e-ISSN: 0975-9506, p-ISSN: 2961-6093

Available online on www.ijpqa.com doi: 10.25258/ijpqa.16.4.43

International Journal of Pharmaceutical Quality Assurance 2025; 16(4); 243-247

Original Research Article

An Observational Study on the Effectiveness of Amantadine in Enhancing Cognitive Recovery in Adults with Severe Traumatic Brain Injury

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Received: 10-02-2025 / Revised: 17-03-2025 / Accepted: 20-04-2025
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Conflict of interest: Nil

Abstract:

Background: Traumatic brain injury (TBI) is among the leading causes of chronic disability, particularly among economically productive adults in India. Cognitive impairment after TBI is a major challenge in rehabilitation. Pharmacologic agents such as amantadine, which facilitate dopaminergic mechanisms, can potentially enhance recovery but have not been properly investigated in India.

Objective: To determine the effectiveness and safety of amantadine in inducing cognitive recovery in adults with severe TBI.

Methodology: Single-center, prospective observational study that recruited 60 adults (18–65 years) with severe TBI and persistent cognitive dysfunction. Patients were treated with amantadine 200 mg/day for 4 weeks. Cognitive and functional recovery was measured using the Full Outline of Unresponsiveness (FOUR) score, Disability Rating Scale (DRS), and Glasgow Outcome Scale (GOS) at baseline, 1 week, 4 weeks, and 6 weeks. Adverse events were recorded.

Results: Statistically significant gains ($p < 0.001$) were seen on all the measuring tools. Median FOUR scores increased from 10.5 to 15.0, DRS decreased from 21.0 to 13.5, and GOS increased from 3.0 to 4.0 after 6 weeks. The most common adverse events were spasticity (20%), agitation (17%), and gastrointestinal (10%), but were, in general, manageable.

Conclusion: Amantadine was linked to notable cognitive and functional improvement in extreme TBI in adults and a favorable safety profile. The results warrant its use as an adjunct in neurorehabilitation treatment protocols.

Keywords: Amantadine, Cognitive Recovery, India, Neurorehabilitation, Observational Study, Traumatic Brain Injury.

Introduction

Traumatic brain injury (TBI) remains being a foremost cause of death and disability throughout the world and is one of the most significant public health concerns, particularly in low- and middle-income countries such as India. Approximately 9.7 million people in India alone suffer from the consequences of TBI, of which close to 16% of these have sustained injuries of a severe degree. These numbers clearly indicate the extent of the burden that TBI places on health care services, rehabilitation centers, and socioeconomic systems [1].

Most TBI cases, especially those caused by road traffic accidents, happen to people between the ages of 20 and 40 years. This is the working age, and most of the victims are productive citizens of society or the breadwinners of their households. TBI therefore not only causes suffering and harm to people and their families but also has serious economic impacts, including impoverishing families and depriving society of skilled professionals, entrepreneurs, and other crucial economic contributors.

There have been developments in emergency management and neurosurgical treatment to enhance the survival of patients with severe head injury. Nevertheless, a significant number of such survivors still experience persistent neurological dysfunction. Cognitive dysfunction, a frequent complication of severe TBI, presents long-term recovery, rehabilitation, and reintegration challenges to society. Such impairments frequently consist of attention, memory, executive function, and processing speed, resulting in decreased independence and quality of life [2].

Today, therapeutic management of post-severe TBI cognitive impairment is limited. While traditional rehabilitation interventions like occupational, speech, and cognitive therapy continue to be the mainstay of recovery, they do not cover the entire range of neurobehavioral disabilities in such

patients. This unmet need has prompted researchers to investigate the application of pharmacological interventions to enhance cognitive recovery, based on a better understanding of the neurochemical alterations of TBI.

Among the pharmacologic treatments suggested, amantadine has been noteworthy in that it alters dopaminergic neurotransmission. TBI generally leads to impairment of the dopaminergic system, and amantadine, a dopamine agonist and NMDA antagonist, has been shown to reverse several of the neurobehavioral impairments of this dysfunction. Amantadine, by potentiating dopaminergic function, has been shown to improve arousal, attention, and memory and thus is a potential treatment for post-TBI cognitive impairments [3].

Notwithstanding the theoretical basis and some early studies validating its use, clinical usage of amantadine in patients with severe TBI, particularly in the Indian scenario, has not been utilized. Additionally, safety concerns of amantadine in this particular group should be studied in detail. Heterogeneity of the injury pattern, variability in rehabilitation centers, and some of the demographic factors in India require an observational study to evaluate efficacy as well as safety of this treatment.

Against this backdrop, the current research was designed to fill these important gaps in clinical science. The main objective of this research was to assess the effectiveness of amantadine in enhancing cognitive impairment in adult Indian patients of severe TBI. A secondary but no less important objective was to establish the safety of amantadine administration in these patients. Through its contribution to the increasing body of evidence on neuropharmacological rehabilitation strategies, this research seeks to inform clinical practice and set the stage for future controlled trials and treatment protocols for cognitive recovery following severe TBI.

Methodology

Study Design: This was a prospective, single-center, observational study conducted to evaluate the effectiveness of amantadine in enhancing cognitive recovery in adults with severe traumatic brain injury (TBI). The study aimed to observe and compare changes in neurological function before, during, and after administration of amantadine using validated clinical scales.

Study Area: The study was conducted at Department of Neurosurgery, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India.

Study Duration: The study was conducted from January 2024 to December 2024.

Sample Size: A total of 60 adult patients with severe TBI were enrolled in the study based on predefined eligibility criteria.

Sample Population: The study population included adult patients (age ≥18 years) who survived severe TBI and were admitted to the neurocritical care unit of the participating center. All patients were either intubated or unable to fully participate in the Glasgow Coma Scale (GCS) assessment, hence the use of Full Outline of Un Responsiveness (FOUR) score.

Inclusion Criteria

- Adults aged 18–65 years
- Documented cognitive dysfunction that is stable, static, deteriorating, or not clearly improving, and present at 2 months post-TBI
- Evidence of intracranial pathology on CT or MRI imaging
- Cognitive dysfunction that has reached a plateau or is deteriorating
- No identifiable cause for cognitive impairment (e.g., narcotic drug or alcohol use, hydrocephalus, infection, etc.)
- No preexisting psychiatric comorbidities prior to the TBI
- Absence of seizure disorder before injury

Exclusion Criteria

- Patients showing functional neurological improvement
- Posttraumatic epilepsy disorder
- Ischemic heart disease, congestive heart failure, myocardial infarction, spinal cord injury, ongoing malignancy, or other severe systemic illnesses affecting assessment
- Preexisting chronic renal disease
- Major depression or any other psychiatric illness requiring ongoing treatment
- History of prior significant TBI, brain tumor, cerebrovascular event, or other stable brain injury
- Addiction to narcotic drugs or alcohol

Data Collection: Data were collected at multiple time points: at enrollment (baseline), after 1 week and 4 weeks of treatment, and 2 weeks after cessation of treatment. The following clinical scales were used:

- **Full Outline of Un-Responsiveness (FOUR) Score**: Used to assess level of consciousness and brainstem function.
- **Disability Rating Scale (DRS)**: Used to evaluate cognitive and functional changes.
- **Glasgow Outcome Scale (GOS)**: Used to assess overall functional outcome and recovery.

All scores were recorded by trained medical personnel following standard protocols.

Procedure: Eligible patients were enrolled into the study and commenced amantadine at the standard dosage of 200 mg/day (100 mg twice daily).

Amantadine could be administered orally or through an enteral feeding tube for a period of four weeks. Patient clinical assessments using FOUR, DRS, and GOS scales were completed at baseline, the end of week one, the end of week four and two weeks after the end of treatment to evaluate functional and cognitive recovery. Patients were closely observed for adverse drug reactions during the treatment period.

Statistical Analysis: The data were compiled and analyzed using statistical software SPSS version 25. Descriptive statistics (mean, standard deviation, percentages) were calculated to summarize demographic and baseline characteristics of the patients. Repeated measures ANOVA or Friedman test (for non-parametric data) was used to compare scores across time points. A p-value <0.05 was deemed statistically significant.

Result

Table 1 displays the Full Outline of Unresponsiveness (FOUR) score values for functional assessment over time. At enrollment, the median FOUR score was 10.5 (IQR ±2.3), ranging from 6 to 13. By 1 week, the median increased to 12.5 (IQR ±2.1), with a range of 8.5 to 14.5. At 4 weeks, the score further improved to a median of 14.5 (IQR ±1.9), ranging from 9.5 to 16. By 6 weeks, the median reached 15.0 (IQR ±1.5), with scores ranging from 10 to 16. All improvements were statistically significant with P-values less than 0.001, indicating a steady and meaningful recovery in patient responsiveness over time.

Table 1: Full Outline of Unresponsiveness (FOUR) Score Values for Functional Assessment

FOUR score	n	Median±IQR	Minimum	Maximum	P-value
At enrollment	60	10.5±2.3	6	13	<0.001
At 1 week	58	12.5±2.1	8.5	14.5	<0.001
At 4 weeks	56	14.5±1.9	9.5	16	<0.001
At 6 weeks	54	15.0±1.5	10	16	<0.001

Table 2 presents the Disability Rating Score values for functional assessment over time. At enrollment, the median score was 21.0 (IQR ±5.0), with scores ranging from 16 to 27. By 1 week, the median decreased to 18.5 (IQR ±5.2), with a range of 12 to 26. At 4 weeks, the median further declined to 14.5 (IQR ±5.0), with scores between 8 and 23. By 6 weeks, the median score reached 13.5 (IQR ±4.5), ranging from 8 to 22. All changes were statistically significant with P-values less than 0.001, indicating a consistent and significant improvement in functional ability over time.

Table 2: Disability Rating Score Values for Functional Assessment

Disability Rating Score	n	Median±IQR	Minimum	Maximum	P-value
At enrollment	60	21.0±5.0	16	27	<0.001
At 1 week	58	18.5±5.2	12	26	<0.001
At 4 weeks	56	14.5±5.0	8	23	<0.001
At 6 weeks	54	13.5±4.5	8	22	<0.001

Table 3 outlines the Glasgow Outcome Score values for functional assessment across different time points. At enrollment, the median score was 3.0 (IQR ±1.0), with values ranging from 2 to 3. After 1 week, the median remained at 3.0 (IQR ±1.0), though the range extended from 2 to 4. At 4 weeks, the median increased to 3.5 (IQR ±1.0), with scores between 2 and 4. By 6 weeks, the median further improved to 4.0 (IQR ±0.5), ranging from 3 to 5. All changes were statistically significant with P-values less than 0.001, indicating progressive and significant improvement in patient outcomes over the follow-up period.

Table 3: Glasgow Outcome Score Values for Functional Assessment

Glasgow Outcome Score	n	Median±IQR	Minimum	Maximum	P-value
At enrollment	60	3.0±1.0	2	3	<0.001
At 1 week	58	3.0±1.0	2	4	<0.001
At 4 weeks	56	3.5±1.0	2	4	<0.001
At 6 weeks	54	4.0±0.5	3	5	<0.001

Table 4 summarizes the adverse events observed during the study. The most common adverse event was spasticity, affecting 12 participants (20%), followed by agitation in 10 participants (17%). Vomiting and generalized tonic-clonic seizures (GTCS) were each reported in 6 participants (10%), while restlessness and rash occurred in 5 participants each (8%). Focal convulsions and diarrhea were noted in 4 participants each (7%), and elevated liver function tests (LFT) and constipation were seen in 3 participants each (5%). Nausea was the least common, affecting 2 participants (3%).

Table 4: Adverse Events	
Adverse Event	**Affected (%)**
Spasticity	12 (20)
Agitation	10 (17)
Vomiting	6 (10)
GTCS	6 (10)
Restlessness	5 (8)
Rash	5 (8)
Focal convulsions	4 (7)
Elevated LFT	3 (5)
Diarrhea	4 (7)
Constipation	3 (5)
Nausea	2 (3)

Discussion

The observational trial of the effectiveness of amantadine to enhance cognitive recovery in adults with severe traumatic brain injury had progressive enhancement of functional outcomes at six weeks, as measured by the Full Outline of Unresponsiveness (FOUR) score, Disability Rating Score (DRS), and Glasgow Outcome Score (GOS), with all statistically significant differences ($p < 0.001$) at all time points.

Our own observation of a consistent increase in the FOUR score—from median 10.5 at admission to 15.0 at six weeks—correlates with previous reports of enhanced neurological responsiveness among amantadine-treated TBI patients. Improvement in brainstem reflexes and motor function within the first weeks of amantadine treatment has been described in a number of uncontrolled series, with one series reporting increases in the range of 2–3 points on FOUR-like scales by day 28 [4]. Differing from one report of plateau or minimal decline following drug withdrawal, our washout data showed that in spite of reduced rate of recovery, the acquired responsiveness was still evident throughout the two-week posttreatment interval [5]. This lends credence to the hypothesis that, at least within six-week time frame, Amantadine's modulatory influence on dopaminergic circuits may produce more long-lasting changes at the synaptic level than have been recognized.

The downward trend of our group's Disability Rating Score—from a median of 21.0 at baseline to 13.5 at week six—also aligns with the functional recovery shown in earlier observational studies. Giacino et al. had thus earlier reported a median reduction of 5–6 points on DRS at four weeks in amantadine-started patients at an equivalent post-injury interval [4]. But those authors had seen a broad interpatient variability, with some subjects reverting to higher disability scores on withdrawal from amantadine [6]. Our findings, however, show a narrower IQR at week six, indicating that the benefit was not only significant but also fairly consistent across our Indian cohort. This consistency may be an artefact of differences in initial demographics or rehabilitation protocols, but it does address the external validity of amantadine's functional effect.

Our Glasgow Outcome Score improvement—improvement of more than half at "severe disability" (median 3.0) to "moderate disability" or "good recovery" (median 4.0)—is also consistent with earlier reports. Small series have documented changes of at least one GOS category in 40–60% of patients by six to eight weeks of amantadine treatment [7,8],. Interestingly, a few of those series noted a partial return toward baseline values with drug withdrawal, implying a transient pharmacologic effect [9]. In our series, however, the trend continued through the washout, affirming our impression that starting amantadine at two months post-injury may take advantage of an important window for neuroplasticity without risking rebound worsening.

Safety-wise, our patients' adverse event profile—spasticity (20%), agitation (17%), GI complaints (10% vomiting, 7% diarrhea), and seizures (10%)—is consistent with the tolerability data obtained in Parkinson populations. Although generalized tonic-clonic seizures and restlessness were periodically debilitating, life-threatening events and protracted side effects were not experienced, and all side effects were reversible with dose adjustment or discontinuation. This is consistent with the overall amantadine literature, which has very infrequently experienced severe hepatic or cardiac toxicity even at high doses [10]. Our results thus confirm that a 200 mg daily regimen remains within a safe therapeutic range for recovery from severe TBI.

Together, these comparisons highlight that our Indian adult population had comparable improvements in consciousness, disability, and outcome to other populations with the advantage of long-term post-washout improvement. Reproducibility across populations and study designs adds strength to speculation that amantadine's dopaminergic enhancement supports both acute and prolonged recovery trajectories in severe TBI.

Conclusion

In conclusion, findings from this investigation suggest that amantadine may improve cognitive recovery among adults with severe traumatic brain injury. Patients demonstrated steady and significant improvements over a 6-week period reliably measured by FOUR Score, Disability Rating Score, and Glasgow Outcome Score. Statistically, improvements in each of the outcomes was significant at all assessment points and persisted in a pattern representing progressive recovery. Some adverse events were noted, including spasticity, agitation, and gastrointestinal constipation; the observed adverse effects were, however, mostly tolerable and did not impede therapy and treatment benefits. On the basis of the available data, a role for amantadine would appear to be a safe adjunct therapy that may also have significant therapeutic effects in neurorehabilitation following severe TBI.

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