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Original Article

Efficacy of Amantadine in Improving Cognitive Dysfunction in Adults with Severe Traumatic Brain Injury in Indian Population: A Pilot Study

Prajakta Suresh Ghate, Ashok Bhanage, Hrishikesh Sarkar[1], Anand Katkar

Department of Neurosurgery, Ruby Hall Clinic, Pune, [1]Department of Neurosurgery, Holy Family Hospital, Mumbai, Maharashtra, India

Abstract

Background: Severe traumatic brain injury (TBI) is associated with disabling cognitive impairment. Currently available options to improve the cognitive function have been futile. However, recently, commonly used medicine for Parkinson's disease, amantadine, has been shown to assist in the improvement of cognitive function. **Methodology:** We conducted a single institution-based observational study in adult Indian population. Fifty consecutive patients with documented static or declining cognitive function at 2 months of severe TBI fulfilling the inclusion/exclusion criteria received amantadine 200 mg/day (100 mg twice a day) orally or through enteral feeding tube for the duration of 4 weeks. The functional assessment done with Full Outline of Unresponsiveness (FOUR) score, Disability Rating Scale (DRS), and Glasgow Outcome Scale (GOS) during 4 weeks of treatment and 2 weeks posttreatment was assessed. **Results:** The cognitive function improved progressively during the 4-week treatment interval as shown by significant improvement on FOUR score, DRS, and GOS. However, after discontinuation of the drug, the speed of recovery slowed down significantly, but the achieved recovery was not lost. Out of fifty, eight patients had convulsions as an adverse effect of amantadine, of which five patients required discontinuation of the drug with treatment for convulsions. **Conclusions:** This study indicates the safety and efficacy of amantadine in partial reversal of cognitive dysfunction in adults with severe TBI in adult Indian population.

Keywords: *Amantadine, cognitive dysfunction, severe traumatic brain injury*

Introduction

Traumatic brain injury (TBI) constitutes a major public health problem.[1] The estimated prevalence of patients with TBI in India is 9.7 million, and approximately 16% sustain severe TBI.[2] 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.[3] Administration of amantadine promotes dopaminergic activity and hence is a proposed therapeutic option to improve cognition.[3]

There is a desperate need for the development of treatment strategies for cognitive dysfunction in severe TBI, while there is a paucity of significant evidence for the use of amantadine, which led to formulation of this study. The aim of this study was (1) to study the efficacy of amantadine in improving cognitive dysfunction in patients with severe TBI in adult Indian population and (2) to evaluate the safety of administration of amantadine.

Methodology

We conducted a single institution-based observational study in the adult Indian population in a tertiary health-care center. We obtained informed consent from the legal representative or next of kin/relative for each patient to be enrolled and have their data published. We also obtained Institutional Review Board approval for

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Address for correspondence:
Dr. Prajakta Suresh Ghate, Department of Neurosurgery, Ruby Hall Clinic, 40, Sassoon Road, Pune - 411 001, Maharashtra, India.
E-mail: drghateprajakta@gmail.com

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conducting the study and publication. 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 [Table 1], 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

Primary analysis along with graphical representation of the data was carried out using MS Excel. Statistical comparisons were done using nonparametric Wilcoxon's tests. $P < 0.05$ was considered statistically significant. The entire statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Version 20.0, Armonk, NY, USA: IBM Corp.) for MS Windows. The cognition improved rapidly during 4 weeks of treatment as shown in improvement on FOUR score, DRS, and GOS [Tables 2-4 and Figures 1-3]. At the end of 4 weeks, the improvement in the cognitive function was significant ($P < 0.001$). However, after discontinuation of treatment, the speed of recovery slowed down, but the achieved recovery was not lost ($P < 0.001$). At the end of 6 weeks, the scores remained almost same.

The adverse effects included spasticity, agitation, vomiting, rash, restlessness, diarrhea, elevated liver function tests, generalised tonic clonic seizures (GTCS), constipation, focal convulsions, and nausea [Table 5]. All patients received symptomatic treatment for the respective adverse effects. Out of fifty, five patients (10%) suffered disabling GTCS requiring discontinuation of the drug with treatment for convulsions, whereas three patients (6%) had focal convulsions and could be continued with symptomatic treatment. There were no deaths or significant life-threatening conditions.

Discussion

In this single institution-based observational study in adult Indian population, we found that the administration

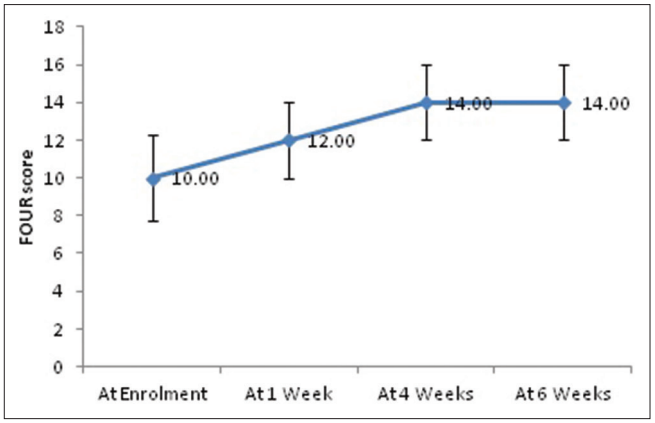

Figure 1: Mean Full Outline of Unresponsiveness score during the 6-week assessment period Full Outline of Unresponsiveness score ranges from 0 to 16; lower scores indicate more severe functional recovery. Full Outline of Unresponsiveness score improved rapidly up to the 4-week treatment interval and remained same but did not fall during drug washout period (week 4–6)

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age group of 18-65 years of age	Patient showing functional neurological improvement
Documented cognitive dysfunction which is stable, static, deteriorating, not clearly improving, present at 2 months following TBI	Patient with posttraumatic epilepsy disorder
Documentation of intracranial pathology with imaging - CT/MRI	Ischemic heart disease or congestive heart failure, myocardial infarction, spinal cord injury with ongoing deficits, cancer, or any other severe illnesses which would affect the assessment of the patient
The cognitive dysfunction should have reached a plateau or is deteriorating	
There is no identifiable cause for cognitive impairment such as addiction with narcotic drugs or alcohol, hydrocephalus, infection, etc.	Patient with preexisting chronic renal disease
The patient should not have any preexisting psychiatric comorbidities before the TBI	History of major depression or any other psychiatric illness requiring ongoing medication
Absence of seizure disorder before injury	History of prior significant TBI, brain tumor, cerebral vascular event, or any other stable brain injury
	Addiction with narcotic drugs or alcohol

TBI – Traumatic brain injury; CT/MRI – Computed tomography/magnetic resonance imaging

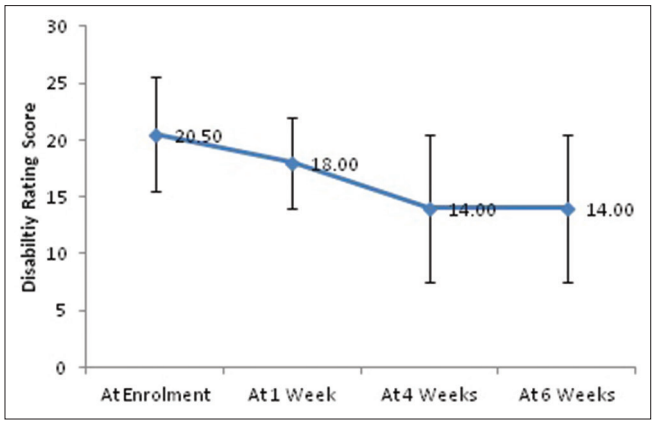

Figure 2: Mean Disability Rating Scale during the 6-week assessment period Disability Rating Scale scores range from 0 to 29; higher scores indicate more severe functional recovery. Disability Rating Scale scores improved rapidly up to the 4-week treatment interval and remained same but did not fall during drug washout period (week 4–6)

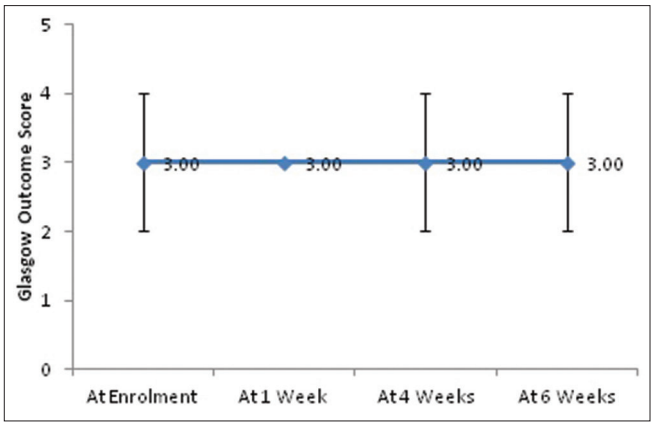

Figure 3: Mean Glasgow Outcome Scale during the 6-week assessment period Glasgow Outcome Scale ranges from 1 to 5; lower scores indicate more severe functional disability. Glasgow Outcome Scale improved rapidly up to the 4-week treatment interval and remained same but did not fall during drug washout period (week 4–6)

Table 2: Full Outline of Unresponsiveness score values for functional assessment

FOUR score	*n*	Median±IQR	Minimum	Maximum	*P*
At enrollment	50	10.00±2.25	6.00	12.00	
At 1 week	48	12.00±2.00	8.00	14.00	<0.001
At 4 weeks	45	14.00±2.00	9.00	16.00	<0.001
At 6 weeks	45	14.00±2.00	9.00	16.00	<0.001

IQR – Interquartile range; FOUR – Full Outline of Unresponsiveness

Table 3: Disability rating score values for functional assessment

Disability rating score	*n*	Median±IQR	Minimum	Maximum	*P*
At enrolment	50	20.50±5.00	16.00	27.00	
At 1 week	48	18.00±4.00	11.00	25.00	<0.001
At 4 weeks	45	14.00±6.50	8.00	24.00	<0.001
At 6 weeks	45	14.00±6.50	8.00	24.00	<0.001

IQR – Interquartile range

Table 4: Glasgow Outcome Score values for functional assessment

Glasgow Outcome Score	*n*	Median±IQR	Minimum	Maximum	*P*
At enrolment	50	3.00±1.00	2.00	3.00	
At 1 week	48	3.00±0.00	2.00	4.00	<0.001
At 4 weeks	45	3.00±1.00	2.00	4.00	<0.001
At 6 weeks	45	3.00±1.00	2.00	4.00	<0.001

IQR – Interquartile range

Table 5: Adverse events

Adverse event	Affected (%)
Nausea	1 (2)
Constipation	2 (4)
Diarrhea	3 (6)
Elevated LFT	3 (6)
Focal convulsions	3 (6)
Rash	4 (8)
Restlessness	4 (8)
GTCS	5 (10)
Vomiting	7 (14)
Agitation	9 (18)
Spasticity	10 (20)

LFT – Liver function test; GTCS – Generalised tonic clonic seizures

of amantadine 2 months after severe TBI significantly improved cognitive function recovery in patients. We enrolled patients with documented static or declining cognitive function at 2 months of severe TBI in our study, in an attempt to exclude spontaneous cognitive recovery and hence to rule out confabulation of results. During the posttreatment 2-week washout period, the achieved benefit was not lost though the speed of recovery slowed down significantly. During the 6-week observation period, administration of amantadine did not increase the risk of any life-threatening adverse effects suggesting that amantadine use at a dose of 200 mg is safe. There was almost negligible recovery during the washout period suggesting that the response was drug dependent. 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.[4-9] We could not find any similar study carried out in the adult Indian population affected by severe TBI.

Amantadine is an old drug and since its serendipitous discovery in 1969 has been abundantly used for Parkinson's disease. The various studies carried out on safe use of amantadine have not reported any significant life-threatening adverse effects for treatment of Parkinson's disease.[10] The underlying pathophysiology postulated for posttraumatic cognitive dysfunction is similar to that of Parkinson's disease, depletion of neurotransmitter – dopamine levels; hence, supplementation is theorized to give better functional recovery.[5] Amantadine facilitates presynaptic dopamine

release and delays postsynaptic reuptake. This results in enhanced neurotransmission in the dopamine-dependent nigrostriatal, mesolimbic, and frontostriatal circuits that are responsible for mediating arousal, drive, and cognitive functions and producing favorable neurobehavioral effects.[9]

Limitations of our study

Our study does not address the effect of prolonged treatment on long-term outcome, as the treatment interval was brief with the assessment of the short-term outcome. However, we are still keeping a follow-up of the patients to assess the long-term outcome, to publish later. Second, we did not cut down the standard rehabilitation interventions, so the degree to which the benefits of amantadine are independent of or synergistic with such standard treatments could not be determined. Third, we did not use electroencephalographic monitoring to detect any subclinical seizures that may have occurred due to amantadine. Fourth, this is not a placebo-controlled randomized study but an observational study.

Conclusions

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.

An initial pilot 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. We plan for a large-scale study in the future with an attempt to eliminating the shortcomings of this pilot study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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