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Research Article

Impact of Amantadine on Inflammatory Biomarkers in Traumatic Brain Injury Patients: A Randomized Controlled Trial

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ABSTRACT

Background and Aim Traumatic brain injury (TBI) is considered a challenge for health care systems. This study aimed to assess amantadine as an add-on therapy for TBI patients.
Method Fifty TBI patients were divided randomly into two groups (n=25 each) to receive either placebo or amantadine (100 mg twice daily) for 6 weeks. Neuron-specific enolase (NSE), neurotensin 3 (NT3), interleukin-18 (IL-18) serum levels and the Glasgow coma score (GCS) were assessed before and after treatment.
Results There was a significant difference in NSE (p=0.01), NT-3 and IL-18 (p<0.001) after 6 weeks of treatment between the two groups. The extended Glasgow Outcome Scale (GOS-E, p=0.008) and GCS (p=0.04) scores after six weeks were significantly different between both groups. Insignificant difference was found between the two groups regarding the overall survival (p = 0.653). NT3 was the most sensitive predictor of good prognosis (AUC= 1.000, p<0.001), followed by IL-18 (AUC=0.997, p<0.001).
Conclusions: As an adjunctive treatment, amantadine may protect neurons throughout the later stages of traumatic brain injury (TBI). Compared with placebo, amantadine therapy was associated with a higher GCS score six weeks after admission and greater reductions in NSE, NT-3, and IL-18. Additionally, NT-3 and IL-18 are promising prognostic biomarkers for TBI patients.

Keywords: Traumatic brain injury, Neurotensin-3, Interleukin-18, Amantadine, GCS score, Overall survival.

1. INTRODUCTION

Traumatic brain injury (TBI) is a serious health problem that has a considerable impact on communities around the world.[1] TBI, in addition to being one of the main causes of death, can impair a patient's cognitive ability, resulting in a socioeconomic burden.[2] According to prior research, the exact pathophysiology of TBI is still unknown. In general, there are two stages: first, brain damage caused by direct mechanical compression of brain tissues, which causes contusion and hemorrhage,[3] and second, brain damage caused by indirect mechanical compression of brain tissues, which causes contusion and hemorrhage. The secondary stage follows the primary stage and is characterized by neurological damage mediated mostly by neurotransmitter release.[4]

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Amantadine, a well-known dopaminergic agonist, has been licenced for the management of a variety of neurological illnesses, involving Parkinson's disease. Amantadine is also hypothesized to block the N-methyl-d-aspartate (NMDA) receptor, resulting in a reduction in glutaminergic release, which is involved in TBI pathophysiology.[5]

Neuron specific enolase (NSE) is a biomarker produced during brain injury and has also been associated with worse outcomes in individuals with TBI. This biomarker might aid in the prognostication of TBI patients.[6]

In the central nervous system (CNS), neurotensin is a recognized neurotransmitter/neuromodulator. Neurotensin (NT) is involved in a variety of important activities in the CNS, involving sleep and wakefulness, temperature regulation, and dopamine production. NT1, NT2, and NT3 are the three subtypes of NT.[7] In animal models, NT3, also known as sortilin, has been shown to be distributed in a variety of CNS areas.[7, 8]

Human microglia express NT3, which has a protective effect on the brain. Microglia move to injured brain tissue after activation in response to inflammation and injury.[9, 10] According to a prior study, only NT3 is expressed in these cells, and it is assumed to increase microglial migration as well as the production of chemokines in response to injured tissue or invading microorganisms.[11]

However, the specific mechanism of the pathophysiology of the subsequent TBI phase is still unknown. Many prior investigations have shown that inflammatory mediators mediate the subsequent phase.[12, 13]

Interleukin-18 (IL-18) is a proinflammatory cytokine that is develops within the brain following head injury in both people and animals.[14, 15] Ido Yatsiv et al. reported that inhibiting IL-18 in the first week following brain injury was linked to a lower risk of later neurological complications.[14] This has piqued researchers' curiosity in discovering neuro-markers that could aid in the diagnosis or follow-up of patients' prognoses and treatment outcomes. Additionally, the effect of amantadine in TBI, particularly in treating the secondary neurological problems associated with TBI, such as persistent vegetative state, severe or moderate disability, has been studied extensively, with mixed results. Additionally, the exact time at which amantadine is started in patients who had TBI and the optimal duration of therapy are still unknown.

In this context, we carried out a double-blind, randomized trial to measure the effects of early amantadine administration during the acute phase of TBI on the Glasgow Coma Scale (GCS), ICU stay and overall survival; the associations between biomarkers NSE, NT3, and IL-18; and whether any of those biomarkers could be used to assess prognosis.

2. PATIENTS AND METHODS

2.1. Study design and Ethical approval

This was a double-blind (participants and investigators), randomized, placebo-controlled study including individuals with TBI who met the inclusion criteria between September 2020 and October 2021. Patients were selected from the Emergency Medicine and Traumatology Department, Tanta University Hospital, Tanta, Egypt.

This study was approved by the Ethical Committee of Faculty of Pharmacy, Damanhour University, Egypt with an approval number (820PP29), registration date: 05-08-2020. This research was carried out according to the Declaration of Helsinki. Prior to enrolment, patients or their legally authorized representatives were required to provide written informed consent. Clinical trials.gov was used to register the study protocol prior to patient enrolment. *Its* ClinicalTrials.gov identifier (NCT number): NCT04527289. (first trial registration date: 26-08-2020).

2.2. Patients and interventions

Individuals aged 18 to 70 years exhibiting clinical manifestations of TBI were evaluated for eligibility. The inclusion criteria were lower than 24 h since traumatic injury and the ability to tolerate enteral feeding. The exclusion criteria for patients were penetrating head trauma, age younger than 18 years, renal failure with estimated creatinine clearance lower than 60 ml/min, known ischemic heart disease or congestive heart failure, known previous brain disease, including brain tumors, or unknown identity. Patients were managed in accordance with the institutional protocol that adheres to the guidelines established by the Brain Trauma Foundation. Emergency surgical intervention was determined by the neurological status of the patients and the findings obtained from head computed tomography (CT) imaging criteria.

2.3. Randomization

Patients were randomized in a 1:1 ratio via computer-generated random sequence into two groups: the treatment group, which received either amantadine 100 mg or placebo two times every day either orally or through feeding tubes for six weeks. A random allocation sequence was performed by a study-independent pharmacist using sequentially similar white numbered containers. The capsules were dissolved in sterile water and then administered immediately via a syringe for enteral feeding. The tubes were flushed before and after each dose was administered to avoid any remaining residue. The first dose for both groups started within 24 hours of hospital admission.

2.4. Patient assessment and follow-up

Patient demographics, medical history, medication history, cause and severity of injury, and GCS score were determined for each patient at admission. Independent investigators who were blinded to the treatment allocations examined the GCS score. Treatment allocation was hidden from the outcome assessors and patients. The GCS[16] was characterized as moderate (GCS 9–12) or severe (GCS 3–8). Scores were

evaluated at admission and at discharge for each patient in the treatment and placebo groups.

The recovery level was evaluated by the Glasgow Outcome Scale-Extended score (GOS-E),[17] and overall survival was assessed three months after randomization. Patients or first-degree relatives were contacted to measure survival and the GOS-E score. The GOS-E score is defined as 1–4 (dead, vegetative or severe disability) or 5–8 (moderate disability or good recovery)[18] as shown in **supplementary Tables 1** and **2**.

2.5. Study Outcomes

The primary outcome of the investigation was the difference in GCS, NSE, NT3, and IL-18 levels between the two study groups after 6 weeks. Differences in mortality rates and GOS-E scores after 3 months were also secondary end goals of the study.

2.6. Biochemical analysis

Venous blood specimens were obtained from all patients to evaluate NT3, NSE and IL-18 levels. The serum was isolated through centrifugation at 3000 rpm for a duration of 10 minutes, after which the separated serum was immediately frozen at −80°C. The levels of NSE, NT3, and IL-18 were assessed utilizing enzyme-linked immunosorbent assay kits in accordance with the manufacturer's guidelines.

2.7. Statistical analysis

The necessary sample size was determined utilizing G*Power software, version 3.1.0, developed by the Institute for Experimental Psychology at Heinrich Heine University, Düsseldorf, Germany. It was determined that a total sample size of 50 patients would yield a statistical power of 96% to identify a medium to large effect size of 0.96 in the primary outcome measure. Statistical analyses were conducted utilizing version 26.0 of the Statistical Program for Social Sciences (SPSS) software (Inc, Chicago, IBM®, IL). Numerical data are presented as means and standard deviations or medians and ranges, as considered appropriate. Qualitative data are represented in terms of frequencies and percentages. The data were evaluated for normality utilizing the Shapiro–Wilk and Kolmogorov–Smirnov tests, revealing an unusual distribution. The chi-square test was utilized to analyze and compare categorical data between both categories under examination. The student's t-test was employed for the analysis of quantitative variables that exhibit a normal distribution. The Mann-Whitney test was employed for the analysis of quantitative variables that do not conform to a normal distribution. Survival was assessed utilizing the Kaplan–Meier with log rank method. The correlation of the spearman was employed to analyze the bivariate relationship. A receiver operating characteristic (ROC) curve was employed to measure the comparative performance of the two tests. P values below 0.05 were considered statistically significant.

3. RESULTS

Figure 1 demonstrates the CONSORT Flow Diagram for allocation and follow-up of the patients during the study. Eighty-eight TBI patients were screened for eligibility from September 2020 until October 2021. Fifty-five patients (n=55) met the inclusion criteria and were randomly allocated to the placebo or amantadine group. Only fifty patients completed the research and were involved in the final analysis as shown in **Figure 1**.

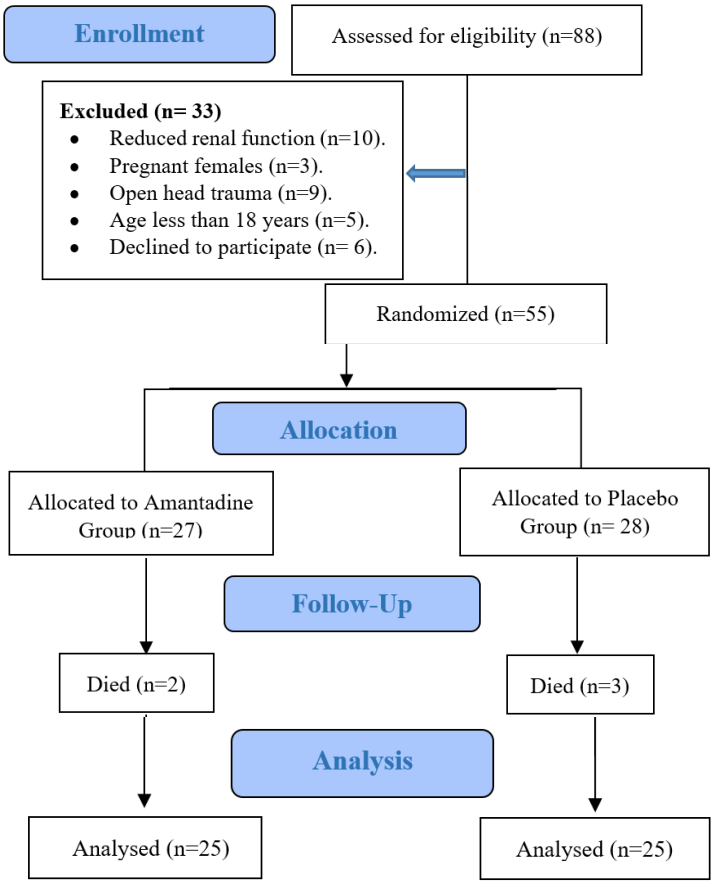


Figure 1. CONSORT Flow Diagram for allocation and flow-up of the patients during the study.

The baseline patient demographics are demonstrated in **Table 1**. The physiological variables and baseline characteristics were matched between both groups. Most of the participants were men, accounting for 75% and 92.6% of the patients in the placebo group and amantadine group, respectively (p=0.08). The mean of the participants age was 35.79 ± 14.49 years in the placebo group and 42.37 ± 1.02 years in the amantadine group (p=0.143). The aetiology of TBI was matched between the two groups (p =0.92), although road traffic accidents were the most common aetiology in both groups. Other causes included human assault and falling dawn from hight.

Table 1. Basic demographic data, cause of TBI, CT findings, and TBI severity in the two groups.

	Placebo group (n=28)	Amantadine group (n=27)	P value
Gender (Male/ Female)	21/7 (75.0 % /25.0%)	25/2 (92.6%/ 7.4%)	0.08†
Age (years)	35.79 ± 14.49	42.37 ± 1.02	0.143*
Weight (Kg)	85.32 ± 16.97	82.74 ± 18.02	0.587*
Height (cm)	171.71 ± 8.00	174.33 ± 8.04	0.232*
Cause of TBI			
-Road traffic accident	15 (53.6%)	15 (55.6.0%)	0.964†
-Human assault	6 (21.4%)	5 (18.5%)	
-Falling down	7 (25.0%)	7 (25.9%)	
CT brain findings			
-Extradural hematoma	5 (17.9.0%)	6 (22.2%)	0.921†
-Subarachnoid hemorrhage	13 (46.4%)	12 (44.4%)	
-Subdural hematoma	10 (35.7%)	9 (33.3%)	
Severity of TBI			
-Mild	2 (7.1 %)	1 (3.7 %)	0.508†
-Moderate	22 (78.6%)	19 (70.4%)	
-Severe	4 (14.3%)	7 (25.9%)	
GCS on admission	9.61 ± 2.28 10.00 (5-11)	9.19 ± 2.34 9.50 (3-13)	0.335‡
Medical History			
HTN	8 (28.6%)	5 (18.5 %)	0.380†
DM	8 (28.6 %)	7 (25.9 %)	0.826†
CAD	2 (7.1 %)	2 (7.4 %)	0.681†
DVT	4 (14.3 %)	5 (18.5 %)	0.671†
NSE (ng/ml)	15.65 ± 0.81	15.78 ± 1.27	0.673*
NT-3 (ng/ml)	8.38 ± 0.30	8.32 ± 0.74	0.745*
IL-18 (ng/L)	54.33 ± 1.85	55.26 ± 1.83	0.080*

Data are reported as mean ± SD, Median (Min-Max) or number (percentages). P values were obtained by † chi-square test or Fisher' s exact test, * Independent t test or ‡Mann–Whitney *U* test with significance set at $p < 0.05$. TBI: traumatic brain injury; GCS: Glasgow coma scale; HTN: hypertension; DM: diabetes mellites; CAD: coronary artery diseases; DVT: Deep Vein Thrombosis; NSE: neuron specific enolase; ng: nanogram; NT-3: neurotensin -3; IL-18: interleukin -18.

Brain CT findings revealed an insignificant difference between the placebo and amantadine groups (p=0.92). Subarachnoid haemorrhage was the most common finding in both groups, followed by subdural hematoma and extradural haemorrhage. Most of our patients had moderate TBI (78% and 70% of patients in the placebo group and amantadine group, respectively), whereas the remaining patients had severe TBI. Both groups were comparable with respect to their medical history ($p \geq 0.05$). The mean baseline GCS score was 9.61 ± 2.28 and 9.19 ± 2.34 (p=0.34) in the placebo and amantadine groups, respectively, with an insignificant difference between both groups, as shown in **Table 1**. Biomarkers baseline levels were comparable between the placebo group and the amantadine group, with an insignificant difference in NSE (15.65 ± 0.81 ng/ml vs 15.78 ± 1.27 ng/ml, p= 67), NT-3 (8.38 ± 0.30 ng/ml vs 8.32 ± 0.74 ng/ml, p= 0.75), or IL-18 (54.33 ± 1.85 ng/L vs 55.26 ± 1.83 ng/L, p=0.8) levels. Three patients died in the placebo group, whereas two patients died in the amantadine group (p= 67). The duration of ICU stay ranged between 0 and 20 days (median = 9.00) in the placebo group, while it ranged between 0 and 19 days in the amantadine group (median = 7.00), with an insignificant difference between the groups (p=0.296). In addition, the duration of mechanical ventilation ranged from 0–18 days (median=7) and 0–16 days (medina=5) in the placebo and amantadine groups, respectively, with an insignificant difference between the groups (p=0.42), as demonstrated in **Table 2**.

Table 2. Primary and secondary outcomes in intervention and control group.

		placebo group (n=25)	Amantadine group (n=25)	P value
GCS		11.54 ± 1.92 12.00 (7-15)	12.38 ± 2.12 13.00 (10-14)	0.04‡
GOS-E (n,%)	**GOS-E 1-4**	14 (56%)	5 (20%)	0.02†
	GOS-E 5-8	11 (44%)	20 (80%)	
ICU stay (days)		9.00 (0-20)	7.00 (0-19)	0.296‡
Duration of ventilation (days)		7.00 (0- 18)	5.00 (0-16)	0.422‡
Duration of hospitalization (days)		13 (3-29)	9 (2-27)	0.307‡
Vegetative (n, %)		2 (8%)	3 (12%)	0.637†
Death n (%)		3 (10.7%)	2 (7.4%)	0.670†
NSE (ng/ml)		10.78 ± 0.95	9.50 ± 2.11	0.01
NT-3 (ng/ml)		7.45 ± 0.33	6.40 ± 0.53	<0.001
IL-18 (ng/L)		42.64 ± 1.73	33.43 ± 2.46	<0.001

Data are reported as mean ± SD, number (percentages), or Median (Min-Max) as appropriate. P values were obtained by † chi-square test or Fisher' s exact test, Independent t test or ‡Mann–Whitney *U* test for comparisons between groups. Significance set at $p < 0.05$. GCS; Glasgow coma scale; ICU; intensive care unit; ng, nanogram; NT-3: neurotensin -3; IL-18: interleukin -18; GOS- E, Extended Glasgow Outcome Scale; NSE: neuron specific enolase.

The amantadine group presented higher GCS scores six weeks after admission (12.38± 2.12 vs. 11.54 ± 1.92 in the

placebo group, p = 0.04). The NSE, NT-3 and IL-18 levels significantly decreased after treatment in the placebo group compared with those in the amantadine group (10.78 ± 0.95 ng/ml vs 6.40 ± 0.53 ng/ml, p=0.01; 7.45 ± 0.33 ng/ml vs 6.40 ± 0.53 ng/ml, p <0.001 and 42.64 ± 1.73 ng/L vs 33.43 ± 2.46 ng/L, p <0.001, respectively). A significantly higher percentage of patients with an increased GOS-E score were in the amantadine group, indicating a more favourable outcome (**GOS-E score of 1-4:** 14 (56%) in the placebo group vs. 5 (20%) in the amantadine group and **GOS-E score of 5-8:** 11 (44%) in the placebo group vs. 20 (80%) in the amantadine group, p= 0.02), as demonstrated in **Table 2**. There was a significant negative correlation between IL-18 levels after six weeks of follow-up and the GCS score (r=-0.324, p= 0.022). There was a significant positive correlation between IL-18 and NT3 (r=0.739, p=0.000), as shown in **Table 3**.

Table 3. Spearman Correlation between the levels of IL-18 with NSE, NT-3, GCSE and GCS in the current study after intervention in both groups (n=50).

	IL-18	
	r	p
GCS	-0.351*	0.012
GOS-E	-0.386**	0.007
NT-3	0.775**	0.000
NSE	0.355*	0.011

IL-18: interleukin -18; GCS; Glasgow coma scale after 6 weeks; NT-3: neurotensin -3; GOS- E, Extended Glasgow Outcome Scale; NSE: neuron specific enolase. Significance set at p < 0.05.

Figure 2 demonstrates the Kaplan-Meier survival curve with a log rank for cumulative survival and hazard in both studied groups. The overall survival and hazard were an insignificantly different between both groups (p = 0.653). **Figure 3** demonstrates the ROC-AUC values of the biomarkers in the treated groups. NT3 was the most sensitive predictor of good prognosis (AUC= 1.000, p<0.001), followed by IL-18 (AUC=0.997, p<0.001).

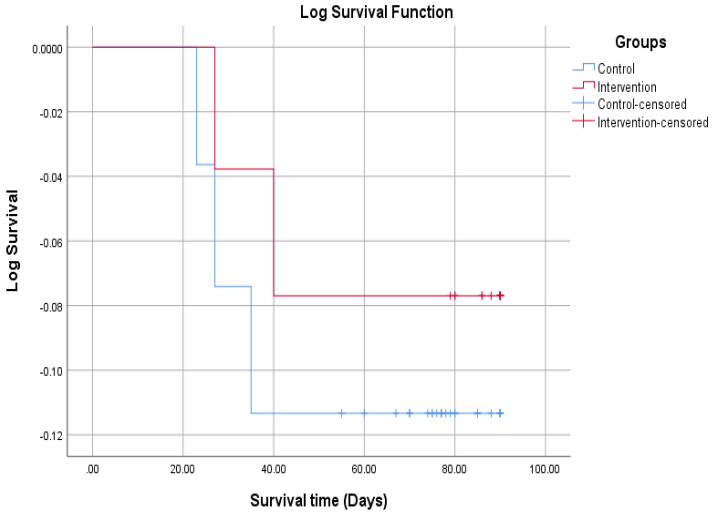
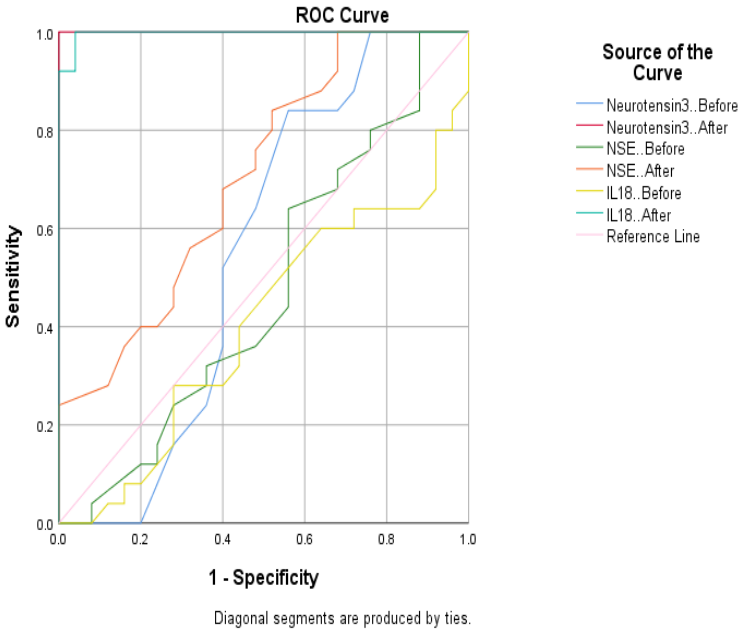


Figure 2. Kaplan-Meier survival curves with Log rank in both studied groups. Significance set at p< 0.05.



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	P-Value[b]	Asymptotic 95% Confidence Interval Lower Bound	Upper Bound
NSE. Before	0.473	0.083	0.742	0.310	0.636
NSE. After	0.706	0.073	0.013	0.563	0.848
Neurotensin3..Before	0.553	0.087	0.522	0.383	0.723
Neurotensin3..After	1.000	0.000	0.000	1.000	1.000
IL18 .Before	0.404	0.081	0.244	0.245	0.563
IL18..After	0.997	0.004	0.000	0.988	1.000

The test result variable(s): NSE.Before, NSE.After, Neurotensin3..Before, IL18..Before has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. Significance set at p < 0.05.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

Figure 3. Area under ROC curve of different measured parameters in both studied groups before and after intervention for 6 weeks (n=50). NSE: neuron specific enolase IL-18: interleukin -18.

4. DISCUSSION

The objective of this investigation was to detect whether the administration of amantadine during the acute phase of TBI has a protective effect on secondary neurological outcomes and the biomarkers NT3 and IL-18. The findings of the present study revealed that adding amantadine to the treatment protocol for TBI patients resulted in a better GOS-E, which may provide a protective effect for those patients. Our findings aligned with previous results by Giacino *et al.*,[19] who reported that, compared with placebo, the administration of amantadine between 4 and 16 weeks after injury

significantly accelerated the functional recovery rate during active treatment in patients with posttraumatic disorders of consciousness. Meythaler *et al*.[12] reported that, regardless of when amantadine was started on amantadine in a patient with diffuse axonal damage (DAI)-associated TBI, in the first three months following injury, there was a constant tendency toward more rapid functional improvement. Improvements in awareness levels have been demonstrated to last even after amantadine treatment is completed, which generally occurs after 60–90 days.[20]

Amantadine appears to be well tolerated and may promote cognitive recovery in the short term.[21] Consistently with our study a previous research shows that amantadine treatment may improves short-term consequences in traumatic brain injury rats, by reducing inflammatory biomarkers as well as decrease glutamate level.[20] A recent study revealed that TBI patients experienced favourable short-term outcomes in terms of GCS scores with improved inflammatory biomarkers at the end of the treatment period but patients were treated with doxycycline.[22] In contrast, a previous, smaller RCT (N = 40) indicated that amantadine medication had no effect on the degree of disability, cognition, awareness, memory, mortality, or performance six months following amantadine BID treatment.[23] Amantadine appears to help individuals recover from brain injuries more quickly. However, the evidence for the use of amantadine in individuals with nontraumatic brain injuries is less convincing.[24]

Our results revealed an insignificant difference between the groups regarding the duration of ICU stay or the duration of mechanical ventilation. According to a study by Gramish *et al*., TBI patients who received amantadine after admission to a tertiary ICU had longer durations of stay in the ICU.[25] Conversely, Ghalaenovi *et al*. demonstrated that severe TBI patients who were treated with amantadine had longer hospital stays and a greater rate of improvement in their GCS scores within the first week of therapy, without functional changes at the 6-month reassessment.[26]

Our findings revealed that there was an insignificant difference in overall survival between the two groups. Similarly, according to Ghalaenovi *et al*., data from the first week and six months of follow-up revealed that administering amantadine had no discernible effects on patients' level of awareness, disability, memory, mortality, performance, or cognition.[26] In contrast, our study revealed a higher GOS-E score in the amantadine group than in the placebo group.

The present investigation revealed that amantadine treatment significantly decreased NSE, NT-3 and IL-18 levels compared with those in the placebo group. Additionally, a significant negative correlation was noted between IL-18 levels after six weeks of follow-up and the GCS and GOS-E scores, and a significant positive correlation was noted with NSE, NSE, and NT3 levels. Our results revealed that NT3 was the most sensitive predictor of good prognosis, followed by IL-18. This study is, to our knowledge, the inaugural randomized clinical trial examining the effects of amantadine on NT-3 and IL-18. Additionally, a previous study using a murine model revealed that NT can increase glutamate levels and is involved in NMDA-induced excitotoxicity.[27, 28]

Moreover, amantadine has an NMDA antagonist effect.[12] Our study revealed a significant difference in NT3 and IL-18 levels after six weeks of intervention between the two groups, with better GOS-E scores in the amantadine group than in the control group. These findings are consistent with those of a previous study that demonstrated that blockage of IL-18 in head trauma decreased neurological complications after closed head trauma.[14] In agreement with Ciaramella A. *et al*., who demonstrated that elevated IL-18 was linked to long-term outcomes in patients who had TBI and secondary neurological symptoms, such as cognitive impairment and disability, compared with healthy volunteers.[29] Moreover, Ramlackhansingh *et al*. reported that the inflammatory cascade is activated after TBI injury, with increased microglial activation even after 17 years of injury.[30] These findings may facilitate the development of new strategies for directly targeting the secondary phase of brain trauma via the use of pharmacological agents that antagonize IL-18 release. The present study revealed a significant negative correlation between the GCS score and NSE, NT3 and IL-18 levels after six weeks of follow-up. Inconsistent with previous studies,[22, 31] NSE was found to be negatively correlated with the GCS.

Amantadine also has anti-inflammatory effects. Amantadine has been found in cell cultures to inhibit the production of proinflammatory molecules from activated microglia while enhancing the production of neurotropic protective factors such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF).[32] Both BDNF and GDNF can protect dopaminergic neurons in the nigrostriatal region from neurotoxins.[33] In general, amantadine is indicated to patients who have a change in consciousness following a traumatic brain injury.[34]

5. CONCLUSION

Amantadine, as an add-on therapy, may have a neuroprotective effect on TBI patients when it is started during the initial phase of the insult. Amantadine therapy was associated with greater reductions in NSE, NT-3, and IL-18 along with better GCS and GOS-E scores. Accordingly, NT-3 and IL-18 may be considered promising biomarkers for predicting good prognosis in TBI patients. Larger sample sizes and longer duration studies are recommended to confirm our results.

STUDY LIMITATIONS

The relatively short follow-up period and the use of a fixed dose of amantadine may represent limitations for this study. Furthermore, the sample size was not very large, and our study did not include patients with mild injury. Therefore, more longitudinal studies with larger samples with different types of injury that involving different doses of amantadine are still necessary.

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AUTHORS' CONTRIBUTIONS

R.H.W., M.G.E. and A.G. reviewed the literature and constructed the study design. Eligibility assessment and enrolment of participants were performed by M.S. Collection of clinical data and laboratory investigations of the collected samples were performed by R.H.W, M.G.E., and M.S. Blood sample analysis, statistical analysis and interpretation of data were performed by R.H.W. and M.G.E. All authors wrote, revised and approved the final manuscript.

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DECLARATION OF CONFLICTING INTERESTS

Authors declare no conflict of interest.

AVAILABILITY OF DATA AND MATERIAL

The data are available from the corresponding author on reasonable request.

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