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Role of amantadine in traumatic brain injury for cognitive function improvement

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ABSTRACT:

Background:The present study was conducted to investigate the role of amantadine in traumatic brain injury for cognitive function improvement.
Materials and methods:A total of 300 patients were included in the study who were randomly divided into two groups: AMH group and placebo group. The drug was administered for 6 weeks. Patients were evaluated on the first day (day of starting AMH), after 7 days and after 3 months from starting drug with GCS score, KPS score, DRS score and MOCA score.
Results:The GCS, KPS and DRS scores were significantly improved in AMH group after 3 months (p=0.034, 0.006 and 0.011 respectively). The MOCA score was significantly higher in Amantadine group after 7 days and after 3 months (p=0.033 and 0.038respectively). The change of MOCA score from day 1 to day 7 and day 7 to 3 months were significantly greater in Amantadine group (p=0.029 and p=0.046 respectively).
Conclusion:Amantadine produced significant effects in the improvement of the patients' cognitive function with respect to GCS, KPS, DRS and MOCA scores.

KEYWORDS: Traumatic brain injury; amantadine; cognitive function

INTRODUCTION

Globally, traumatic brain injury (TBI) is a significant socioeconomic and public health issue. Due to an increase in the number of motor vehicles, even in nations with poor socio economic condition, these injuries are occurring more frequently across the globe.[1] The goal of treating TBI's neurological and behavioural sequel is to help patients regain their ability to interact with others and function in their previous occupations.[2] A small percentage of these patients (5%) have long-term disabilities such memory loss, focus and concentration problems, irritability, depression, and violent behaviour.[3] About 2% of people with severe TBI require ongoing assistance with activities of daily living.[4]

There is a significant number of patient which has post traumatic cognitive deterioration, according to studies.[5] Following a TBI, the nervous system may experience a number of neurotransmitter alterations. Excitatory chemicals like glutamate and aspartate can be released when there is severe and extensive damage to the brain's tissue. Apoptosis, or the active death of cells, is therefore increased as a result, which in turn drives the entry of huge amounts of calcium ions into the neurons.[6-8] The central nervous system's (CNS) dopamine (DA) levels, on the other hand, display a biphasic pattern following the damage. Working memory processes are modulated by dopaminergic systems, however DA-D1 receptor binding has a temporary reduction that impairs this function.[9,10]

Many neurotransmitter was found in brain which regulate cognitive function, in which important transmitter were Dopamine, serotonin and nor epinephrine. Amantadine was DA receptor agonist. After a TBI, the DA receptor agonist amantadine hydrochloride (AMH) can activate and may aid in the recovery of the cognitive function.[11] AMH also suppresses the activity of postsynaptic membrane calcium channels and, in turn, lowers the uptake of calcium into the neurons, which may have neuroprotective benefits. AMH is a direct

antagonist of NMDA-receptors and a down-regulator of glutaminergic pathways in the brain.[12,13] Studies have demonstrated that it works even when taken in the first week following an injury to improve the cognitive function. [14,15] In order to better understand how amantadine helps traumatic brain injury patients with their cognitive function, the current investigation was carried out.

MATERIALS AND METHODS:

Sampling

This prospective study was conducted on the 300 patients admitted in the Department of Neurosurgery, SMS trauma centre, Jaipur from June 2021 to December 2022. The ethical approval was obtained from the institutional ethical committee. The study was done in following the ethical standards of the Declaration of Helsinki. The sample size calculation was done using G*Power 3.1.9.2 software. Considering 5% alpha error, 10% beta error and 90% power for the study, the sample size was calculated as 294. We had taken a total of 300 samples after matching the inclusion and exclusion criteria. The patients were enrolled in the study after obtaining informed and written consent. Patients with age 18 years or higher, having non-penetrating head injury GCS more than 9 on the beginning day were included in the study. Patients with known congestive heart failure or ischemic heart disease, severe brain diseases, penetrating head trauma requiring operation, renal failure or with positive pregnancy test (females) were excluded from the study.

Methodology

In our study, the patients were randomly divided into two groups: AMH group (n-150) and placebo group (n-150). All sedative (Midazolam, Thiopental etc.) or stimulants (Ritalin, Caffeine etc.) drugs were discontinued several hours before starting drug. The drug was administered for 6 weeks. Amantadine was administeredas 100 mg twice a day. Patients were evaluated on the first day (day of starting AMH), after 7 days and after 3 months from starting drug with GCS score, KPS score, DRS score and MOCA score.

Statistical analysis

The data are tabulated in Microsoft excel and analysed with SPSS V.24 software. The continuous variables are presented with mean and standard deviation. The categorical variables are presented with frequency and percentage. Independent t test, Chi square test and repeated measures ANOVA are used for the statistical analysis. The p value ≤ 0.05 is considered statistically significant.

RESULTS

Table 1 and 2 show the comparisons of various parameters between the groups. The demographic characteristics were comparable in both the groups.

On the day 1, the GCS score was slightly higher in Placebo group ; on the day 7, it was slightly higher in Amantadine group and after 3 months, it was significantly higher in Amantadine group ($p=0.034$). The change of GCS score from day 1 to day 7 and day 7 to 3 months was comparable in both the groups. The change of GCS score There were significant change in GCS score from day 1 to 3 months in both the groups ($p<0.001$) (Figure 1).

On the day 1, the KPS score was slightly lower in Amantadine group ; on the day 7, it was slightly lower in Amantadine group and after 3 months, it was significantly lower in Amantadine group ($p=0.006$). The change of KPS score from day 1 to day 7 and day 7 to 3 months were comparable in both the groups. There were significant change in KPS score from day 1 to 3 months in both the groups ($p<0.001$) (Figure 2).

On the day 1, the DRS score was slightly higher in Amantadine group; on the day 7, it was slightly higher in Placebo group and after 3 months, it was significantly lower in Amantadine group ($p=0.011$). The change of DRS score from day 1 to day 7 and day 7 to 3 months were comparable in both the groups. There were significant change in DRS score from day 1 to 3 months in both the groups ($p<0.001$) (Figure 3).

On the day 1, the MOCA score was slightly higher in Placebo group; on the day 7, it was significantly higher in Amantadine group ($p=0.033$) and after 3 months, it was significantly higher in Amantadine group ($p=0.038$). The change of MOCA score from day 1 to day 7 and day 7 to 3 months were significantly greater in Amantadine group ($p=0.029$ and $p=0.046$ respectively). There were significant change in MOCA score from day 1 to 3 months in both the groups ($p<0.001$) (Figure 4).

Table 1. Comparison of various parameters between the groups

Parameters	Amantadine (N=150)	Placebo (N=150)	p value
Male sex	126 (84%)	123 (82%)	0.644
Age (years)	35.53±13.74	36.93±13.24	0.432
GCS			
Day 1	12.43±4.40	12.58±4.31	0.395
Day 7	14.26±5.84	14.24±5.91	0.737
3 Months	14.98±7.13	14.76±6.23	0.034*
Change from Day 1 to Day 7	1.85±1.08	1.65±0.94	0.150
Change from Day 7 to 3 Months	0.72±0.26	0.52±0.32	0.186
KPS			
Day 1	77.63±9.93	78.76±8.78	0.360
Day 7	89.15±9.02	90.44±7.61	0.242
3 Months	95.56±8.98	98.85±3.20	0.006*
Change from Day 1 to Day 7	11.53±4.46	11.68±4.98	0.802
Change from Day 7 to 3 Months	6.41±4.66	8.41±6.35	0.224
DRS			
Day 1	18.85±8.03	18.27±8.90	0.206
Day 7	12.54±3.48	11.58±4.26	0.649
3 Months	5.07±2.73	2.65±2.99	0.011*
Change from Day 1 to Day 7	8.31±2.19	7.69±2.52	0.078
Change from Day 7 to 3 Months	7.47±2.30	8.93±2.69	0.763

*Statistically significant difference

Table 2. Comparison of MOCA scores between the groups

Parameters	Amantadine (N=150)	Placebo (N=150)	p value
MOCA			
Day 1	18.91±1.13	19.64±1.97	0.070
Day 7	24.48±2.31	23.35±2.63	0.033*
3 Months	28.31±3.11	26.23±2.30	0.038*
Change from Day 1 to Day 7	5.57±2.02	3.71±1.03	0.029*
Change from Day 7 to 3 Months	3.83±1.85	2.88±1.23	0.046*

*Statistically significant difference

Figure 1. Change in GCS scores over time

	Day 1	Day 7	3 Months
Amantadine	12.43	14.28	14.98
Placebo	12.58	14.24	14.76

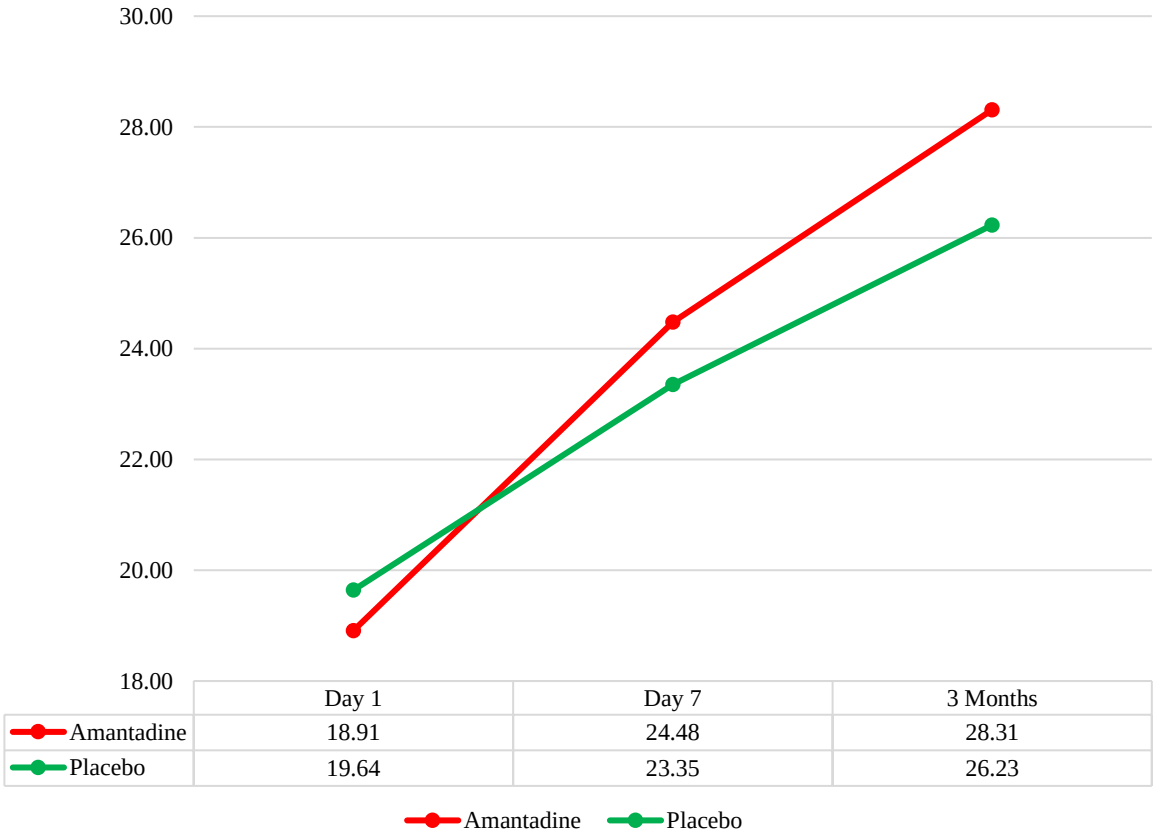
Figure 2. Change in KPS scores over time

	Day 1	Day 7	3 Months
Amantadine	77.63	89.15	95.56
Placebo	78.76	90.44	98.85

Figure 3. Change in DRS scores over time

	Day 1	Day 7	3 Months
Amantadine	18.85	12.54	5.07
Placebo	18.27	11.58	2.65

Figure 4. Change in MOCA scores over time



	Day 1	Day 7	3 Months
Amantadine	18.91	24.48	28.31
Placebo	19.64	23.35	26.23

DISCUSSION

The present study was carried out toevaluate the efficiency of AMH immediately to improve the cognitive function in patients with moderate–severe TBI and whether the use of AMH in acute phase of post-injury period for 6 weeks can improve cognitive function of them on 3 months later. The GCS, KPS and DRS scores were found to be significantly improved in AMH group after 3 months (p=0.034, 0.006 and 0.011 respectively). The MOCA score was significantly higher in Amantadine group after 7 days and after 3 months (p=0.033 and 0.038respectively). The change of MOCA score from day 1 to day 7 and day 7 to 3 months were significantly greater in Amantadine group (p=0.029 and p=0.046 respectively).

Meythaler et al. (2002)[16] conducted a study on amantadine to improve neuro-recovery in traumatic brain injury–associated diffuse axonal injury. 35 subjects, who had a TBI in a transportation accident and were initially seen with a GCS score of 10 or less within the first 24 hours after admission, were randomly assigned into Amantadine and placebo groups. Amantadine, 200 mg, or placebo was each administered for 6 weeks to patients who wererecruited consecutively. There was significant improvement in DRS score and cognitive function in the Amantadine group in comparison to the placebo group. Giacino et al. (2012)[17] conducted a placebo-controlled trial of amantadinefor severe traumatic brain injury. 184 patients who were in a vegetative or minimally conscious state 4 to16 weeks after traumatic brain injury and who were receiving inpatient rehabilitation were included in the study.The rate of functional recoveryon the Disability Rating Scale was compared over the 4 weeks of treatment. During the 4-week treatment period, recovery was significantly faster in the amantadinegroup than in the placebo group, as measured by the DRS score. Amantadine accelerated the pace of functional recovery during active treatment inpatients with post-traumatic disorders of consciousness.

Hammond et al. (2015)[18] reported that theuse of AMH twice a day, for 60 days, may reduce irritabilityand irritability-associated perceived distress at sixtieth day. This significant difference can bedue to faster recovery in the AMH group or, on the otherhand, due to the higher mean baseline GCS in the AMHgroup than in the placebo group. Ghalaenovi et al (2018)[19], in their study on the effects of amantadine on traumatic brain injury outcome to show the effects of a dopaminergic drug, AMH, on patients with moderate to severe TBI in the first week of the post-traumatic period and then, on arousal, responsiveness, cognition and function of these patients after 6 months. They included 40 patients in the study. Significant difference between AMH and placebo groups were seen in reduction of GCS score at day 7. Overall AMH was not found to have any significant effects on the patients' level of consciousness, memory, disability,cognition, mortality, and performance. A systematic review by Loggini et al. (2020)[20] reported that amantadine seems to be well tolerated and might hasten the rate of cognitive recovery in the intermediate-term outcome and the long-term effect of amantadine in cognitive recoveryis not well defined and further large randomized clinical trials in refined subgroups of patients are needed tobetter define its application.Based on the findings of the current study, overall better recovery in the AMH group can be predicted.

CONCLUSION

The present study was one of the largest cohart study, which designed to show the effects of amantadine on the cognitive functions of these patients with moderate to severe TBI after 3 months. The results showed that amantadine produced significant effects in the improvement of the patients' cognitive function with respect to GCS, KPS, DRS and MOCA scores. However, multicetric research on larger samples is recommended.

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