ORIGINAL RESEARCH

Assessing the effectiveness of amantadine in enhancing cognitive impairment in individuals with severe traumatic brain injury (TBI): An observational study

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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: This is an observational study conducted in a tertiary care hospital in Telangana state, India. We obtained informed consent from the legal representative or next of kin or relative for each patient who enrolled in this study with their willingness and have their data published. 70 patients were included in the study. The patients who survived severe TBI were observed for 2 months with a Full Outline of Unresponsiveness (FOUR) score.

Results: Over the course of the 4-week treatment and follow up period, there was a gradual and noticeable enhancement in cognitive function, as seen by substantial improvements in the FOUR score, DRS, and GOS. The negative reactions included spasticity, agitation, vomiting, rash, restlessness, diarrhea, increased liver function tests, generalized tonic clonic seizures (GTCS), constipation, focal convulsions, and nausea.

Conclusion: Amantadine administration is both safe and linked to rapid cognitive enhancement in individuals with stagnant or deteriorating cognitive function after severe traumatic brain injury (TBI). This improvement serves as the basis for achieving functional independence.

Key words: Amantadine, cognitive dysfunction, severe traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and illness, and even those who survive initially have a high risk of illness and death owing to chronic secondary pulmonary issues.[1,2] In addition, brain injuries are recognized as a prominent contributor to disability on a global scale.[3] Approximately half of individuals who survive traumatic brain injuries, particularly those who experience severe complications, will continue to endure long-term and severe disability, even after undergoing an appropriate rehabilitation program.[4,5] Consequently, these individuals pose a significant socioeconomic burden.[6] Consciousness has two primary elements: alertness, or arousal, and conscious perception, or awareness.[7] The brainstem and thalami primarily sustain the state of arousal, whereas the cerebral cortex and the fronto-parietal network underlie awareness.[8] From a clinical standpoint, the act of opening one's eyes can indicate alertness, whereas response to commands frequently indicates awareness. Awareness can be further categorized into two categories: self-awareness and environmental awareness.[9] Due to the limited options available for treating cognitive impairment in severe traumatic brain injury (TBI), researchers have experimented with pharmaceutical therapies to improve neurobehavior. The theory is that improving dopaminergic neurotransmitter systems, which TBI

disrupts,may be beneficial. Amantadineadministrationenhances dopaminergic activity, making it a potential treatment choice for enhancingcognition.[10] The research was conducted due to the lack of substantial data supporting the use of amantadine in treating cognitive impairment in severe traumatic brain injury (TBI), highlighting the urgent need for the development of effective treatment options. This research aimed to assess the effectiveness of amantadine in enhancing cognitive impairment in individuals with severe traumatic brain injury (TBI) and evaluate the safety of administering amantadine.

MATERIALS AND METHODS

This is an observational study in a tertiary care hospital,Telangana,India. Ethical clearance was taken from institute ethics committee. We obtained informed consent from the legal representative or next of kin or relative for each patient to be enrolled and have their data published. 70 patients were included in the study and this study was conducted in the year 2023 (January to November 2023).

Patients who attended the Neurosurgery department and those who survived severe traumatic brain injury (TBI) were treated and followed up for a period of 2 months using the Full Outline of Unresponsiveness (FOUR) score. We chose to use the FOUR score instead of the Glasgow Coma Scale (GCS) because it has the advantage of assessing nonverbal signs of consciousness in patients who are intubated and unable to perform all components of the GCS. Additionally, the FOUR score can be used later on to compare the cognitive and functional status of the patient.

In this study we excluded the patients who either did not show any improvement from the day of the trauma or those who stopped improving after a certain number of days. A total of seventy patients were enrolled in the study and received amantadine at a dose of 200 mg/day (100 mg twice a day) orally or through an enteral feeding tube for a duration of 4 weeks.

During the selection process, we deliberately excluded individuals who had known comorbid disorders due to past research indicating that adverse effects are more likely to arise and worsen in patients with preexisting diseases like Diabetes,Hypertension.

Throughout the study, the patients were closely observed for the presence of any negative consequences/complications. A comparative analysis was conducted on the functional evaluation performed during the enrollment, 1-week and 4-week treatment periods, and 2-week post-treatment period using the FOUR score, Disability Rating Scale (DRS)and Glasgow Outcome Scale (GOS).

RESULTS

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

Full Outline of Unresponsiveness 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.Total of 68 were studied among the 70 patients enrolled as two of the patients were lost to follow up during the treatment.

DISCUSSION

Due to advancements in head trauma management, there has been a rise in the number of patients who survive but still experiencing neurological impairments, leading to significant morbidity. Due to the limited options for treating cognitive dysfunction in severe traumatic brain injury (TBI), researchers have experimented with pharmacological treatments to improve neurobehavior. The theory is that supplementing the dopaminergic neurotransmitter systems, which TBI disrupts, may result in improvement. Amantadine administration enhances dopaminergic activity, making it a potential treatment choice for enhancing cognition.[11]

Over the course of the 4-week treatment period, there was a gradual and noticeable enhancement in cognitive function, as evidenced by significant improvements in the FOUR score, DRS, and GOS. The complications encompassed spasticity, agitation, vomiting, rash, restlessness, diarrhea, elevated liver function tests, generalized tonic clonic seizures (GTCS), constipation, focal convulsions, and nausea. The results of our study align with observational reports that indicate an increase in cognitive recovery in severe traumatic brain injury (TBI) patients who receive amantadine. However, our findings contradict reports that suggest a decline in the progress made after discontinuing the medication.[12-15]

In contrast to the findings and existing literature, Hammond *et al*.[16] observed no significant disparities in cognitive functions between amantadine and placebo. It encompassed individuals with chronic, complicated, mild-to-severe traumatic brain injury (TBI) lasting for over 4 months, whereas the present study focused on patients with acute TBI. In addition, Hammond's study consisted of 119 participants who were divided into two groups, resulting in a relatively small sample size for drawing a definitive conclusion. Ultimately, they determined that the effect size was minimal, indicating that the observed changes in assessments may not have practical importance. Tan *et al*.[17] conducted a study to elucidate the positive impact of amantadine. In a rat model of TBI, they saw lower levels of dopamine in the striatum and more damage and death of dopaminergic neurons in the substantia nigra. Depression-like behaviors were present along with these changes. However, the researchers found that amantadine therapy reversed these effects and attributed its antidepressant effect to these actions. Amantadine has primarily been studied in patients with severe traumatic brain injury (TBI), based on the existing literature. While the definition of severe traumatic brain injury (TBI) is clearly defined and accepted, it encompasses a broad range of varied clinical manifestations and varying degrees of potential for recovery. Recently, researchers have shown that the detection of hidden awareness during the first phase of brain damage has proven to be of great importance in predicting outcomes. 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 a machine-learning processed electroencephalogram (EEG) in 15% of the cohort, defining it as cognitive-motor dissociation (CMD).[18]

At 12 months following injury, 44% of patients with CMD had a GOS-E level of 4 or greater, compared to just 14% of patients without early brain activation. The 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 outcomes 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*.(2013), might enhance the testing accuracy for cognitive recovery.[13]

CONCLUSION

This study observed that giving amantadine is safe and has been linked to quick cognitive improvement in people whose cognitive function has been stable or declining after a severe traumatic brain injury (TBI). This is what is needed to become functionally independent.Further large setting studies can help in strengthening this study results and amantadine may be declared as wonder drug in TBI to improve the Cognitive function.

CONFLICT OF INTEREST: None to be Declared.

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