e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2023; 13(10); 369-373

Original Research Article

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

Dhiraj Kumar[1], Mukesh Kumar[2], Anil Kumar Peethambaran[3]

[1]Senior Resident, Department of Neurosurgery, Medical College Trivandrum Thiruvananthapuram, Kerala, India

[2]Senior Resident, Department of Neurosurgery, Medical College Trivandrum Thiruvananthapuram, Kerala, India

[3]HOD, Department of Neurosurgery, Medical College Trivandrum Thiruvananthapuram, Kerala, India

Received: 10-08-2023 / Revised: 15-09-2023 / Accepted: 25-10-2023
Corresponding Author: Dr. Dhiraj Kumar
Conflict of interest: Nil

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 in the Department of Neurosurgery, Medical College Trivandrum Thiruvananthapuram, Kerala, India from August 2016 to August 2017. 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, diarrhea, 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 and its attending alterations of central functional and chemical imbalances lead to region-selective modifications of pro-inflammatory processes and neurotransmitter changes that underpin the cognitive and neuro-behavioural consequences of the injury. The acute phase of recovery from severe TBI is characterized by a brief period of hyperexcitability followed by a longer period of hypo-excitability resulting from the depletion of multiple neurotransmitters one of which is dopamine (DA). [1] Amantadine has the capacity to promote dopaminergic activity via multiple mechanisms including the facilitation of the synaptic release of DA together with the blockade of DA re-uptake. Furthermore, amantadine has the capacity to stimulate the enzyme L-Dopa decarboxylase (DDC) resulting in increased DA synthesis, a process that is functionally-related to the antagonism of NMDA receptors. Stimulation of DDC activity secondary to NMDA receptor antagonism has been demonstrated in humans by the technique of Positron Emission Tomography (PET). [2] Moreover, PET studies in TBI patients lend credence to the notion that amantadine has the potential to improve CNS function via actions on the dopaminergic system that include significant improvements in prefrontal energy metabolism and function indicated by increased F18-deoxyglucose-PET with concomitant increases in dopamine-D2 receptor availability. [3]

Traumatic brain injury is a broad term that encompasses concussion, closed head injury, and blast-induced traumatic injury, which can cause different levels of neurological and chemical imbalances in the brain, leading to temporary or permanent disability. The external force that causes injury propels the brain to move rapidly inside the skull, resulting in damage to the gray matter and

the cerebrovasculature. [4] The ensuing inflammatory process can last a few hours to days after the initial injury and causes neurological deficits with neurochemical imbalances developing hours after the brain injury because of nerve cell damage. This creates a disproportionate amount of glutamate receptors, free radicals, and intracellular calcium production, causing detrimental changes in ion homeostasis. [5]

Amantadine hydrochloride is an FDA-approved medication for the treatment of dyskinesia in Parkinson's disease9 and influenza prophylaxis. [6] 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. [7] 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 [8,9], the effect of amantadine in treating cognitive deficits after TBI remains controversial.

Kraus and colleagues [10] 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 [11] 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 in the Department of Neurosurgery, Medical College Trivandrum Thiruvananthapuram, Kerala, India from August 2016 to August 2017. 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
Constipation	3
Diarrhea	5
Elevated LFT	5
Focal convulsions	5
Rash	7
Restlessness	6
GTCS	8
Vomiting	11
Agitation	12
Spasticity	15

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. [12] The estimated prevalence of patients with TBI in India is 9.7 million, and approximately 16% sustain severe TBI. [13] 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. [14]

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. [15-19]

On contrary to the obtained results and that previously documented in literature, Hammond et al [20] reported non-significant differences on cognitive functions between amantadine and placebo. However, Hammond's study20 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 [20] 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 [21] 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. 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 [22], 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.

References

1. Giacino JT, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, Eifert B, Long D, Katz DI, Cho S, Yablon SA. Placebo-controlled trial of amantadine for severe traumatic brain injury. New England Journal of Medicine. 2012 Mar 1;366(9):819-26.
2. Deep P, Dagher A, Sadikot A, Gjedde A, Cumming P. Stimulation of dopa decarboxylase activity in striatum of healthy human brain secondary to NMDA receptor antagonism with a low dose of amantadine. Synapse. 1999 Dec 15;34(4):313-8.
3. Kraus MF, Smith GS, Butters M, Donnell AJ, Dixon E, Yilong C, Marion D. Effects of the dopaminergic agent and NMDA receptor antagonist amantadine on cognitive function, cerebral glucose metabolism and D2 receptor availability in chronic traumatic brain injury: a study using positron emission tomography (PET). Brain Injury. 2005 Jul 1;19(7):471-9.
4. Rabinowitz AR, Levin HS. Cognitive sequelae of traumatic brain injury. Psychiatric Clinics. 2014 Mar 1;37(1):1-1.
5. Wheaton P, Mathias JL, Vink R. Impact of early pharmacological treatment on cognitive and behavioral outcome after traumatic brain injury in adults: a meta-analysis. Journal of clinical psychopharmacology. 2009 Oct 1;29 (5):468-77.
6. Elkurd MT, Bahroo LB, Pahwa R. The role of extended-release amantadine for the treatment of dyskinesia in Parkinson's disease patients. Neurodegenerative disease management. 2018 Apr;8(2):73-80.
7. Galvão MG, Santos MA, da Cunha AJ. Amantadine and rimantadine for influenza A in children and the elderly. Cochrane Database of Systematic Reviews. 2014(11).
8. Kornhuber J, Weller M. Psychotogenicity and N-methyl-D-aspartate receptor antagonism: implications for neuroprotective pharmacotherapy. Biological psychiatry. 1997 Jan 15; 41(2):135-44.
9. Wang T, Huang XJ, Van KC, Went GT, Nguyen JT, Lyeth BG. Amantadine improves cognitive outcome and increases neuronal survival after fluid percussion traumatic brain injury in rats. Journal of neurotrauma. 2014 Feb 15;31 (4):370-7.
10. Giacino, J.T., Katz, D.I., Schiff, N.D., Whyte, J., Ashman, E.J., Ashwal, S., Barbano, R., Hammond, F.M., Laureys, S., Ling, G.S. and Nakase-Richardson, R., 2018. Practice guideline update recommendations summary: disorders of consciousness: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. Archives of physical medicine and rehabilitation, 99(9), pp.1699-1709.
11. Kraus MF, Smith GS, Butters M, Donnell AJ, Dixon E, Yilong C, Marion D. Effects of the dopaminergic agent and NMDA receptor antagonist amantadine on cognitive function, cerebral glucose metabolism and D2 receptor availability in chronic traumatic brain injury: a study using positron emission tomography (PET). Brain Injury. 2005 Jul 1;19(7):471-9.

12. Reddy CC, Collins M, Lovell M, Kontos AP. Efficacy of amantadine treatment on symptoms and neurocognitive performance among adolescents following sports-related concussion. The Journal of head trauma rehabilitation. 201 3 Jul 1;28(4):260-5.
13. Ghajar J. Traumatic brain injury. The Lancet. 2000 Sep 9;356(9233):923-9.
14. Gururaj G. Epidemiology of traumatic brain injuries: Indian scenario. Neurological research. 2002 Jan 1;24(1):24-8.
15. Karli DC, Burke DT, Kim HI, Calvanio R, Fitzpatrick M, Temple D, Macneil M, Pesez K, Lepak P. Case study: effects of dopaminergic combination therapy for frontal lobe dysfunction in traumatic brain injury rehabilitation. Brain Injury. 1999 Jan 1;13(1):63-8.
16. Giacino JT, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, Eifert B, Long D, Katz DI, Cho S, Yablon SA. Placebo-controlled trial of amantadine for severe traumatic brain injury. New England Journal of Medicine. 2012 Mar 1;366(9):819-26.
17. Schneider, Jessie Drew-Cates, Tony M. Wong, Mary L. Dombovy WN. Cognitive and behavioural efficacy of amantadine in acute traumatic brain injury: an initial double-blind placebo-controlled study. Brain Injury. 1999 Jan 1;13 (11):863-72.
18. Meythaler JM, Brunner RC, Johnson A, Novack TA. Amantadine to improve neurorecovery in traumatic brain injury–associated diffuse axonal injury: a pilot double-blind randomized trial. The Journal of head trauma rehabilitation. 2002 Aug 1;17(4):300-13.
19. Nickels JL, Schneider WN, Dombovy ML, Wong TM. Clinical use of amantadine in brain injury rehabilitation. Brain Injury. 1994 Jan 1; 8(8):709-18.
20. Hammond FM, Sherer M, Malec JF, Zafonte RD, Dikmen S, Bogner J, Bell KR, Barber J, Temkin N. Amantadine did not positively impact cognition in chronic traumatic brain injury: a multi-site, randomized, controlled trial. Journal of neurotrauma. 2018 Oct 1;35(19): 22 98-305.
21. Tan L, Ge H, Tang J, Fu C, Duanmu W, Chen Y, Hu R, Sui J, Liu X, Feng H. Amantadine preserves dopamine level and attenuates depression-like behavior induced by traumatic brain injury in rats. Behavioural brain research. 2015 Feb 15; 279:274-82.
22. Schneider, Jessie Drew-Cates, Tony M. Wong, Mary L. Dombovy WN. Cognitive and behavioural efficacy of amantadine in acute traumatic brain injury: an initial double-blind placebo-controlled study. Brain Injury. 1999 Jan 1;13 (11):863-72.