ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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A Short Question: Can Amantadine Sulfate Infusion be a Life Saver in Intensive Care Unit?

Kısa Bir Soru: Amantadin Sülfat İnfüzyonu Yoğun Bakım Ünitesinde Hayat Kurtarıcı Olur mu?

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ABSTRACT Objective: Traumatic brain injury (TBI) is one of the leading causes that cognitive and behavioral problems. Many pharmacological therapies reveal early neurochemical changes. The CRS-R is a standardized neuro-behavioral evaluation tool comprising six organized subscales (auditory, visual, motor, oromotor–verbal, communication, and arousal). We hypothesized that, the effect of amantadine sulfate infusion treatment on conscious recovery and clinical improvement in patients with severe head injury in terms of CRS-R and clinical recovery. **Material and Methods:** Patients' age, gender, days of hospitalization, pre-treatment and post-treatment GCS, education level, day of amantadine sulfate, intubated or non-intubated when he/she come to intensive care unit (ICU), recovery time of conscious, discharge time, CT or MR pathology will be retrospectively recorded. Patients were aged >18 years, had brain trauma, had amantadine sulfate therapy in ICU were included the study between June 2016-June 2017. **Results:** A total of 40 patients using amantadine sulfate infusion were included in the study. It was determined that 13 of patients had mortality. Improvement in CT and MRI findings were detected in 21 of the living patients (77.8%). There were no differences between the mean starting time according to the clinical recovery levels and recovery status on CT-MRI. There were statistically significant differences between starting time and time of extubation and starting time of consciousness recovery and discharge time. **Conclusion:** In conclusion, we believe that amantadine treatment accelerates neurological recovery in terms of CRS-R and clinical recovery in TBI patients.

Keywords: Amantadine sulfate; cerebral injury; traumatic brain injury

ÖZET Amaç: Travmatik beyin hasarı (TBH), bilişsel ve davranışsal sorunların önde gelen nedenlerinden biridir. Birçok farmakolojik tedavi erken nörokimyasal değişiklikleri açıklamaktadır. CRS-R, altı organize alt ölçek (işitsel, görsel, motor, oromotor-sözel, iletişim ve uyarılma) içeren standartlaştırılmış bir nöro davranışsal değerlendirme aracıdır. Biz CRS-R ve klinik iyileşme açısından ağır kafa travmalı hastalarda amantadin sülfat infüzyon tedavisinin bilinç düzeyinde ve klinik iyileşme üzerindeki etkisini sunmayı amaçladık. **Gereç ve Yöntemler:** Hastaların yaşı, cinsiyeti, hastanede yatış günleri, tedavi öncesi ve tedavi sonrası GKS, eğitim düzeyi, amantadin sülfat günü, entübe gelip gelmediği, bilinçte düzelme zamanı, taburculuk süresi, BT veya MR patolojileri retrospektif olarak kaydedildi. Haziran-Haziran 2017 tarihleri arasında 18 yaş üstü, beyin travması geçiren, yoğun bakımda amantadin sülfat tedavisi alan hastalar çalışmaya dahil edildi. **Bulgular:** Çalışmaya amantadin sülfat infüzyonu kullanan toplam 40 hasta dahil edildi. Hastaların 13'ünde mortalite olduğu tespit edildi. Yaşayan hastaların 21'inde (%77,8) BT ve MR bulgularında iyileşme saptandı. Klinik iyileşme düzeylerine ve BT-MR'da iyileşme durumuna göre ortalama başlangıç zamanı arasında fark yoktu. Başlangıç zamanı ve ekstübasyon zamanı ile bilincin düzelme ve taburculuk süresinin zamanı arasında istatistik olarak anlamlı fark gözlendi. **Tartışma:** Sonuç olarak, amantadin sülfat tedavisinin, CRS-R açısından da değerlendirildiğinde TBH hastalarında klinik iyileşme ve nörolojik iyileşmeyi hızlandırdığını düşünüyoruz.

Anahtar Kelimeler: Amantadin sülfat; serebral yaralanma; travmatik beyin hasarı

Traumatic brain injury (TBI) is one of the leading causes that cognitive and behavioral problems. Many pharmacological therapies reveal early neurochemical changes. The target for treatment includes the dopaminergic pathway. Decreases in patients with dopamine levels may lead to decreased frontal lobe stimulation. Manipulation of dopamine receptors to improve circulatory levels can improve cognitive and functional outcomes.[1] Amantadine, well known for Parkinson's disease and cognitive dysfunction, has been used in patients with traumatic brain injury. It affects dopamine levels by facilitating neural oscillation. Amantadine provides important neuroprotective effects with the antagonism of N-methyl-D-aspartate receptors. Amantadine sulfate, a direct effect of neuroprotective drugs, is an effect of dopamine agonist and activates an enhanced alertness, concentration, EEG alpha wave enhancement, hippocampus, and neocortical synchronization.[2]

For evaluation the status of neuro-behavioral evaluation, there is a need for scores that measure the recovery of neurological and behavioral symptoms such as this studies. One of this score is CRS-R for gauge. The CRS-R is a standardized neuro- behavioral evaluation tool comprising six organized subscales (auditory, visual, motor, oromotor–verbal, communication, and arousal).[3]

In our study, we hypothesized that, the effect of amantadine sulfate infusion treatment on conscious recovery and clinical improvement in patients with severe head injury in terms of CRS-R and clinical recovery.

MATERIAL AND METHODS

In this study, patient files and computer system records of patients who were followed up for head trauma in the intensive care unit between June 2016-June 2017 will be retrospectively screened.

Patients' age, gender, additional disease, days of hospitalization, pre-treatment and post-treatment GCS, education level, day of amantadine sulfate, intubated or non-intubated when he/she come to ICU, recovery time of conscious, discharge time, CT or MR pathology will be retrospectively recorded. Patients were aged >18, had brain trauma, had amantadin sulfate therapy in ICU were included the study. Exclusion criteria of the study was patients aged <18.

This study was certified by the local ethics committee with date and number of 2018.4.16.

RESULTS

A total of 40 patients using amantadine sulfate infusion were included in the study. It was determined that 13 of patients had mortality. Twenty-three of the 27 patients were male and 4 were female. Twenty-five patients were intubated during admission of ICU.

Educational status and demographic and clinical characteristics of patients were showed at Table 1 and Table 2.

A total of 7 patients continued the therapy with oral form. The mean starting time to the oral form were 14.29 (±7.43) days. Of the 27 patients, only 23 had extubation and mean extubation time were 12.96 (±9.3) days. The mean time to recovery in consciousness was 13.48 (±10.4) days. The average discharge time of 27 patients was 33.18 (±40) days.

Frequency of recovery of key behavioral benchmarks on the Coma Recovery Scale–Revised and consciousness level after 4 weeks were showed at (Table 3 and Table 4).

Clinical Recovery of patients were showed at (Table 5).

Improvement in CT and MRI findings were detected in 21 of the living patients (77.8%).

Arrhythmia in ECG was seen in only 1 patient (3.7%). There were no differences between the mean starting time according to the clinical recovery levels. The mean of moderate recovery was found in 3 patients (13±8), good recovery in 4 patients, mean value of 5 (±4.7), and very good recovery in 6 patients (6.5±8).

There was no significant difference between starting time according to recovery status on CT-

TABLE 1: Educational status of patients.

Educational status	Frequency (n:27)	Percent (%)
1 (elementary school)	5	18.5
2 (secondary school)	8	29.6
3 (high school)	12	44.4
4 (University)	2	7.4
Total	27	100

TABLE 2: Demographic and clinical characteristics.

	Mean	Min-max
Age	35.41 (± 14.695)	18-75
Admission GCS	5.04 (± 3)	3-13
Treatment GCS	12.70 (± 2.6)	5-15
Extubation time (day)	12.96 (± 9.3)	2-40
Starting time (day)	7.04 (± 7.8)	1-40

TABLE 3: Frequency of recovery of key behavioral benchmarks on the coma recovery scale-revised.

Clinical status	Frequency (n)	Percent (%)
Consistent command	24	88.9
Object recognition	24	88.9
Functional Object Use	23	85.2
Intelligible Verbalization	17	63
Reliable Yes-or-No communication	24	88.9
Sustained attention	24	88.9

TABLE 4: Consciousness level after 4 weeks.

	Frequency (n)	Percent (%)
0 part of CRS-R	3	11.1
4 parts CRS-R	2	7.4
5 parts CRS-R	5	18.5
6 parts CRS-R	17	63
Total	27	100

TABLE 5: Clinical recovery of patients.

	Frequency (n)	Percent (%)
Moderate	3	11.1
Good	4	14.8
Very good	20	74.1

MRI. Amantadine sulfate infusion was started later with without recovery patients, but the difference was not statistically significant. No improvement was seen on CT-MRI images in 6 patients (7.83± 7.6), and but in 21 patient positive clinical improvement was seen (7±8). Amantadine sulfate infusion was started later in 13 patients who were exitus but the difference was not statistically significant (p> 0.005). Mean value of starting day was found 10.23 (±7.6).

In living 27 patients, the starting day of amantadine sulfate was found 7 (±7.8).

Comparison of the starting time of Amantadine sulfate infusion to the day of extubation were showed at (Figure 1). There were statistically significant differences between starting time and time of extubation (p <0.005).

Comparison of starting time and starting time of consciousness recovery were showed at (Figure 2). There were statistically significant differences

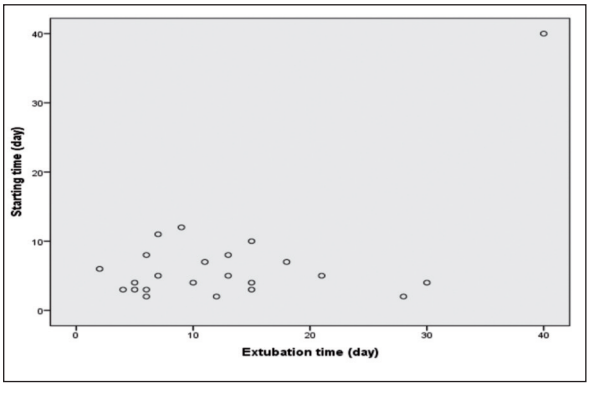

FIGURE 1: Comparison of the starting time of Amantadine sulfate infusion to the day of extubation.

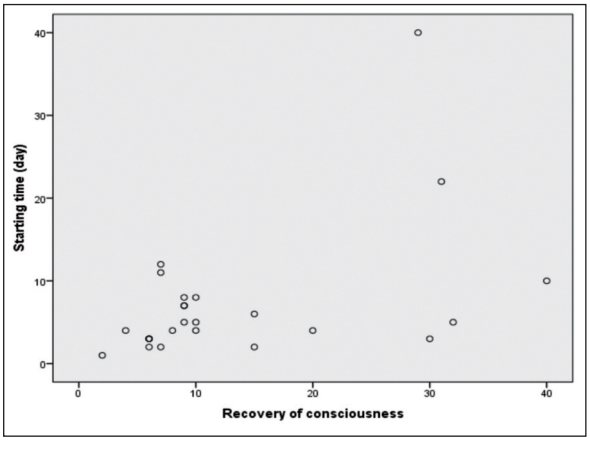

FIGURE 2: Comparison of starting time and starting time of consciousness recovery.

between starting time and starting time of consciousness recovery (p <0.005).

Comparison of starting time and discharge time were showed at (Figure 3). There were statistically significant differences between starting time and discharge time (p <0.005).

DISCUSSION

Amantadine is a dopaminergic agonist and increases presynaptic dopamine discharge and inhibits dopamine reuptake, resulting in enhanced amount of dopamine in synaptic split. Amantadine likes N-methyl-D-aspartate (NMDA) receptor antagonist, blocking glutamate, an NMDA channel activator. That may be responsible for amantadine's feasible beneficial action after TBI.[4]

The acute phase of recovery from TBI is characterized by short period of hypoexcitability, involving consume of many neurotransmitters, including dopamine and catecholamine levels are enhanced in the cerebrospinal fluid (CSF).[5] It has been known that the mechanism or anatomical site of injury may result in differences in the metabolism of neurotransmitters.[6]

Amantadine may promote dopaminergic activity by facilitating presynaptic release and blocking uptake postsynaptically.

Plasma norepinephrine has been shown to correlate with changes in the Glasgow Coma Scale (GCS) score and, therefore, may correlate with the outcome of TBI.[7] Specific treatment early in traumatic brain injuries targeted at neurocyte protection by direct NMDA receptor antagonist, amantadine sulfate, should be started immediately. Between other neuroprotective drugs, amantadine sulfate is specific directly acting dopamine agonist and characteristic by it's central action. This effect is described clinically as a developed vigilance and as a result recovery of perception and concentration, improved forethought and a general raising of mood.[2] In some studies, the influence of amantadine sulfate consists of increasing lucidity of consciousness which was discovered by Glasgow Coma Scale (GCS) measurement.[2,8] Saniova et al. reported a significant improvement in the Glasgow scale and lower mortality rates than those who did not receive amantadine treatment in a retrospective study of 74 patients.[2] Giacino et al. compared the effect of amantadine and placebo on functional recovery in patients with traumatic brain injury and reported that amantadine increased the cognitive and functional recovery rate of the study.[3] Sawyer et al. similarly, in patients with traumatic brain injury, alertness and alertness and found that 200-400 mg/day of amantadine therapy was effective.[4] Nickels et al. reported that amantadine administration in patients with traumatic brain injury is beneficial for neurological recovery.[9] In our study, significant increases were found between at the beginning of the intensive care unit admission GCS and at the end of the hospitalization GCS.

The benefit of amantadine appeared to be consistent, regardless of the interval since injury or whether patients were in a vegetative state or a minimally conscious state at enrollment. Side effects of amantadine sulfate infusion have been reported as decrease in creatinine clearance and changes in ECG rhythm. No side effects related to renal function were recorded in any of our patients. Only one patient had ECG arrhythmia.

Krivanus et al. showed that the use of 200 mg/day amantadine sulfate treatment as an adjunct to conventional treatment for 10 days in acute stroke patients reduced the incidence of neurological deficit.[10] Wu et al. were showed that in a case

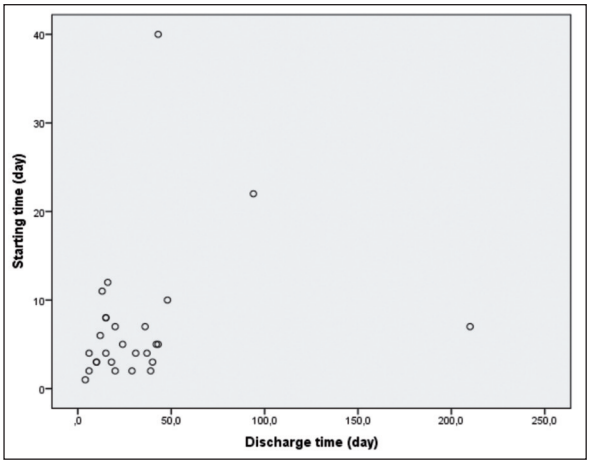

FIGURE 3: Comparison of starting time and discharge time.

who arrested and had ventricular fibrillation, had spontaneous circulation on 20-25th minutes and they were started amantadine sulfate infusion for 11-22nd day.[11] The patient on the 22nd day they reported that the patient could stand up with the help. Aksu et al were started amantadine infusion in a patient whose unconsciousness could not be identified for ten days. A dramatic recovery was detected on the second day following amantadine infusion. The patient was extubated on forth day and discharged on the twenty-first treatment day with a 15 GCS score and they suggested that Amantadine may be added to the standard therapy in comatose patients as it accelerates neurological functional recovery.[12] A recently completed multicenter, trial in an inpatient rehabilitation setting showed that amantadine accelerates the rate of functional recovery.[1] These patients were started on amantadine several weeks after injury. However, at our institution, amantadine is commonly started early after TBI, while patients are in the intensive care unit. In our study, amantadine sulfate infusion was started on the first day of intensive care unit admission for some patients and mean of first day was 7 days and mean extubation day was.[12]

In a case report, a female with improved ability to function after use of amantadine for TBI.[11] She remained unresponsive after a ventricular fibrillation arrest with a GCS of 6 and MRI showing minimal diffuse axonal injury. After 6 doses of amantadine 150 mg, she could withdraw from pain, open her eyes spontaneously, and respond to her name. By day 7, she was alert and oriented, and with little assistance was able to carry out her activities of daily living. With continued physical and occupational therapy, she improved nearly to baseline. Objective measures of her neurologic improvement were not provided. In a study, they recommended that in TBI patients amantadine sulfate infusion has beneficial effects on neurological recovery.[13] In our patients, in 21 patients will improve results on CT or MRI images after amantadine sulfate treatment.

In a clinical study, results showed that in patients with severe brain injury, disturbances of arousal and drive can be favorably influenced by high doses of amantadine sulfate, with a low rate of complications. They said that positive EEG changes were statistically significant with amantadine sulfate therapy and they suggested that in the appropriate individual indication this form of drug therapy should certainly be an addition to neurorehabilitative management.[14] In our study, there were no difference between the beginning day and according to the clinical improvement levels. Moderate improvement was 3 patients, good improvement was 4 patients, very good improvement was 20 patients.

In our study, we evaluated the CRS-R scores. The CRS-R is a standardized neuro-behavioral evaluation tool comprising six organized subscales (i.e., auditory, visual, motor, oromotor–verbal, communication, and arousal).[3] To measure the clinical importance of the effects of amantadine, clinically relevant behavioral criteria were assessed by study personnel using the CRS-R. We used the CRS-R as a qualitative measure to better understand the effects of the study amantadine on associated with a vegetative state, a minimally conscious state, and emergence from a minimally conscious state.[15] In our study, %44.4 of patients graduated from high school so we think that they answered the questions correctly on high rates. In 24 patients, consistent command, object recognition, reliable Yes-or-No communication, sustained attention was detected. In 23 patients Functional Object Use and in 17 patients Intelligible Verbalization were evaluated. According to that, 17 patients (%63) have all six part of this score after 4 weeks.

Steube et al. showed that therapeutic outcomes, overall, very good to good results have been achieved in 66% of cases and their results lie in the middle of the range of various other authors.[14] The nature of the brain injury, the presence of traumatic subarachnoid hemorrhage, neurosurgical interventions, post-contusional changes, and the development of hydrocephalus or its aggravation seem to have no influence on the effects of therapy. They suggested that, their results showed in patients with severe brain injury, disturbances of arousal and drive can be favorably influenced by high doses of amantadine sulfate, with a low rate

of complications.[14] In our study 74.1% of patients have very good clinical recovery with amantadine sulfate infusion therapy.

Limitation of our study, it is not a comparable study. But when we used amantadine sulfate infusion in our ICU to TBI patients, we saw that the patients' neurobehaverial recovery was better than non amantadine sulfate used patients.

In conclusion, we believe that amantadine treatment accelerates neurological recovery in terms of CRS-R and clinical recovery in TBI patients. However, more prospective studies of the effect of amantadine on neurological status are needed.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ayça Sultan Şahin;* ***Design:*** *Ece Salihoğlu;* ***Supervision/Consultancy:*** *Ayça Sultan Şahin;* ***Data Collection and/or Processing:*** *Ayça Sultan Şahin;* ***Analysis and / or Interpretation:*** *Ece Salihoğlu;* ***Source Scanning:*** *Ece Salihoğlu;* ***Written by Makalen:*** *Ayça Sultan Şahin;* ***Critical Review:*** *Ece Salihoğlu;* ***Resources and Funding:*** *Ayça Sultan Şahin;* ***Materials:*** *Ayça Sultan Sahin.*

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