Full Outline of Unresponsiveness score values for functional assessment

FOUR score	N	Median±IQR	Minimum	Maximum	P Value
At enrollment	70	11.00±2.28	7.00	11.00	
At 1 week	65	13.00±2.00	8.00	13.00	<0.001
At 4 weeks	68	15.00±2.01	9.00	16.00	<0.001
At 6 weeks	68	15.00±2.01	9.00	16.00	<0.001

The cognition improved rapidly during 4 weeks of treatment as shown in improvement on FOUR score.

Table 2: Disability rating score values for functional assessment

Disability rating score	N	Median±IQR	Minimum	Maximum	P Value
At enrollment	70	21.45±5.00	17.00	28.00	
At 1 week	65	17.00±3.00	12.00	26.00	<0.001
At 4 weeks	68	14.00±6.54	8.00	24.00	<0.001
At 6 weeks	68	14.00±6.55	8.00	24.00	<0.001

The cognition improved rapidly during 4 weeks of treatment as shown in improvement on Disability rating score.

Table 3: Glasgow Outcome Score values for functional assessment

Glasgow Outcome score	N	Median±IQR	Minimum	Maximum	P Value
At enrollment	70	3.00±1.00	2.00	3.00	
At 1 week	65	3.00±0.00	2.00	4.00	<0.001
At 4 weeks	68	3.00±1.00	2.00	4.00	<0.001
At 6 weeks	68	3.00±1.00	2.00	4.00	<0.001

The cognition improved rapidly during 4 weeks of treatment as shown in improvement on Glasgow Outcome Score.

Table 4: Adverse events

Adverse events	N%
Nausea	1 (1.42)
Constipation	2 (2.85)
Diarrhea	4 (5.71)
Elevated LFT	4 (5.71)
Focal convulsions	4 (5.71)
Rash	6 (8.57)
Restlessness	6 (8.57)
GTCS	7 (10)
Vomiting	10 (14.28)
Agitation	12 (17.14)
Spasticity	14 (20)

The adverse effects included spasticity, agitation, vomiting, rash, restlessness, diarrhea, elevated liver function tests, generalised tonic clonic seizures (GTCS), constipation, focal convulsions, and nausea.

Discussion

Traumatic brain injury (TBI) constitutes a major public health problem. [19] The estimated prevalence of patients with TBI in India is 9.7 million, and approximately 16% sustain severe TBI. [20] Most road traffic accident victims are in the 20–40‑year age group, the economically productive years, and are many times the main bread earners of the family, putting the whole family below the poverty line in many cases while depriving society of vital drivers of economy as in many cases these are entrepreneurs or professionals. With advances in the management of head trauma, an increasing number of patients are surviving with residual neurological impairments causing significant morbidity. As the treatment for cognitive dysfunction in severe TBI is relatively limited, pharmacological treatments to enhance neurobehavior have been tried and tested, on the premise that TBI‑induced derangements in dopaminergic neurotransmitter systems may improve through supplementation. Administration of amantadine promotes dopaminergic activity and hence is a proposed therapeutic option to improve cognition. [21]

The cognitive function improved progressively during the 4‑week treatment interval as shown by significant improvement on FOUR score, DRS, and GOS. The adverse effects included spasticity, agitation, vomiting, rash, restlessness, diarrhea, elevated liver function tests, generalised tonic clonic seizures (GTCS), constipation, focal convulsions, and nausea. Our findings were consistent with observational reports suggesting acceleration of cognitive recovery in severe TBI patients receiving amantadine but differed with those suggesting loss of achieved recovery after discontinuation of the drug. [22-25]

On contrary to the obtained results and that previously documented in literature, Hammond et al [26] reported non-significant differences on cognitive functions between amantadine and placebo. However, Hammond's study [26] included individuals with chronic complicated mild-to-severe TBI since more than 4 months, while the current study included patients with acute TBI. Also, Hammond's study included 119 individuals divided into two groups, so sample size was small to get a final conclusion. Finally, Hammond et al [26] concluded that the effect-size was small suggesting that changes observed across assessments may not have functional significance. In trial to explain the beneficial effect of amantadine, Tan et al [27] detected, in rat model of TBI, decreased dopamine concentration in the striatum, degeneration and apoptosis of dopaminergic neurons in the substantia nigra with depression-like behavior and found these effects were reversed by amantadine therapy and attributed its anti-depression effect to these actions.

In the available literature, amantadine has been mainly tested in patients who suffered from severe TBI. Although the definition of severe TBI is well described and established, this term subtends a wide spectrum of diverse clinical presentations and different potentials for recovery. Recently, the discovery of covert consciousness in the early stage of brain injury has been shown to have prognostic significance. Specifically, among other studies, Claassen et al. meticulously studied 104 unresponsive brain injured patients admitted to the intensive care unit and demonstrated early brain activation on machine-learning processed electroencephalogram (EEG) in 15 % of the cohort, defining it as cognitive-motor dissociation (CMD). [28] At 12 months after injury, 44 % of patients with CMD had a GOS-E level of 4 or higher, compared to only 14 % of patients without early brain activation. Presence of CMD seems to be associated with a better potential for long-term cognitive recovery. Thus, this could be a group of patients that potentially merits targeted treatment in future clinical trials. Cognitive outcomes were

greatly diverse across the studies. DRS and GOS are currently the most commonly utilized scales to assess outcome in TBI. Although these scales are widespread, objective, and represent a simple evaluation of independence in daily activities, they might miss important endpoints related to cognitive capacities, quality of life and more broadly patient-centered outcomes. Therefore, a more comprehensive cognitive evaluation through batteries of neuropsychological testing, like the one proposed in the work of Sneider et al [29], might enhance the testing accuracy for cognitive recovery.

Conclusion

Administration of amantadine is safe and associated with rapid cognitive improvement in patients with static or declining cognitive function occurring after severe TBI, which is the foundation for functional independence. The study was conducted to check correct operation, reliability, and validity of the result; identify adverse effects caused and effectiveness of actions to reduce them; examine feasibility of large‐scale study; enhance data integrity, opportunity to develop consistent practices such as source documentation, informed consent procedures, data collection tools, and regulatory reporting procedures; and examine feasibility of adverse event reporting system.

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