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Effect of amantadine in comatose patients: Traumatic brain injury versus post-cardiac resuscitation syndrome

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Abstract

Background & Objective: Amantadine is considered to be effective in facilitating awakening from a coma both after traumatic brain injury (TBI) and following the return of spontaneous circulation (ROSC) after cardiac arrest. The aim of this study is to share our observations of TBI and ROSC patients in the intensive care unit (ICU) who were administered amantadine to enhance wakefulness. *Methods:* This retrospective study involved patients treated in a tertiary ICU. The patients were divided into two groups: TBI group and ROSC group. Demographic data such as age, gender, reason for hospital admission, and comorbidities were recorded. The outcomes assessed included length of ICU stay, duration of hospital stay, mortality rates, and discharge rates. *Results:* TBI group had a mortality rate of 23.4% and a survival rate of 76.6%, while the ROSC group had a mortality rate of 46.4% and a survival rate of 53.6%, with TBI group experiencing significantly better outcomes. Regarding patients' GCS scores at the start and end of amantadine treatment, in TBI group, the average GCS was 5.7 on the first day and 9 on the last day of treatment ($p < 0.001$). In ROSC group, the average GCS was 5 on the first day and 7.1 on the last day of treatment ($p < 0.001$). These changes were found to be statistically significant.
Conclusion: This study demonstrated that amantadine treatment effectively improved GCS scores in both TBI and ROSC patients. However, this study also showed that TBI patients experienced better outcomes than ROSC patients.

Keywords: Amantadine, coma, brain injury, cardiac resuscitation

INTRODUCTION

Traumatic brain injury (TBI) is a significant cause of mortality in individuals under the age of 40 worldwide. The mortality rate ranges from 4% to 8% in cases of mild injury, and it can rise as high as 50% in severe cases.[1] Among survivors of TBI, the morbidity rate is notably high, with some patients relying on medical devices to continue living.[2] The administration of amantadine in TBI patients is known to accelerate awakening from a coma.[3,4] Amantadine is a glutamate/N-methyl-D-aspartate (NMDA) receptor antagonist and has a broad range of clinical effects, including antiviral and antiparkinsonian properties.[5-7] By upregulating dopamine activity, amantadine plays a crucial role in arousal. It increases dopamine production and inhibits dopamine reuptake presynaptically and enhances dopamine receptor activation postsynaptically.[5]

Amantadine is frequently used in patients with TBI and has gradually been employed in different patient groups to facilitate awakening from comas.[4,9,10] It promotes increased levels of alertness and attention, which leads to better participation in early rehabilitation, consequently resulting in improved functional outcomes for patients. In patients with diffuse axonal injury, a comparison between amantadine and placebo revealed that the group receiving amantadine had higher Glasgow Coma Scale (GCS) scores and lower mortality rates.[10] Similarly, a study conducted on patients with successful return of spontaneous circulation (ROSC) following cardiopulmonary resuscitation reported that amantadine could be effective in enhancing wakefulness.[9]

Amantadine is considered to be effective in facilitating awakening from a coma after both TBI and ROSC. In our literature review, we did not encounter any studies comparing the use of amantadine in ROSC patients and TBI patients.

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The aim of this study is to share our observations of TBI and ROSC patients in the ICU who were administered amantadine to enhance wakefulness.

METHODS

This study was conducted retrospectively in accordance with the Helsinki Declaration, after receiving approval from the Sakarya University Medical Faculty Local Ethics Committee (Approval No. 71522473/050.01.04/608). The study sample included patients who were followed and treated in a tertiary ICU between January 2016 and December 2023. The patients included in the study were those treated for cerebral hemorrhage or subarachnoid hemorrhage, who underwent successful in-hospital or out-of-hospital cardiopulmonary resuscitation, and who were administered amantadine to enhance wakefulness during these treatments. Patients who underwent recurrent cardiopulmonary resuscitation within the first 6 hours, those with TBIs requiring surgery, those not treated with amantadine and/or treated with modafinil, those who died within 48 hours of admission, and those who were administered amantadine for reasons other than the aforementioned conditions were excluded from the study. In our ICU, amantadine is routinely administered at a dosage of 200 mg per day, divided into two doses. The criteria for discontinuing the drug in our clinic included an improvement of more than 3 points on the Glasgow Coma Scale (GCS), improvements regarding arousal or response documented in caregiver notes, and clinical improvements in arousal or response documented in physiotherapy notes. Patients who received at least 10 days of amantadine therapy were included in the study.

The patients were divided into two groups: the TBI group and the ROSC group. Demographic data such as age, gender, reason for hospital admission, and comorbidities were recorded. Additionally, GCS scores were documented during the initial assessment; on days 1, 2, 3, 4, 5, 6, 7, 14, and 28; and at the discontinuation of amantadine therapy. The usage and dosage regimen of analgesic and anesthetic drugs were also recorded. Neurological damage serum markers, such as neuron-specific enolase or s100b, could not be evaluated because they were not utilized in our facility. The outcomes assessed included length of ICU stay, duration of hospital stay, mortality rates, and discharge rates.

Statistical analysis

The statistical analysis of the data was performed using the SPSS 20 software package. The Pearson chi-square test was used to compare qualitative data, and the results were presented as numbers and percentages (for gender, comorbidity, sedation, and outcome). To compare quantitative data, the Student's t-test was applied to normally distributed variables, with the results expressed as means and standard deviations (for comparison of GCS, and age). For non-normally distributed groups, the Mann-Whitney U test was employed, with the results presented as medians and interquartile ranges [IQR] (for length of hospital stay, length of intensive care unit, and day of amantadine initiation). A p-value of 0.05 was considered statistically significant for all tests.

RESULTS

A total of 133 patients were evaluated. In the TBI group, there were 18 female and 46 male patients, while in the ROSC group, there were 22 female and 47 male patients, with no significant difference regarding gender distribution between the groups ($p = 0.637$). In the TBI group, the most frequent comorbidities were hypertension (HT) at 21.9%, diabetes mellitus (DM) at 14.1%, and cerebrovascular disease (CVD) at 10.9%. In the ROSC group, the most frequent comorbidities were coronary artery disease (CAD) at 44.9%, HT at 39.1%, and DM at 31.9%. HT, DM, CAD, chronic obstructive pulmonary disease (COPD), and heart failure (HF) were significantly higher in the ROSC group ($p = 0.031$, 0.015, $<$ 0.001, 0.005, and 0.001, respectively). The most commonly used sedative drug in both groups was fentanyl, with usage rates of 73.4% in the TBI group and 73.9% in the ROSC group ($p = 0.950$). There was a significant difference in the use of propofol between the groups, with greater use in the TBI group ($p = 0.014$). The average hospital stay was 46 days in the TBI group and 87 days in the ROSC group, but there was no significant difference between the groups ($p = 0.061$). The average length of ICU stay was 25 days in the TBI group and 45 days in the ROSC group, with a significant difference between the groups ($p = 0.046$). The TBI group had a mortality rate of 23.4% and a survival rate of 76.6%, while the ROSC group had a mortality rate of 46.4% and a survival rate of 53.6%, a significant difference was found between the groups, with TBI group experiencing lower mortality and higher survival rates ($p = 0.006$). The average number of days

before starting amantadine was 5.5 days in the TBI group and 6 days in the ROSC group, with the average duration of amantadine use being 12 days in both groups, showing no significant difference (p = 0.814 and 0.549, respectively; Table 1).

Regarding the GCS scores from the start of amantadine treatment up to the fourth week, the initial GCS was 5.7 in the TBI group and 5 in the ROSC group. During the follow-up, there was a daily increase in GCS scores with amantadine use, although a decrease of approximately 1 point was observed only in the ROSC group from the third to the and fourth week (Table 2; Figure 1).

Regarding patients' GCS scores at the start and end of amantadine treatment, in the TBI group, the average GCS score was 5.7 on the first day and 9 on the last day of treatment. In the ROSC group, the average GCS score was 5 on the first day and 7.1 on the last day of treatment. These changes were found to be statistically significant (p < 0.001 for both groups; Table 3).

DISCUSSION

NMDA receptor antagonists, such as amantadine, are used to enhance wakefulness in the treatment of anoxic brain injury and TBI-affected patients. Studies have shown a wide range of results regarding the duration of amantadine use, its effects on consciousness, and associated complications. Variables such as patient selection and drug administration methods, durations, and initiation times differ among these studies. We planned this study to share our experience with amantadine, which we have used for an extended period in the ICU. Our analysis revealed a significant increase in GCS scores between hospital admission and discharge for both patient groups. Additionally, we found that in patients with TBI, GCS scores were higher both during hospitalization and following amantadine treatment compared to the ROSC group.

Amantadine is known to enhance brain metabolism and is widely used as a neurostimulator

Table 1: Descriptive analysis and outcome

	TBI group n=64	ROSC group n=69	p value
Gender, n (%)			
Male	18 (28,1)	22 (31,9)	0,637
Female	46 (71,9)	47 (68,1)	
Age	50,8 ± 18,5	63,3 ± 14,9	<0,001
Comorbidity, n (%)			
Chronic kidney disease	1 (1,6)	5 (7,2)	0,115
Malignancy	1 (1,6)	1 (1,4)	0,957
Chronic obstructive pulmonary disease	-	8 (11,6)	0,005*
Cerebrovascular disease	7 (10,9)	7 (10,1)	0,882
Heart failure	-	11 (15,9)	0,001*
Coronary artery disease	5 (7,8)	31 (44,9)	<0,001*
Hypertension	14 (21,9)	27 (39,1)	0,031*
Diabetes Mellitus	9 (14,1)	22 (31,9)	0,015*
Total	20 (31,3)	48 (70,6)	<0,001*
Sedation, n (%)			
Propofol	17 (26,6)	7 (10,1)	0,014*
Fentanyl	47 (73,4)	51 (73,9)	0,950
Midazolam	29 (45,3)	40 (58)	0,144
Dexmedetomidine	3 (4,7)	6 (8,7)	0,358
Length of hospital stay, mean [IQR]	46 [30-82]	87 [43-145]	0,061
Length of intensive care unit, mean [IQR]	25 [18-51]	45 [23-74]	0,046*
Day of amantadine initiation, mean [IQR]	5,5 [3-8]	6 [4-9]	0,814
Outcome, n (%)			
Excitus,	15 (23,4)	32 (46,4)	0,006*
Survival	49 (76,6)	37 (53,6)	

*:p≤0.05, TBI: Traumatic brain injury, ROSC: Return of spontaneous circulation

Table 2: Comparison of GCS scores during amantadine treatment between groups

	TBI group n=64	ROSC group n=69	p value
1. day	5,7 ± 2,0	5,0 ± 2,0	0,028*
2. day	6,1 ± 2,4	5,1 ± 2,1	0,011*
3. day	6,5 ± 2,7	5,3 ±2,3	0,009*
4. day	7,1 ± 2,9	5,5 ± 2,3	0,001*
5. day	7,3 ± 2,9	5,9 ± 3,0	0,009*
6. day	7,6 ± 2,9	5,9 ± 3,1	0,013*
7. day	8,1 ± 3,1	6,3 ± 3,2	0,004*
8. day	8,3 ± 3,1	6,5 ± 3,4	0,004*
9. day	8,5 ± 3,4	6,7 ± 3,5	0,004*
10. day	8,8 ± 3,5	6,7 ± 3,5	0,002*
11. day	8,6 ± 3,4	6,9 ± 3,5	0,010*
12. day	8,5 ± 3,3	6,8 ± 3,4	0,010*
13. day	8,3 ± 3,2	6,9 ± 3,4	0,052
14. day	8,5 ± 3,3	7,1 ± 3,4	0,051
3. week	8,9 ± 2,9	7,6 ± 3,2	0,053
4. week	9,3 ± 3,0	6,8 ± 3,3	0,003*

*:p≤0.05, TBI: Traumatic brain injury, ROSC: Return of spontaneous circulation

to improve levels of consciousness.[11,12] However, sufficient clinical evidence for its use is believed to exist only for TBI patients.[11,13] The American Academy of Neurology guidelines indicate level B evidence for the use of amantadine in disorders of consciousness.[14] In a recent systematic review, Loggini *et al*. showed that amantadine appears safe for use in TBI patients and is beneficial for medium-term cognitive improvement.[4] Spritzer *et al*. also evaluated amantadine use in TBI patients using the Disability Rating Scale and demonstrated that it accelerated recovery in their

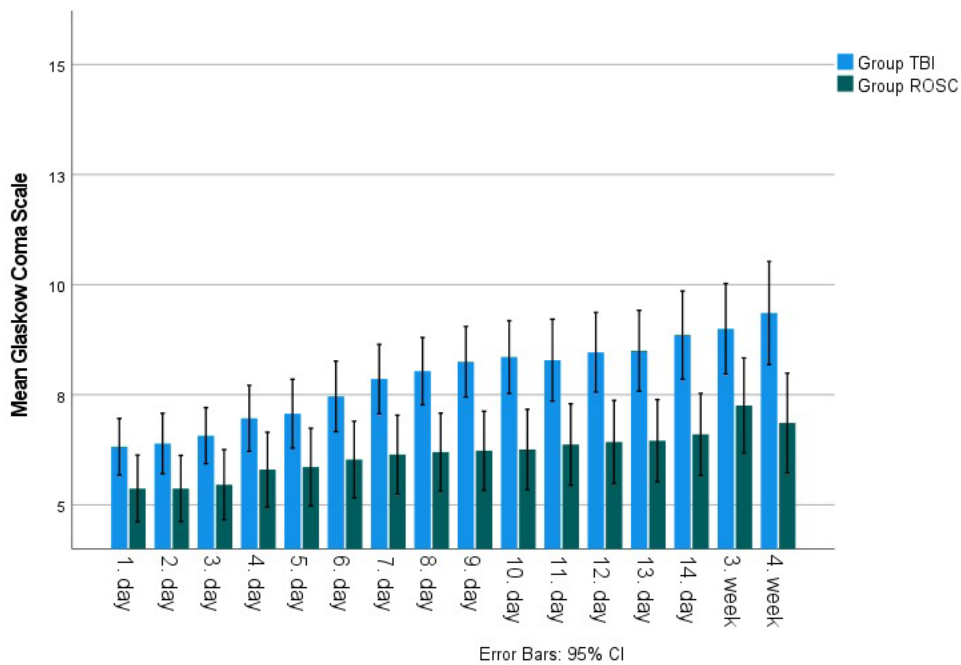

Figure 1. Comparison of GCS scores during amantadine treatment between groups

Table 3: Comparison of GCS scores at the start and end of amantadine treatment within groups

	Amantadine 1st day	Amantadine last day	p value
TBI group n=64	5.7 ± 1.9	9.0 ± 3.8	<0.001*
ROSC group n=69	5.0 ± 2.0	7.1 ± 3.8	<0.001*

*:p≤0.05, TBI: Traumatic brain injury, ROSC: Return of spontaneous circulation, GCS: Glasgow Coma Scale

patients.[15] In another study involving 42 patients, a comparison between amantadine and placebo groups revealed a significant difference in GCS changes after one week with greater improvement found in amantadine users. In their study of patients with traumatic brain injury, Saniova *et al*. reported that GCS scores increased from an average of 4.47 to 9.76 with amantadine use, noting that amantadine provided higher GCS scores and reduced mortality in these patients.[3] Sahin *et al*. reported that patients treated with amantadine for TBI had average GCS scores of 3 at the start of treatment and 11.5 at the end of treatment.[16] In our study, the average GCS score in the TBI group was 5.7 at the start of amantadine therapy, which increased to an average of 9 at the end of treatment, and this improvement was statistically significant.

One of the primary purposes of using amantadine is to provide better functional outcomes for patients, but its use also affects mortality rates, survival, and hospital stay durations. In their study of TBI patients, Ghalaenovi *et al*. reported that the average hospital stay in the amantadine group was 24.96 days, with 31.6% of patients experiencing mortality.[17] In their recent study, Ozlem *et al*. found an average hospital stay of 29 days for TBI patients, with an average ICU stay of 14.5 days and a mortality rate of 6.8%.[18] Saniova *et al*. reported a mortality rate of 6.6% for TBI patients who started amantadine with a GCS below 8.[3] Another study involving amantadine in TBI patients reported a mortality rate of 32.5%.[16] In our study, the average hospital stay in the TBI group was 46 days, the average ICU stay was 25 days, and the mortality rate was 23.4%. The wide range of mortality rates reported in the literature, from 6% to 32%, is thought to be related to the varying severity of TBI in hospitalized patients. The length of ICU stay observed in our study appears to be longer compared to some literature data. This might be due to the difficulties of discharging the patients to ward or home.

In a randomized controlled trial published in 2024, the average hospital stay for ROSC patients receiving amantadine was reported to be 14 days, with a mortality rate of 57.1%.[19] Reynolds *et al*. found an average hospital stay of 14.5 days, with 56% of these patients being discharged from the hospital.[9] In our study, the average hospital stay in the ROSC group was 87 days, the average ICU stay was 45 days, and the mortality rate was 46.4%. Although the mortality rates in our study were consistent with those reported in the literature, the longer ICU stays are notable. The prolonged ICU stays in both the TBI and ROSC groups can be attributed primarily to the lack of a palliative care service at our hospital and difficulties in procuring medical devices for patients dependent on such equipment.

In the literature, studies comparing mortality rates between ROSC and TBI groups have shown that mortality in ROSC patients is approximately 50%, while in TBI patients, it ranges from 6% to 32%. These rates are similar to those observed in our study. Mortality is inevitably higher in ROSC patients due to the global ischemic insult affecting the entire body, as opposed to the localized brain injury seen in TBI cases.

While there is evidence supporting the use of amantadine in patients with coma or minimal consciousness following TBI, studies specifically investigating its use in patients with anoxic brain injury are limited. In 2013, Reynolds *et al*. published the first report on amantadine use in ROSC patients, noting that 38.6% of the patients emerged from coma and followed commands while in a state of minimal consciousness.[9] In a randomized controlled study with 14 ROSC patients, Coppler *et al*. assessed two-stage command responses and found no significant difference between the amantadine group and the placebo group.[19] In our study, the average GCS score in ROSC patients at the start of amantadine treatment was 5, increasing to 7.1 at the end of treatment. This improvement was statistically significant, although its clinical significance is limited.

The most significant limitation of this study was the retrospective nature of patient assessment. Additionally, neurological damage serum biomarkers, such as neuron-specific enolase or s100b, were not evaluated because they are not

tested at our hospital. Another limitation is the absence of a control group, as nearly all patients diagnosed with TBI or ROSC in our clinic received amantadine treatment.

In conclusion, this study evaluating TBI and ROSC patients demonstrated that amantadine treatment effectively improved GCS scores in both groups. However, it also showed that TBI patients experienced better outcomes than ROSC patients. We believe that further research is needed, particularly focusing on ROSC patients, to explore this topic more thoroughly.

DISCLOSURE

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Conflict of interest: None

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