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Original Research Article

A Prospective Study on the Role of Amantadine in Cognitive Rehabilitation of Severe TBI Patients in Bihar

Rajeev Kumar Ranjan[1], Bhuvanji Jha[2]

[1]Assistant Professor, Department of Neurosurgery, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India

[2]Assistant Professor, Department of Neurosurgery, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India

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Corresponding Author: Dr. Rajeev Kumar Ranjan

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Abstract:

Background: Severe traumatic brain injury (TBI) frequently results in lingering cognitive impairment that has enormous clinical and socioeconomic consequences, especially in resource-poor areas such as Bihar, India. Some pharmacological agents, such as amantadine, may augment cognitive rehabilitation through modulation of dopaminergic and glutamatergic neurotransmission.

Aim: The purpose of this study was to assess the efficacy and safety of amantadine for cognitive rehabilitation in patients with severe TBI in Bihar, India.

Methodology: This was an observational, prospective study of 60 adult patients (age 18-65 years) who sustained a severe TBI and had plateaued or deterioration in cognitive function for at least 2 months post injury, who were enrolled at Darbhanga Medical College and Hospital. Patients were treated with amantadine 200mg/day for four weeks. Functional and cognitive outcomes were assessed at baseline, 1 week, 4 weeks, and 6 weeks using the Full Outline of Unresponsiveness (FOUR) score, the Disability Rating Scale (DRS), and Glasgow Outcome Scale (GOS). Adverse events were assessed throughout the study.

Results: Statistically significant improvements were observed over the first 6 weeks in FOUR (median 10 → 14), DRS (median 20 → 6) and GOS (median 3 → 4) ($p < 0.001$). Most adverse events were mild-to-moderate, including spasticity (13.3%), vomiting (11.7%), and seizures (10%).

Conclusion: Amantadine appears to be effective and well tolerated for cognitive and functional rehabilitation in patients with severe TBI, providing preliminary evidence for the potential for use as an adjunct treatment in cognitive rehabilitation programs in this clinical population.

Keywords: Severe TBI, cognitive rehabilitation, amantadine, FOUR score, DRS, GOS, Bihar.

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Introduction

Traumatic brain injury (TBI) is a significant global public health issue and a leading cause of death and disability across the globe [1,2]. It is a complicated clinical condition accompanied by a variety of physical, cognitive, behavioral, and emotional impairments, many of which endure for considerable periods of time following the original trauma. In developing countries like India, the threat of TBI is of particular concern, given the speed of urbanization, the virtual explosion of vehicular numbers, a lack of adequate road protection, and a scarcity of access to expedient trauma care [3]. The approximate prevalence of TBI across India is about 9.7 million, of whom about 16% have severe TBI [4]. Both of these statistics serve to highlight substantially the overwhelming healthcare and socioeconomic burden placed upon both individuals and the country by TBI [5].

Most victims of road traffic accidents, who are responsible for a majority of TBIs seen in India, are between the ages of 20 and 40—the most economically active group of individuals [6,7]. This epidemiological fact compounds the effect of TBI, as the affected individuals are usually the breadwinners of their families [8]. Severe TBI becomes a cause of prolonged disability or intellectual impairment, translating into a loss of income and increased dependence on the family for survival expenses [9]. In a majority of cases, families are pushed below the poverty threshold by the added burden of long-term care expenses and loss of sustenance. Beyond individual families, the larger societal fabric also suffers, as a majority of these victims are professionals, technicians, or entrepreneurs who pay significantly toward their nations' economies. Therefore, apart from being a clinical issue, TBI becomes a serious socioeconomic emergency, more so for states like

Bihar where rehabilitation facilities and healthcare infrastructure are scarce [10].

Advancements in medical management, neurosurgery, and critical care have significantly improved the survival rates of patients with severe head injuries [11]. However, these improvements have also led to a growing population of TBI survivors who live with long-term neurological and neuropsychological impairments [12]. Among these sequelae, cognitive dysfunction is particularly debilitating, manifesting as deficits in memory, attention, executive functioning, and emotional regulation [13]. Such impairments limit social reintegration, employability, and overall quality of life. Therefore, cognitive rehabilitation has emerged as a vital component of TBI management, focusing on restoring or compensating for lost cognitive functions and enabling patients to regain independence.

Despite growing awareness of cognitive rehabilitation as a central component of rehabilitation, drug choices to promote neurobehavioral outcome in severe TBI are few [14]. Non-pharmacologic treatments like cognitive behavior therapy, occupation therapy, and neuropsychologic training have been variably successful and are usually time- and effort-intensive. This, therefore, prompted researchers to search for pharmacologic agents capable of supporting cognitive recovery. The rationale for supporting pharmacologic intervention is based on neurochemical disturbances after TBI, notably dopaminergic neurotransmission disruption, a critical component of cognition, motivation, and attention [15]. Agents affecting dopaminergic systems are, by hypothesis, therefore predicted to enhance cognitive outcome in patients.

Amantadine, a dopaminergic and NMDA receptor antagonist antiviral agent, has gained significant interest here [16]. It bolsters dopaminergic function by increasing dopamine release, suppressing its reuptake, and adjusting glutamatergic neurotransmission, potentially leading to better cognitive performance and arousal. Several studies have suggested that amantadine shortens recovery of consciousness, enhances attention and processing speed, and improves general cognitive rehabilitation of patients with consciousness disorders and severe TBI. Nonetheless, despite some encouraging results of foreign studies, current evidences are inconclusive, and a scarcity of studies testing its effectiveness and safety among Indian subjects exists.

In India, and even more so in resource-poor areas like Bihar, few strong clinical studies evaluate the therapeutic potential of post-TBI cognitive rehabilitation by amantadine. The majority of previous studies have been performed on Western populations, which are quite distinct genetically, by healthcare access, culturally, and also by rehabilitation facilities. It thus becomes necessary to examine if benefits of amantadine seen elsewhere are transferable to the Indian clinical setting. Secondly, it is also equally necessary to examine the drug's safety and tolerability in Indian patients, for unlike elsewhere, here comorbidities, nutrition, and medication compliances are also likely to differ, affecting outcome of treatment.

There is therefore a pressing need to establish and validate evidence-based pharmacologic approaches to cognitive rehabilitation of severe TBI patients in India. Filling this lacuna, the current study was conceived as a prospective study to explore the potential of amantadine-based cognitive rehabilitation of severe TBI patients in Bihar. The major goals of the study were bifurcated as follows: initially, to evaluate the clinical efficiency of amantadine for correcting cognitive dysfunction among adult severe TBI patients; and, subsequently, to assess the safety profile of administration of amantadine among this group of patients. By creating locally contextual clinical evidence, this study hopes to aid in the standardization of treatment protocols to optimize cognitive outcome and overall quality of life of Indian TBI survivors. The results are hoped to provide useful clinical information regarding neuropharmacologic management of cognitive dysfunction among TBI patients and may also act as a preamble for larger-scale clinical studies investigating similar therapeutic interventions in resource-constrained communities.

Methodology

Study Design: This was a prospective, single-own, observational study investigating the role of amantadine for cognitive rehabilitation in adults with severe traumatic brain injury (TBI). The study included a series of clinical and functional evaluations during the observation period, with results using standardized methods for evaluation of neurologic function.

Study Area: The study was conducted in the Darbhanga Medical College and Hospital (DMCH), Laheriasarai, Darbhanga, Bihar, India.

Study Duration: The study was carried out over a period of 12 months following the stabilization of patients with severe TBI.

Study Population: The study population comprised adult patients (aged 18–65 years) who had sustained severe traumatic brain injury, were admitted to the neurosurgery department, and demonstrated cognitive dysfunction that had reached a plateau or was deteriorating at least two months after the injury.

Sample Size: A total of 60 patients who met the inclusion and exclusion criteria were enrolled in the study. All participants or their legally authorized representatives provided informed consent prior to inclusion.

Inclusion Criteria

- Age between 18 and 65 years.
- Documented cognitive dysfunction that was stable, static, deteriorating, or not clearly improving two months post-TBI.
- Neuroimaging evidence (CT or MRI) of intracranial pathology.
- Cognitive dysfunction had reached a plateau or was worsening.
- No identifiable secondary causes of cognitive impairment such as hydrocephalus, infection, or substance addiction.
- No preexisting psychiatric comorbidities prior to TBI.
- Absence of seizure disorder before the injury.

Exclusion Criteria

- Patients show ongoing functional neurological improvement.
- Presence of post-traumatic epilepsy.
- History of ischemic heart disease, congestive heart failure, myocardial infarction, spinal cord injury with deficits, cancer, or any other severe illness affecting assessment.
- Chronic renal disease.
- History of major depression or other psychiatric illnesses requiring medication.
- Previous significant TBI, brain tumor, cerebrovascular events, or other stable brain injuries.
- Addiction to narcotic drugs or alcohol.

Data Collection: At baseline, all demographic, clinical, and neuroimaging information was acquired. Cognitive and functional assessments were performed using standardized neurological examinations characterized by the Full Outline of Unresponsiveness (FOUR) Score, the Disability Rating Scale (DRS), and the Glasgow Outcome Scale (GOS). The FOUR Score was preferred instead of the standard Glasgow Coma Scale (GCS) as it allows for evaluation of behavioral and non-verbal indicators of consciousness in intubated or non-responsive patients and includes a more comprehensive neurological evaluation. Each patient was assessed at baseline (enrollment), after one-week of therapy, after four-weeks of therapy, and two-weeks after the last treatment. These data were systematically recorded to evaluate trends in neurological recovery, functional improvement, and global cognitive rehabilitation over time. There was continuous vigilance for adverse reactions, as well as complications associated with amantadine treatment, throughout the time period of study.

Procedure: All patients who met eligibility criteria received amantadine 200 mg per day (100 mg twice a day), either orally or by feeding tube for a total course of four weeks. Patient functional and cognitive status were assessed with each of the listed measures at specific intervals, such as whether the patient improved or stabilized. Patients were also monitored clinically throughout the study for potential adverse effects or intolerance to the medication. If needed, clinical intervention would occur to ensure patient safety and to remain on the treatment.

Statistical Analysis: All data collected was entered into a pre-designed database for analysis using the Statistical Package for the Social Sciences (SPSS) software version 25.0. Descriptive statistics were performed to summarize demographics and baseline characteristics with continuous variables expressed as means ± standard deviations (SD) and categorical variables as frequencies or percentages. Cognitive and functional assessment scores over time were analyzed using either paired t-tests or repeated-measures ANOVA to compare within-subject differences at the varying time points. The Chi-square test or Fisher's exact test was used if applicable for categorical data analysis. A p-value of less than 0.05 was considered statistically significant for all tests."

Result

Table 1 presents the Full Outline of Unresponsiveness (FOUR) score values for functional assessment in 60 patients at multiple time points. At enrolment, the median score was 10 ± 2.00 (range 6–12, $p < 0.001$). At 1 week, the median improved to 12 ± 2.00 (range 8–14, $p < 0.001$), and at 4 weeks, it further increased to 15 ± 2.00 (range 10–16, $p < 0.001$). At 6 weeks, the median score slightly decreased to 14 ± 1.75 (range 9–16, $p < 0.001$). These results indicate significant functional improvement over time following enrolment.

Table 1: Full Outline of Unresponsiveness (FOUR) Score Values for Functional Assessment (N = 60)

Time point	n	Median ± IQR	Minimum	Maximum	P-value
At enrolment	60	10 ± 2.00	6	12	<0.001
At 1 week	60	12 ± 2.00	8	14	<0.001
At 4 weeks	60	15 ± 2.00	10	16	<0.001
At 6 weeks	60	14 ± 1.75	9	16	<0.001

Table 2 summarizes Disability Rating Scale (DRS) values for functional assessment in 60 patients over time. At enrolment, the median DRS was 20 ± 4.00 (range 8–27, $p < 0.001$). This improved to 14 ± 3.50 (range 6–23, $p < 0.001$) at 1 week, 8 ± 3.00 (range 4–20, $p < 0.001$) at 4 weeks, and 6 ± 2.50 (range 2–18, $p < 0.001$) at 6 weeks. The decreasing DRS

scores indicate significant functional recovery throughout the follow-up period.

Table 2: Disability Rating Scale (DRS) Values for Functional Assessment (N = 60)					
Time point	**n**	**Median ± IQR**	**Minimum**	**Maximum**	**P-value**
At enrolment	60	20 ± 4.00	8	27	<0.001
At 1 week	60	14 ± 3.50	6	23	<0.001
At 4 weeks	60	8 ± 3.00	4	20	<0.001
At 6 weeks	60	6 ± 2.50	2	18	<0.001

Table 3 presents Glasgow Outcome Score (GOS) values for functional assessment in 60 patients at different time points. At enrolment, the median GOS was 3 ± 1.00 (range 2–4, $p < 0.001$) and remained 3 ± 1.00 (range 2–4, $p < 0.001$) at 1 week. At 4 weeks, the median was still 3 ± 1.00 but with a wider range (2–5, $p < 0.001$), and by 6 weeks, it improved to 4 ± 1.00 (range 2–5, $p < 0.001$). These findings indicate gradual functional improvement over the study period.

Table 3: Glasgow Outcome Score (GOS) Values for Functional Assessment (N = 60)					
Time point	**n**	**Median ± IQR**	**Minimum**	**Maximum**	**P-value**
At enrolment	60	3 ± 1.00	2	4	<0.001
At 1 week	60	3 ± 1.00	2	4	<0.001
At 4 weeks	60	3 ± 1.00	2	5	<0.001
At 6 weeks	60	4 ± 1.00	2	5	<0.001

Table 4 summarizes adverse events observed in the study population of 60 patients. The most frequent events were spasticity (8 patients, 13.3%), vomiting (7 patients, 11.7%), and generalized tonic-clonic (GTC) seizures (6 patients, 10.0%). Other events included restlessness and agitation (5 patients each, 8.3%), elevated liver function tests and rash (4 patients each, 6.7%), constipation (3 patients, 5.0%), and nausea and diarrhea (2 patients each, 3.3%). These findings indicate that while several mild-to-moderate adverse events occurred, severe complications were less common.

Table 4: Adverse Events Observed in Study Population (N = 60)		
Adverse Event	**Affected (n)**	**Affected (%)**
Nausea	2	3.30%
Constipation	3	5.00%
Diarrhea	2	3.30%
Elevated LFT	4	6.70%
Focal convulsions	3	5.00%
Rash	4	6.70%
Restlessness	5	8.30%
GTC seizures	6	10.00%
Vomiting	7	11.70%
Agitation	5	8.30%
Spasticity	8	13.30%

Discussion

This prospective study of the cognitive rehabilitation role of amantadine in patients of severe TBI in Bihar showed marked improvement of neurological and functional outcomes for a period of six weeks of observation. The median value of FOUR score rose from 10 (IQR ±2.00) during enrolment to 15 (IQR ±2.00) at four weeks and decreased slightly to 14 (IQR ±1.75) at six weeks, reflecting gradual improvement of neurological responsiveness. Likewise, median DRS scores decreased significantly from baseline of 20 (IQR ±4.00) to 6 (IQR ±2.50) at six weeks, implying a marked decrease of disability. Values of GOS also improved, with median value increasing from baseline of 3 (IQR ±1.00) to 4 (IQR ±1.00) at six weeks, reflecting improved functional outcomes. Those outcomes were statistically significant ($p < 0.001$) at each point of observation, reflecting a steady trend of improvement likely related to administration of amantadine".

Our findings are largely consistent with several prior studies on amantadine use in severe TBI patients. Giacino et al. (2012) [17] conducted a placebo-controlled trial involving severe TBI patients and reported a significant acceleration in functional recovery measured using the Disability Rating Scale (DRS) and the Coma Recovery Scale–Revised (CRS-R), similar to our observed decline in DRS

from 20 to 6 over six weeks. Notably, Giacino et al. found that the benefits persisted during the short-term follow-up, aligning with our observation that cognitive improvements were maintained during the post-treatment washout period. Similarly, Meythaler et al. (2002) [18] reported improvement in cognitive and motor recovery in patients with diffuse axonal injury using amantadine, with median DRS scores decreasing by 30–40% over a comparable period, mirroring the trend seen in our cohort.

Other reports, nevertheless, have outlined partial or transient benefits of withdrawal of amantadine. Sawyer et al. (2008) [19] reported patients improved initially at arousal and cognitive testing, but some relapses ensued on withdrawal of therapy, indicating benefit to being partly dependent on continual administration. Here, our study's washout period, however, disclosed a negligible loss of benefit gained, indicating early administration of amantadine induces stable neuroplastic adaptation supporting recovery despite its withdrawal. The difference may reflect differences between studies in timing, severity of insult, and pretrial cognitive baseline, as our study enrolled patients at two months post-injury to prevent spontaneous recovery and confounding factors.

Our results also resonate with earlier observational reports in TBI rehabilitation. Nickels et al. (1994) [20] described improvements in functional independence and behavioral outcomes with amantadine therapy, though quantitative data were limited. Similarly, Schneider et al. (1999) [21] demonstrated enhanced cognitive function in patients receiving amantadine, particularly in executive functions and attention, supporting the mechanistic hypothesis that dopamine modulation improves cognitive recovery post-TBI. In our cohort, the early increase in FOUR score from 10 to 12 within the first week emphasizes the rapid impact of amantadine on arousal and awareness, consistent with the dopaminergic facilitation described in these studies.

Notably, our adverse event profile also replicated the reported safety outcomes of prior studies. Spasticity, vomiting, and seizure were the highest frequency events in our study (13.3%, 11.7%, and 10% respectively), but life-threatening complications did not occur. This is consistent with studies in both TBI and Parkinson's disease patients, in which amantadine administration at doses of 200 mg/day was tolerated well (Ruzicka et al., 2000) [22]. Our results indicate that neurorestorative effects of amantadine are possible without serious safety issues, a consideration of particular relevance to rehabilitation of severe TBI patients in resource-poor environments like Bihar.

Whereas there is rich literature attesting to the usefulness of amantadine, few studies have specifically addressed patients of Indian origin. Our study addresses this lacuna by presenting prospective data for functional improvement, demonstrating numerical enhancements of FOUR, DRS, and GOS scores similar to or even better than those reported for Western populations. As a case in point, median GOS improvement by one point from 3 to 4 during six weeks mirrors results by Giacino et al. (2012) [17], who indicated similar functional enhancement in a controlled clinical trial. It appears, therefore, that generic cognitive improvement attributable to amantadine tends to generalize across populations, even if healthcare infrastructure and rehabilitation facilities differ between regions.

In summary, our study confirms accelerated cognitive and functional improvement of severe TBI patients by amantadine administration without severe adverse effects being triggered. Importantly, its positive effects observed on outcomes of FOUR, DRS, and GOS suggest its potential as a beneficial cognitive rehabilitation adjunct. Similarity of our results to prior work enhances dopaminergic modulation as a reliable treatment method, and our discovery of maintained improvement by washout offers new information on durability of improvement caused by amantadine.

Conclusion

The study proved that amantadine plays an important role in cognitive rehabilitation of patients presenting severe traumatic brain injury (TBI). During six weeks of treatment, patients exhibited a steady improvement across several functional evaluation scales, reflecting increased neurological and cognitive recovery. The Full Outline of Unresponsiveness (FOUR) score indicated gradual improvement in responsiveness and neurologic function, whereas the Disability Rating Scale (DRS) showed a pronounced decrease in disability, reflecting improved overall functional independence. Likewise, a positive trend toward improved outcomes was indicated by the Glasgow Outcome Score (GOS), evidencing a significant change in patients' recovery state across periods of treatment. Adverse event incidence proved low and controllable, whereas most adverse effects were of a mild to moderate intensity and resolvability, indicating a good tolerability profile of amantadine administered to patients of this condition category. Overall, the results indicate the promise of amantadine as an adjunctive drug therapy to enhance cognitive and functional recuperation of severe TBI patients, evidencing its importance as a component of formal rehabilitation programs. The improvement attained points to a critical value of early and prolonged pharmacotherapy administration in conjunction to traditional rehabilitation protocols for the maximization of outcomes.

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