AMANTADINE SULFATE EFFECTS ON THE OUTCOME OF PATIENTS WITH MODERATE AND SEVERE TRAUMATIC BRAIN INJURY

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ABSTRACT

Background: Traumatic brain injury (TBI) is a significant cause of morbidity and mortality. Because of its effect on both dopamine and N-methyl-D-aspartate (NMDA) channels, amantadine has been one of the most commonly prescribed medications for patients with prolonged disorders of consciousness after traumatic brain injury. Preliminary studies have suggested that amantadine may promote functional recovery. **objectives:** The aim of this study was to determine the effectiveness of amantadine sulfate in improving the outcome of patients with moderate and severe TBI. **Patients and methods:** Ninty patients with moderate to severe TBI-were randomly allocated into two groups [45 patients each]. Group A received the usual protocol of management of head injury in our ICU, group B received the usual protocol of management of head injury plus amantadine sulfate i.v infusion 200 mg/12 hours for 14 days. Clinical data of all patients were recorded in the admission sheets of the ICU . The GCS was used to assess level of consciousness. It was recorded on admission, end of the 1st week , 2nd week and 4th week of taruma. Patients outcome were assessed at the end of the 4th week with GOS in both groups. **Results:** There were no statistically significant differences between both groups in GCS on admission to the ICU. While at the end of the 1st , 2nd week and4th week, both groups showed improvement in GCS, however, amantadine group showed better GCS ($p<0.005$) compared to the other group. Also, patients in amantadine group showed better outcome (GOS) in comparison with the other group at the end of the 4th week. **Conclusion:** amantadine can improve the outcome of patients with moderate and severe TBI.

Key Words: amantadine sulfate, traumatic brain injury, outcome, recovery

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INTRODUCTION

Head injury is defined as injuries that affect the brain and also the skull, scalp , maxilla, mandible and special senses as hearing, vision and smell, which also described as brain injury or traumatic brain injury [TBI]. TBI is a result of trauma or insult that affect the brain from an external force, which can lead to partial or complete defect in the psychosocial physical, and cognitive functions and it can be associated with change in the level of consciousness [1].

TBI is one of the main cause of death in childhood and young adults and produce a major public health problem, motor vehicle accidents remain a major cause of TBI followed by falls, and this problem is actually increasing, particularly in developing nations.[2].

Brain trauma occurs due to the direct effect of trauma or by acceleration alone. Beside the damage occurs at the time of injury, brain trauma can result in a secondary insult, which is a group of events happens in the moments,hours and days after the injury.The change in cerebral blood flow and the pressure within the skull as a result of these processes , involved into the damage of the brain from the initial injury [3].

There are different systems to classify TBI. Systems classifying TBI by severity, depending on clinical data at the time the patient came to hospital such as the Glasgow Coma Scale[GCS]. System used to assess level of consciousness, based on the best motor, verbal and eye-opening responses of the patient which classify injury severity as minor [GCS 13–15], moderate [GCS 9–12] and severe [GCS 3–8]. TBI is also classified by biomechanical and neuropathological type i.e. type of insult such as haematoma, haemorrhages and diffuse axonal injury. other

classification systems include classification of TBI by outcome and prognosis. [3].

The NMDAR is a specific type of ionotropic glutamate receptor. calcium flux through NMDA receptors is thought to play a critical role in synaptic plasticity, a cellular mechanism for learning and memory. Acute brain injury causes a rapid release of glutamate with overactivation of NMDA receptors causing increase in intracellular calcium concentration and nerve-cell toxicity, Reduced dopamine levels are also noted after TBI[4].

The dopaminergic agonist amantadine enhances presynaptic dopamine release and inhibits dopamine reuptake, resulting in an increased amount of dopamine in the synaptic cleft. Amantadine may also increase the density of postsynaptic dopamine receptors and alter the conformation of these receptors. Amantadine acts as an NMDA receptor antagonist, blocking glutamate, an NMDA channel activator. This effect may be responsible for amantadine's possible beneficial effect soon after TBI [5].

The aim of the present study was to determine the effectiveness of amantadine sulfate in managment of patients with moderate and severe TBI which may help to improve conscious level and outcome of these patients.

PATIENTS AND METHODS

- This randomized clinical study was carried out at Zagazig University hospitals over a period of two years from first of october 2012 to the end of october 2014. It was done after approval of the local ethics committee and the patient's written informed consent which was obtained from relatives. Inclusion criteria were: (i)traumatic brain injury with a GCS score of moderate (9-12) and sever (3-8), (ii)Age at injury 15-60 years.(iii) patients recently admitted to the ICU. Exclusion criteria were: postcardiac arrest and brain death.

The patients of the present study were randomly allocated into two equal groups [45 patients each] by computer generated randomized table :

- ***Group A*** patients preceived the stander protocol of management of head injury in the ICU.
- ***Group B*** patients preceived the stander protocol of management of head injury plus amantadine sulfate (PK-Merz) i.v infusion in dose of 200 mg/12 hours for 14 days **.**

All patients were transmitted to ICU after receiving initial management (advanced trauma life support protocol) in resuscitation room of the emergency department to receive the following standered protocol of management of head injury in our ICU

Ventilatory support, sedation and analgesia:

Mechanical ventilation was used early in the management of TBI.In order to maintain normal values of arterial oxygen (PaO2 >80 mmHg) and carbon dioxide partial pressures, (PaCO2 35-40mmHg). This was achieved with the help of sedative drugs as propofol i.v Infusion titrated to response (range 0.5–6 mg /kg/h) ,midazolam i.v infusion (0.04–0.2 mg/ kg/h) and opioids as fentanyl i.v infusion (0.3–0.1 µg / kg/h).

Haemodynamic support:

Patients received intravenous fluid (isotonic crystalloids as lactated ringer , colloids and blood if needed) for obtaining haemodynamic stability [SAP >120 mmHg and MAP >90 mmHg], If an adequate blood pressure cannot easily be achieved, introduction of a vasoactive agent was used with good volume status as dopamine (10-20 µg / kg/min) and noradrenaline (20-200ng/kg/min).

Hyperosmolar therapy:

Mannitol, infusion (0.25-1 gm/kg), was given every 4-6 hours to euvolemic patients having Foley catheter , guided with CVP monitoing. Serum osmolality was monitored and did not exceed 320 mosm/kg.

Early posttraumatic seizure prophylaxis [for 7 days]:

Phenytoin (loading dose 10-20 mg/kg followed by maintenance dose 100mg/6-8h) was used in :GCS < 10 , cortical contusion , Depressed skull fracture , Subdural and epidural hematoma , penetrating head wound, Seizure within 24 hours of injury.

Nutritional support:

We started with intravenous fluids however we tried to start enteral feeds as soon as possible as long as there was no vomiting

by using prepared formula (fresubin). Combined or total parenteral nutrition was used in the case of high gastric residual volume or associated abdominal trauma.

Glycaemic control:

As adequate level of glucose in plasma is associated with lower morbidity and better outcome, so a protocol of glycaemic control was derived to maintain a glucose level of [140 -180 mg/dl][6].

Peptic ulcer prophylaxis:

As TBI is a well-known risk factor for stress ulcers in the ICU, so stress ulcer prophylaxis was used for all patients by early enteral feeding, and pharmacological prophylaxis such as H2- blockers (zantac), proton-pump inhibitors (controloc).

Deep venous thrombosis (DVT)prophylaxis:

Patients received DVT prophylaxis with low molecular weight heparin(clexane 40mg/24h) unless contraindicated or intermittent pneumatic compression devices or both.

The following parameters were detected and recorded in each group:

Clinical data on admission:

clinical data of all patients was recorded in the admission sheets of ICU , these data includes : etiology of trauma,basal GCS , vital signs [blood pressure, heart rate, oxygen saturation], Pupil (size, reactivity and if symmetrical or not) and other body trauma as bone fractures, Pneumothorax,others ….

The imaging findings:

CT was done to all patients on admission to ICU to detect the basal pathological lesions as brain odema, hemorrhagic contusions , fracture base extradural hemorrhage , subdural hemorrhage and so on.

Glasgow Coma Scale[GCS]:

The GCS is the most common system used to assess the level of consciousness. It depends on the best motor, verbal and eye-opening responses and is used to classify insult severity as minor [GCS 13–15], moderate [GCS 9–12] and severe [GCS 3–8] it was recorded on admission , end of 1st week , 2nd week and 4th week of trauma to detect the improve in level of consciousness after management in both groups and within the group.

Glasgow Outcome Scale [GOS]:

Patients in both groups were assessed with GOS on the end of 4th week which classify patients into : dead, vegetative state, severe disability, moderate disability and good recovery [7].

Statistical analysis:

All data were analyzed using SPSS 15.0 for windows [SPSS Inc., chicago, IL, USA] & Medcalc 13 for windows [Medcalc Software bvba].

continuous data are expressed as the mean ± SD & median [range], and the categorical data are expressed as a number [percentage]. We checked normality of continuous data by using Kolmogorov-Smirnov test. Independent Student t-test was used to compare two groups of normally distributed data, Mann-Whitney U [MW] test was used to compare non-parametric distributed data between two groups. Friedman test was used to compare more than two items within groups of dependent non-normally distributed data.categorical data were compared using the chi-square [χ^2] test.

$p < 0.05$ was considered statistically significant [S], $p < 0.005$ was considered highly statistically significant [HS], and $p > 0.05$ was considered non statistically significant [NS].

RESULTS

There were no statistical significant differences between both groups as regard sex, and age [table 1].

Statistically, both groups did not differ significantly in the clinical data [table 2] or the CT imaging findings [Table3] that was recorded in the admission sheets of the ICU.

There were no statistically significant differences between both groups in GCS on admission to the ICU, while at the end of the 1st, 2nd and the 4th week, GCS was improved in both groups but this improvement was statistically significantly better in group B in comparison with the other group [Table 4]],[figer 1]

At the end of the 4th week, the number of patients with better GOS was more in amantadine group that indicated better improvement in the recovery ($p<0.05$) than that in the other group [Table 5

Table [1]: Demographic characteristics

Demographic data	Group A [*n*=45]		Group B [*n*=45]		Test	*p*
Age [years]					**t**	
Mean ± SD	30.47 ± 8		29.6 ± 8.26		0.505	0.615
Median [Range]	29 [18 – 43]		29 [18 – 45]			[NS]
Gender					χ^2	
Male [NO (%)]	39	86.7 %	36	80 %	0.720	0.396
Female[NO(%)]	6	13.3 %	9	20 %		[NS]

- t [Independent Student test]
- x² [chi square test].
- Data expressed as Mean ± SD,median , or number [N] and percentage [%].
- p > 0.05 was considered non statistically significant. [NS]

Table [2]: *Clinical* data on admission:

Clinical data			Group A [*n*=45]		Group B [*n*=45]		Test	*p*
Etiology of trauma	NO	%	NO	%			χ^2	
RTA			39	86.7 %	37	82.3 %	3.120	0.210
Fall from height			5	11.1 %	6	13.3 %		[NS]
Gun shoot			1	2.2 %	2	4.4 %		
Systolic blood pressure [mmHg]							**t**	
Mean ± SD			106.33 ± 10.52		109.33 ± 12.64		-1.224	0.224
Median [Range]			110 [90 – 130]		110 [90 – 130]			[NS]
Diastolic blood pressure [mmHg]							**MW**	
Mean ± SD			66 ± 6.17		68 ± 7.56		877.5	0.233
Median [Range]			70 [60 – 80]		70 [60 – 80]			[NS]
Heart rate [b/min]							**t**	
Mean ± SD			76.2 ± 8.22		75.73 ± 7.31		0.284	0.777
Median [Range]			75 [65 – 90]		75 [65 – 90]			[NS]
Oxygen saturation [%]							**MW**	
Mean ± SD			95.47 ± 1.21		95.27 ± 1.40		963.00	0.671
Median [Range]			96 [92 – 97]		96 [92 – 97]			[NS]
Pupil size	NO	%	NO	%			χ^2	
Dilated			43	95.5 %	45	100 %	3.103	0.078
Constricted			2	4.5 %	0	0 %		[NS]
Pupil reaction to light	NO	%	NO	%			χ^2	
Reactive			36	80 %	39	86.7 %	0.559	0.455
Non reactive			9	20 %	6	13.3 %		[NS]
Both pupils	NO	%	NO	%			χ^2	
Symmetrical			33	73.3 %	36	80 %	0.559	0.455
Asymmetrical			12	26.7 %	9	20 %		[NS]
Other body trauma	NO	%	NO	%			χ^2	
Yes			24	53.3 %	21	46.7 %	0.400	0.527
No			21	46.7 %	24	53.3 %		[NS]
Bone fracture			21	46.7 %	24	53.3 %	0.400	0.527 [NS]
Pneumothorax			3	6.7 %	0	0 %	3.103	0.078 [NS]

- RTA : road traffic accident
- MW[Mann-Whitney test]
- t [Independent Student test]
- x² [chi square test].
- Data expressed as Mean ± SD,,Median , or number [N] and percentage [%].
- p > 0.05 was considered non statistically significant. [NS]

Table [3]:the CT imaging findings.

Imaging findings	Group A [*n*=45]		Group B [*n*=45]		χ^2	*p*
	No	%	No	%		
Brain odema	45	100 %	45	100 %	0.011	0.916 [NS]
SAH	9	20 %	12	26.7 %	0.559	0.455 [NS]
SDH	9	20 %	6	13.3 %	0.720	0.396 [NS]
EDH	9	20 %	12	26.7 %	0.559	0.455 [NS]
Pontine hemorrhage	2	4.4%	0	0 %	3.103	0.078 [NS]
Hemorrhagic Contusions	30	66.7 %	36	80 %	2.045	0.153 [NS]
Fracture base	9	20 %	15	33.3 %	2.045	0.153 [NS]
Fracture mandibule	0	0 %	3	6.7%	3.103	0.078 [NS]

- SAH : subarachiniod hemorrhage
- SDH : subdural hemorrhage
- EDH : epidural hemorrhage
- x^2 [chi square test].
- Data expressed as number [N] and percentage [%].
- p > 0.05 was considered non statistically significant[NS].

Table [4] Glasgow Coma Scale.

	Group A [*n*=45]	Group B [*n*=45]	Test	*p*
GCS on admission			**MW**	
Mean ± SD	6.07 ± 1.35	5.82 ± 1.51	925.500	0.472
Median [Range]	6 [4 – 8]	5 [4 – 8]		[NS]
GCS end of 1st week			**MW**	
Mean ± SD	7.13 ± 1.40	8.2± 1.48**	667.500	**0.004**
Median [Range]	8 [4 – 9]	8 [5 – 11]		**[HS]**
GCS end of 2nd week			**t**	
Mean ± SD	8.58 ± 2.50	10.24 ± 2.16**	- 3.373	**0.001**
Median [Range]	8 [4 – 13]	10 [5 – 14]		**[HS]**
GCS end of 4th week			**MW**	
Mean ± SD	11 ± 4.09	13 ± 3.15*	678.000	**0.005**
Median [Range]	12 [3 – 15]	15 [3 – 15]		**[S]**
Friedman χ^2	66.542	111.816		----
P	**<0.001 [HS]**	**<0.001 [HS]**		

- Data expressed as Mean ± SD,,Median
- p > 0.05 was considered statistically non significant. [NS]
- ***** p< 0.05 was considered statistically significant **[S]**
- ****** p< 0.005 was considered statistically highly significant **[HS]**
- MW[Mann-Whitney test]
- t [Independent Student test]
- x^2 [chi square test].

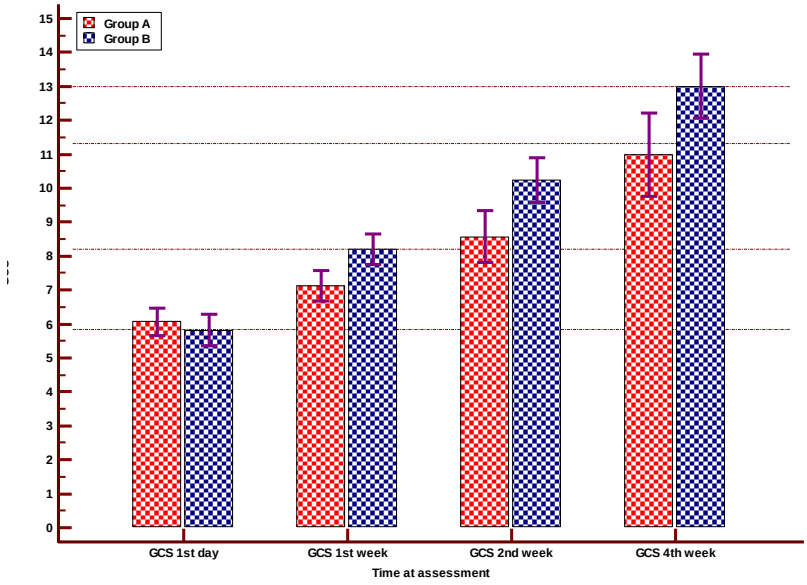

Figure [1] Error bar chart shows comparison between studied groups as regard GCS at different time of assessment showing nearly similar GCS on admission and better GCS at 1st week , 2nd week and 4th week in group B

bar represent mean

error bar around mean represent 95% confidence interval of mean

horizontal line represent reference line.

GCS : Glasgow Coma Scale

Table [5] Glasgow Outcome Scale.

Glasscow Outcome Scale	**Group A [*n*=45]**		**Group B [*n*=45]**		χ^2	***p***
	No	**%**	**No**	**%**		
Good recovery	12	26.7 %	24	53.3 %		
Moderate disability	6	13.3 %	9	20 %		
severed disability	10	22.2 %	3	6.7 %	11.242	**0.024* [S]**
vegetative	9	20 %	6	13.3 %		
Dead	8	17.8 %	3	6.7 %		

- x^2 [chi square test].
- Data expressed as number [N] and percentage [%].

***** $p < 0.05$ was considered statistically significant. compared to the other Group**.**

DISCUSSION

In this study we tried to determine the effect of amantadine sulfate in management of patients with moderate and severe TBI and found that amantadine sulfate improved recovery in those patients as GCS and GOS were statistically significant better compared with patients not received amantadine sulfate.

The result of the present study are consistent with **Spritzer et al.**[8] who

compared the rate of recovery, in a total of 184 patients with severe TBI. Patients were randomized to receive amantadine [87] or visually identical placebo [97] over the 4-week study interval, with the difference that the rate of recovery, was measured by the Disability Rating Scale. They found better outcome in the treatment group as compared with the placebo group over the 4-week treatment interval**,** and they demonstrated that amantadine improved recovery in patients with moderate and severe TBI **.**

Sawyer et al.[9] also concluded that Amantadine 200– 400 mg/day may safely improve arousal and cognition in patients with TBI.

Giacino et al.[10] used amantadine in 184 patients for 4 to 16 weeks after TBI they found that amantadine in patients with post-traumatic disorders of consciousness improved functional recovery.

This study is consistent with other studies in the neuroprotective effects of amantadine when started early after TBI. Rationale for the early effects of amantadine is that amantadine has profound NMDA antagonist effects, It is theorized that it can block the response of glutamate and other activators of the NMDA channel by blocking excessive calcium influx into the cell. Amantadine may promote dopaminergic activity by facilitating presynaptic release and blocking reuptake postsynaptically[8,10].

On the other hand other authors[11,12] defined that it is difficult to document the improvements due to treatment with amantadine for different reasons. First, the biases in patient selection and treatment allocation could not be prevented as some study designs were retrospective. Spontaneous recovery of TBI patients can occurs, making crossover designs problematic. Also this type of recovery could mask whether improvement was truly duto the drug. Causes of TBI were often heterogeneous, and time from injury was also often variable and sometimes not detected. In addition, amantadine dosing and duration of treatment were variable. The outcome measures used was variable, making difficulty in comparing between studies.

Hughes et al.[13] studied 123 adults with severe TBI, 28 cases received 100-200 mg of amantadine twice daily , 13 from 28 cases emerged from coma (46.4%) compared to 36 from 95 of controls(37.9%) .The significant predictor of emergence from coma was Somatosensory evoked potential [SSEP].Hughes and colleagues did not support the view that amantadine can affect recovery of consciousness.

Morris.,et al.[14] concluded failure of the competitive NMDA antagonist in the treatment of severe head injury. The difference can be explaind by the use Selfotel NMDA antagonist.This failure was due to inappropriate design of clinical studies and to the deficient properties of the molecules that entered human trials [15].

Necrosis- and apoptosis-mediated excitotoxic cell death is implicated in the pathophysiology of many neurologic diseases, including stroke, CNS trauma. Excitotoxicity, defined as excessive exposure to the neurotransmitter glutamate or overstimulation of its membrane receptors, has been implicated as one of the key factors contributing to neuronal injury and death. Excitotoxic cell death is due, at least in part, to excessive activation of *N*-methyl-D-aspartate (NMDA)-type glutamate receptors and hence excessive Ca^{2+} influx through the receptor's associated ion channel. Physiological NMDA receptor activity, however, is also essential for normal neuronal function; potential neuroprotective agents that block virtually all NMDA receptor activity will very likely have unacceptable clinical side effects. In contrast, **Lipton**[16] showed that memantine, an adamantane derivative, preferentially blocks excessive NMDA receptor activity without disrupting normal activity.

On the other hand, different studies proved the ability to use amantadine in a clinically well tolerated, non-toxic manner[9,10]. It seems to be quite safe with no serious adverse side effects, and. The reported administration of amantadine was in dose ranged from 50 to 400 mg daily in divided doses for the treatment of TBI for 4 to 16 week and the adverse effects were dose dependent and reversible [17].

The present study has some limitations. The small number of patients that included in present study and the short period of the study may affect the results, so, additional larger randomized trials are needed to better define the role of amantadine in TBI, including its role in specific types of TBI, optimal time for initiation, and duration of therapy

In conclusion, the early use of amantadine sulfate improves the outcome in patients with moderate and severe TBI with our standard protocol of management in the ICU.

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