Archives of Anesthesiology and Critical Care (Autumn 2023); 9(Supplement 2): 516-521.

Available online at http://aacc.tums.ac.ir

Research Article

The Effectiveness of Amantadine in Improving Consciousness in Patients with Acute Brain Injury

Alireza Rahat Dahmardeh[1], Aliakbar Keykha[2,3], Mehdi Rezvani Amin[2,3], Masoum Khoshfetrat[4]*

[1]*Department of Anesthesiology and Critical Care, School of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran.*

[2]*Community Nursing Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.*

[3]*Department of Medical-Surgical Nursing, School of Nursing and Midwifery Zahedan University of Medical Sciences, Zahedan, Iran.*

[4]*Department of Anesthesiology and Critical Care, Khatam-Al-Anbiya Hospital, Zahedan University of Medical Sciences, Zahedan, Iran.*

ARTICLE INFO

Article history:
Received 11 December 2022
Revised 03 January 2023
Accepted 17 January 2023

Keywords:
Acute brain injury;
Glasgow coma scale;
Amantadine;
Impaired consciousness level

ABSTRACT

Background: The improved consciousness level reflects the patient's recovery following acute brain injury. The medications that can regulate neurotransmitter levels, neural synaptic plasticity, and functional connectivity of consciousness networks might play a crucial role in improving the consciousness status of the patients. Thus, this study aims to evaluate the effectiveness of amantadine in improving consciousness in acute brain injury patients.

Methods: The present quasi-experimental study was performed from 2021 to 2022 after obtaining the necessary permissions from Zahedan University of Medical Sciences, Iran. Eighty patients with acute brain injury who met the study inclusion criteria were recruited and randomized into amantadine and placebo groups. The amantadine group was given a daily dose of 100 mg amantadine tablets, while the placebo group received a gavage of amantadine-like placebo tablets twice daily for 14 days. The consciousness level of patients was measured daily until the outcome (ICU discharge or expiration) was established. Eventually, a comparative data analysis was conducted to determine amantadine's efficacy in enhancing consciousness, reducing mechanical ventilation time, and improving patient outcomes.

Results: The mean GCS score in the amantadine group was 5.5±1.4 on admission and 11.9±3.7 at the end of the study, compared to 6.6±1.5 on admission and 11.8±3 at the end of the study, for the placebo group (p=0.154 and p=0.211, respectively). The mean duration of mechanical was 28.87±11.34 days in the amantadine group and 24.13±14.93 days in the placebo group (P=0.329). Twenty-four patients in the amantadine group were discharged from ICU, and 16 were expired. For the placebo group, 21 patients were discharged from ICU, while 16 were expired (p=0.221). No statistically significant difference was found in any of the measured variables between the two groups.

Conclusion: The results demonstrate that amantadine administration had no statistically significant impact on improving consciousness status and clinical outcomes and reducing mechanical ventilation time in acute brain injury patients.

The authors declare no conflicts of interest.

*Corresponding author.
E-mail address: drkhoshfetrat@yahoo.com

Introduction

Impaired consciousness is one of the main symptoms in patients with acute brain injury. Hence, consciousness restoration is one of the key goals of care and treatment in these patients and has a huge effect on deciding the treatment process [1]. Prolonged impaired consciousness contributes to delayed physical and cognitive function recovery because consciousness improvement is the prerequisite of all cognitive and behavioral functions. Thus, any intervention to elevate the consciousness level can improve the clinical outcome of brain injury patients [2]. No effective intervention has been verified to accelerate the recovery of consciousness and functional improvement of patients with brain injury. Neuropharmacological treatments are typically utilized to promote arousal and behavioral reactions, with the hypothesis that they can improve injury-induced disturbances in the dopaminergic and noradrenergic neurotransmitter systems [3]. In recent years, scant studies have highlighted the role of dopaminergic neurotransmitters in improving consciousness levels and regulation of sleep and wakefulness cycles. However, the underlying molecular mechanisms of these processes are yet to be fully understood [4-6]. Amantadine is a pharmacological agent that can lead to analgesic effects, consciousness improvement, functional regulation of the brain's dopaminergic system, and control of motor impairments by increasing brain dopamine levels, particularly in cerebral cortex regions [5, 7-8].

In a study by Hintze et al., amantadine administration did not improve the consciousness level of patients with traumatic brain injury, and further studies were suggested to verify its effects [9]. Conversely, in the study by Giacino et al., patients with traumatic brain injury experienced a significant improvement in consciousness level after receiving a daily dose of 100 mg amantadine for four weeks [3]. In another study by Rühl et al., amantadine treatment improved consciousness in non-traumatic brain injury patients. However, the incidence rate of seizures raised significantly in the group under amantadine treatment. Thus, the authors suggested further research to prove the effectiveness of amantadine in enhancing the consciousness level and determine its adverse effects [10]. Given the inconsistencies in previous studies and suggestions for further studies to verify the beneficial effects of amantadine on improving the consciousness level, the present study aims to evaluate the effectiveness of amantadine in improving the consciousness of acute brain injury patients.

Methods

After obtaining the necessary permissions and the ethical code of IR.ZAUMS.REC.1400.277 from Zahedan University of Medical Sciences, the present quasi-experimental study was performed in its affiliated hospitals between 2021 and 2022. Following previous studies [5] and based on the formulation for the sample size calculation, the sample size of 80 was estimated, considering a type-I error of 0.05 and a power of 80 percent. Based on the study inclusion criteria, 80 patients with acutely impaired consciousness levels were recruited using convenience sampling immediately after admission to the intensive care unit (ICU). The patients were randomly assigned into two amantadine and placebo groups, each of 40 patients. For randomization, given the sample size, eight blocks of 10 cards in either red or blue colors were prepared and placed inside a dark box. After the inclusion of the first patient in the study, one card was taken from the first block. If the card were red, it would be assigned to the amantadine group. Otherwise, it was grouped as a placebo. As sampling continued, the cards were taken from blocks 1 to 8, respectively, until each study group was assigned 40 patients.

The inclusion criteria of the study were patients with acute brain injury who were above 18 years old and had Glasgow Coma Scale (GCS) ≤ 8.

The exclusion criteria included patients with Parkinson's disease, patients with neuropsychiatric disorders, patients under treatment with drugs associated with the brain dopaminergic system (amantadine, Levodopa, Carbidopa, antipsychotics, Bromocriptine, Cabergoline, among others), pregnancy, patients with seizure, abdominal surgery and restrictions for drug gavage, penetrating brain injuries and patient's death before study completion.

After grouping the patients, their initial consciousness level and demographic information were recorded. The amantadine group received a daily dose of 100 mg amantadine tablet (manufactured by Raha Pharmaceutical Co., Iran). Placebo tablets identical to amantadine tablets in shape and size were made of starch paste and rice flour and were given by gavage to the placebo group twice daily for 14 days. One researcher prepared the solutions for gavage by dissolving either amantadine or placebo. Prepared solutions were administered to the patients via gavage by a nurse blinded to the drug type and grouping of the patients. The same nurse measured the consciousness level of patients once a day, two hours after sedation cessation. On day 14, the amantadine and placebo administration was terminated. However, the evaluation of patients continued until their end outcome was established (recovery and ICU discharge or death). Finally, data were analyzed to discern the effect of amantadine on the patients' consciousness level and outcomes.

Statistical analysis

Collected data were analyzed using SPSS software version 27. The demographic variables of patients were compared using descriptive statistics (frequency, mean, and standard deviation). Given that checking data

normality using the Smirnov-Kolmogorov test yielded insignificant results, parametric statistical tests were chosen for data comparison. An independent statistical t-test was applied to compare the two groups regarding mean age, consciousness level scores, mechanical ventilation duration, and length of ICU stay. The gender and outcome comparison of the patients was performed using Chi-square.

Ethical considerations

Before entering the study, the first-degree family members of all patients had been given detailed explanations regarding the study objectives and information confidentiality. Additionally, they were asked to sign informed written consent forms if willing to involve their patients in the study. The data collection form was designed not to include items such as first name and last name in the demographic information section to ensure anonymity. The research plan of this article was approved by the ethics committee of Zahedan University of Medical Sciences under the ethical code of IR.ZAUMS.REC.1400.227. During the course of the study, official correspondence and necessary coordination was established with hospital administrators. All permissions received from the Deputy of Research at Zahedan University were shared with the hospital officials and patients' families to assure them of the procedure's legitimacy and validity.

Results

Of the total of 80 patients examined, 53 (66.25%) patients suffered an acute brain injury and reduced consciousness level due to brain trauma, 18 (22.5%) due to brain ischemia, and 9 (11.25%) due to brain hemorrhage. The amantadine group included 26 (65%) patients with brain trauma, 10 (25%) with ischemia, and 4 (10%) with a brain hemorrhage, while the placebo group had 27 (67.5%) patients with brain trauma, 8 (20%) with ischemia and 5 (12.5%) with a brain hemorrhage. A comparison of patients regarding the cause of acute brain injury revealed no statistically significant difference between the two groups (p=0.310). The mean age of patients was 37.15±9.4 years. 57 (71.3%) patients were male, and 23 (28.8%) were female. The mean age of patients was 37.1±16.7 years in the amantadine group compared to 38.6±16.2 years in the placebo group (p=0.670). There were 28 (70%) men and 12 (30%) women in the amantadine group and 29 (42.15%) men and 11 (27.5%) women in the placebo group. No significant difference was noticed between the two groups regarding age and gender.

The mean GCS score in the amantadine group was 5.5±1.4 on admission and 11.9±3.7 at the end of the study. The same score was obtained as 6.6±1.5 and 11.8±3 on admission and after 14 days in the placebo group. The difference between admission and final GCS scores of patients was 6.4±3.9 in the amantadine group and 5.2±2.8 in the placebo group. The independent t-test found no significant difference in any of the variables between the two groups (Table 1).

The mean difference of GCS score in traumatic, ischemic, and hemorrhagic patients was 7.1±3.1, 5.7±4.3, and 5.3±3.2, respectively, in the amantadine group and 5.2±8.4, 5.1±3.7 and 4.1±2.0, respectively, in the placebo group. Additionally, an independent t-test analysis provided no significant difference between the groups (p=0.098, p=0.594, and p=0.682, respectively) (Table 2).

The mean duration of mechanical ventilation was 28.87±11.34 days in the amantadine group and 24.13±14.93 days in the placebo group. The independent t-test displayed no statistically significant difference in ventilation duration between the two groups (p=0.329). The mean hospitalization duration was 35.75±17.38 and 33.96±18.29 days in the amantadine and placebo groups, respectively. Based on the independent t-test results, no significant difference was observed between the two groups regarding the hospital stay duration (p=0.123). Of 40 patients in the amantadine group, 24 were discharged from ICU, and 16 were expired. The number of discharged and expired patients in the placebo group was 21 and 16, respectively. The chi-square results established no statistically significant difference in the final clinical outcome of acute brain injury patients between the two groups (p=0.88). The mean GCS score on admission was 5.84±1.01 in discharged patients and 6.11±1.98 in expired patients. Given the t-test results, the difference in GCS scores between discharged and expired patients was statistically insignificant (p=0.221). However, despite the lower mean GCS scores on admission in discharged patients, the initial consciousness score was not a determinant of the end outcome in these patients.

Table 1- A comparison of the mean and standard deviation of admission and final GCS scores of patients between the two groups.

Variable	Group		P value
	Amantadine	Placebo	
Mean GCS score on admission	5.5±1.4	6.6±1.5	0.154
Mean final GCS score	11.9±3.7	11.8±3	0.211
The mean difference between admission and final GCS scores	6.4±3.9	5.2±2.8	0.130

Table 2- A comparison of differences in consciousness level score of patients based on the causative mechanism of acute brain injury.

Variable	Group Amantadine	Placebo	P value
The mean difference in GCS score in traumatic patients	7.3±1.1	8.4±5.2	0.098
The mean difference in GCS score in ischemic patients	5.4±7.3	5.1±3.7	0.594
The mean difference in GCS score in hemorrhagic patients	3.5±2.3	2.4±0.1	0.682

Discussion

The study results suggest that amantadine administration has no impact on consciousness improvement, mechanical ventilation time reduction, and end outcomes of patients with acute brain injury. Contrary to the results of this study, Rühl et al. demonstrated that amantadine treatment improved the consciousness level in patients with non-traumatic brain injury. However, their reported result is not reliable per se because they measured the consciousness level of patients only on days 5 and 10 after giving amantadine and placebo, which is insufficient to make conclusions on the effectiveness of this medication for restoring the consciousness level of patients. In addition, changes related to the course of the disease may result in altered consciousness in patients. In contrast to the Rühl et al. study, the patients in the present study were evaluated until the end outcome was determined. Our results indicated the trivial effect of amantadine in improving patients' level of consciousness and end outcomes [10]. Inconsistent with these results, some previous studies have reported that amantadine can lead to neural excitation and consciousness improvement by increasing brain metabolism in the frontoparietal network [11-13]. Although most patients in our study had traumatic brain injuries, we failed to notice any tangible improvement in patients' consciousness after amantadine administration compared to the placebo group. Results from the present study contrasted with those of Meythaler et al., who suggested that daily administration of 200 mg amantadine in traumatic brain injury (TBI) patients with diffuse axonal injury (DAI) improved patients' consciousness state, mental status, function, and outcome. However, the two studies differed in treatment duration. In our study, patients received amantadine treatment only for 14 days, while in the mentioned study, the patients underwent crossover treatment with amantadine and placebo for a 12-week period which can justify the discrepancy in results [14].

Consistent with the findings of this study, Schneider et al. treated ten brain injury patients in the rehabilitation phase with amantadine and placebo in a crossover manner following a washout period for two weeks. They then assessed the neuropsychological outcomes of patients, including orientation, attention, executive function, memory, and behavior. The authors concluded that despite the general improvement in patients, amantadine did not affect functional and cognitive improvement in patients compared to placebo [15]. One study confirmed that although the administration of 100 mg amantadine twice daily can slightly improve the neuropsychological status of people, sufficient evidence is lacking to verify the efficacy of this agent in reducing cerebral irritability [16]. Another study highlighted that despite a slight improvement in the consciousness state of traumatic brain injury patients after amantadine treatment, the administration of this medication could not improve the coma status in these patients [2].

Despite its advances, modern science fails to provide definitive treatment for disorders of consciousness, including the coma state, vegetative state, and minimally conscious state. Structural or functional brain injuries impair neural circuits (ascending reticular activating system and thalamocortical loops) responsible for preserving the wakefulness state and awareness and lead to alterations in the concentration of neurotransmitters. It is hypothesized that pharmacological agents that can regulate the neurotransmitter levels and, consequently, the neural synaptic plasticity and functional connectivity of consciousness networks might play a significant role as beneficial drugs in improving the consciousness state. Thus, studying the effectiveness of pharmacological agents acting on the gamma amino butyric acid (GABA) and dopaminergic systems in improving the patients' consciousness has grabbed the attention of researchers [17]. GABA inhibitors can control the high levels of glutamate, which cause excessive stimulation of brain receptors and induce a cascade of stimulatory mechanisms leading to apoptosis of brain cells due to intracellular invasion of calcium [18-19].

Moreover, structural or functional brain injury leads to deranged levels of acetylcholine and monoamines, such as dopamine, norepinephrine, and serotonin, which regulate the awareness and wakefulness states in the brain [17-18]. Dopamine plays a major role in regulating the wakefulness state, behavior, mood, language, cognition, and motor control [20]. Acute brain injury disrupts dopamine transmission, particularly via D2 receptors. Thus, the inhibition of dopaminergic transmission may be accompanied by neural dysfunction [21-22]. At the presynaptic level, amantadine acts by inhibiting the uptake of dopamine, and at the post-synaptic level by increasing the number of dopamine receptors and changing their structure [23-24]. Although some studies

have underlined the effectiveness of amantadine in patients in a vegetative state and minimally conscious state [25-26], these findings have failed to provide sufficient scientific justification for the general application of this drug in treating patients with reduced consciousness levels [17].

Conclusion

Amantadine administration displayed no significant impact on consciousness improvement, mechanical ventilation time reduction, and outcomes in acute brain injury patients. Thus, the regular application of this drug in the ICU setting to enhance the consciousness level of patients is not recommended. Further clinical trials with large sample sizes are suggested to verify the positive effects of this drug.

Acknowledgments

This article was derived from a research plan approved by the Deputy of Research, Zahedan University of Medical Sciences, with the tracking number 2593. The authors express their sincere gratitude to the respectful personnel of the Deputy of Research and Technology and the ICU staff of hospitals of Zahedan University of Medical Sciences for their cooperation and support in performing this study and collecting data.

Author contributions

Alireza Rahat Dahmardeh: developing the research proposal, supervising the study, collecting data, and revising the manuscript.

Masoum Khoshfetrat: developing the research proposal, executing the research, collecting data, and revising the manuscript.

Mehdi Rezvani Amin: collaboration in executing the research plan and editing the article.

Aliakbar Keykha: collaboration in research, data analysis, and manuscript drafting.

References

[1] Alkhachroum A, Eliseyev A, Der-Nigoghossian CA, Rubinos C, Kromm JA, Mathews E, et al. EEG to detect early recovery of consciousness in amantadine-treated acute brain injury patients. J. Neurol. Neurosurg. Psychiatry. 2020; 91(6):675.

[2] McMahon MA, Vargus-Adams JN, Michaud LJ, Bean J. Effects of amantadine in children with impaired consciousness caused by acquired brain injury: a pilot study. Am J Phys Med Rehabil. 2009; 88(7):525-32

[3] Giacino JT, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med. 2012; 366(9):819-26.

[4] Taylor Norman E, Chemali Jessica J, Brown Emery N, Solt K. Activation of D1 Dopamine Receptors Induces Emergence from Isoflurane General Anesthesia. Anesthesiology. 2013; 118(1):30-9.

[5] Abbasivash R, Valizade Hasanloei MA, Kazempour A, Mahdkhah A, Shaaf Ghoreishi MM, Akhavan Masoumi G. The Effect of Oral Administration of Amantadine on Neurological Outcome of Patients With Diffuse Axonal Injury in ICU. J Exp Neurosci. 2019; 13:1179069518824851.

[6] Lu J, Jhou TC, Saper CB. Identification of wake-active dopaminergic neurons in the ventral periaqueductal gray matter. J Neurosci. 2006; 26(1):193-202

[7] Peeters M, Page G, Maloteaux J-M, Hermans E. Hypersensitivity of dopamine transmission in the rat striatum after treatment with the NMDA receptor antagonist amantadine. Brain Res. 2002; 949(1):32-41.

[8] Monti JM, Monti D. The involvement of dopamine in the modulation of sleep and waking. Sleep Med Rev. 2007; 11(2):113-33

[9] Hintze TD, Small CE, Montgomery J, Reveles KR, Hafeez S, Barthol CA. Comparison of Amantadine, Modafinil, and Standard of Care in the Acute Treatment of Disorders of Consciousness After Severe Traumatic Brain Injury. Clin Neuropharmacol. 2022; 45(1):1-6.

[10] Rühl L, Kuramatsu JB, Sembill JA, Kallmünzer B, Madzar D, Gerner ST, et al. Amantadine treatment is associated with improved consciousness in patients with non-traumatic brain injury. J Neurol Neurosurg Psychiatry. 2022; 93(6):582-7.

[11] Thibaut A, Schiff N, Giacino J, Laureys S, Gosseries O. Therapeutic interventions in patients with prolonged disorders of consciousness. Lancet Neurol. 2019; 18(6):600-14

[12] Chen X, Tang C, Zhou H, Li Z. Effect of amantadine on vegetative state after traumatic brain injury: a functional magnetic resonance imaging study. J Int Med Res. 2019;47(2):1015-24.

[13] Schnakers C, Hustinx R, Vandewalle G, Majerus S, Moonen G, Boly M, et al. Measuring the effect of amantadine in chronic anoxic minimally conscious state. J Neurol Neurosurg Psychiatry. 2008; 79(2):225-7

[14] 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. J Head Trauma Rehabil. 2002; 17(4):300-13.

[15] Schneider WN, Drew-Cates J, Wong TM, Dombovy ML. Cognitive and behavioural efficacy of amantadine in acute traumatic brain injury: an initial double-blind placebo-controlled study. Brain Inj. 1999; 13(11):863-72.

[16] Hammond FM, Sherer M, Malec JF, Zafonte RD,

Whitney M, Bell K, et al. Amantadine Effect on Perceptions of Irritability after Traumatic Brain Injury: Results of the Amantadine Irritability Multisite Study. J Neurotrauma. 2015; 32(16):1230-8.

[17] Ciurleo R, Bramanti P, Calabrò RS. Pharmacotherapy for Disorders of Consciousness: Are 'Awakening' Drugs Really a Possibility? Drugs. 2013;73(17):1849-62.

[18] Clauss RP. Neurotransmitters in Coma, Vegetative and Minimally Conscious States, pharmacological interventions. Medical Hypotheses. 2010; 75(3):287-90.

[19] Clauss R. Neurotransmitters in disorders of consciousness and brain damage. Medical hypotheses. 2011;77(2):209-13.

[20] Oliveira L, Fregni F. Pharmacological and electrical stimulation in chronic disorders of consciousness: new insights and future directions. Brain Injury. 2011; 25(4):315-27

[21] Fridman EA, Calvar J, Bonetto M, Gamzu E, Krimchansky BZ, Meli F, et al. Fast awakening from minimally conscious state with apomorphine. Brain injury. 2009; 23(2):172-7

[22] Fridman EA, Krimchansky BZ, Bonetto M, Galperin T, Gamzu ER, Leiguarda RC, et al. Continuous subcutaneous apomorphine for severe disorders of consciousness after traumatic brain injury. Brain injury. 2010; 24(4):636-41

[23] Chang C, Ramphul K. Amantadine. StatPearls [Internet]: StatPearls Publishing; 2022.

[24] Bailey E, Stone T. The mechanism of action of amantadine in Parkinsonism: a review. Arch Int Pharmacodyn Ther. 1975; 216(2):246-62

[25] Horiguchi J, Inami Y, Shoda Ta. Effects of long-term amantadine treatment on clinical symptoms and EEG of a patient in a vegetative state. Clinical neuropharmacology. 1990; 13(1):84-8

[26] Zafonte tw, nancy r. Mann, ross d. Case study: Amantadine: a potential treatment for the minimally conscious state. Brain injury. 1998; 12(7):617-21.