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Amantadin İnfüzyonunun Travmatik Beyin Hasarında Etkisi

Effect of Amantadine Infusion on Traumatic Brain Injury

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ÖZ

Amaç: Travmatik Beyin Hasarı (TBH), önemli bir sosyoekonomik ve halk sağlığı sorunudur. Amantadin sülfat nöroprotektif olarak kullanılan bir ilaçtır. Bu çalışmada, amantadin infüzyon tedavisinin, ciddi kafa travması olan hastalarda bilincin geri dönmesine pozitif etkisini araştırmayı amaçladık.

Materyal ve Metot: TBH olan hastalar, amantadin infüzyonu kullanma durumarına göre iki gruba ayrıldı. Grup I (n=40): amantadin infüzyonu kullanan grup ve Grup II (n=40): amantadin infüzyonu kullanmayan grup. Hastaların yaşları, cinsiyetleri, Glasgow Koma Skalası (GKS), eğitim seviyeleri, yoğun bakım ünitesine geldiğinde entübe olup olmadıkları, bilincin geri dönüş zamanı, taburculuk zamanı ve BT veya MR sonuçları ve Coma Recovery Scale–Revised (CRS-R) skoru retrospektif olarak kaydedildi.

Bulgular: Bilincin geri dönüş zamanı Grup I de istatistiksel olarak belirgin olarak daha kısaydı. Hastaların eğitim düzeyleri arasında istatistiksel olarak anlamlı bir fark saptanmadı. Grup I de hastaların yoğun bakıma kabulü sırasında GKS daha düşüktü. Fonksiyonel nesne kullanımı ve uzun dönemli dikkat Grup I de CRS-R'ye göre daha yüksekti.

Sonuç: Bu çalışmaya göre, amantadin infüzyonu nörolojik iyileşmeyi ve nörokognitif fonksiyonları olumlu yönde etkilemektedir.

Anahtar Kelimeler: Amantadin infüzyonu, beyin, hasar, travmatik

ABSTRACT

Objective: Traumatic brain injury (TBI) is a significant socioeconomic and public health problem. Amantadine sulfate has been used as a neuroprotective drug. In this study, We aim that amantadine infusion treatment effects positively in patients with a severe head injury on conscious recovery.

Materials and Methods: Patients with TBI were classified into two groups: Patients that used amantadine infusion group was Group I (n=40) and patients that not used amantadine infusion group was Group group II (n=40). Age, gender, Glasgow Coma Scale (GCS), education level, intubated or non-intubated when he/she come to Intensive Care Unit (ICU), the recovery time of conscious, discharge time, recovery of CT or MR scan and Coma Recovery Scale-Revised (CRS-R) were retrospectively recorded.

Results: Time to recovery in consciousness was statistically significant shorter in group I. There were no statistically significant differences between the educational status of patients. The GCS of patients, when admitted to ICU, was lower in group I. Functional object use and long-term attention were have higher scores in group I when compared to CRS-R.

Conclusion: Amantadine infusion affects positively neurological recovery and neurocognitive function for TBI in this study.

Keywords: Amantadine ınfusion, brain, ınjury, traumatic

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INTRODUCTION

Traumatic brain injury (TBI) is a complex condition with important socioeconomic and public health problems around the world. Traumatic brain injury causes some cognitive and behavioral problems that may require long-term treatment. In TBI, dopamine is significantly distributed, and dopaminergic agonists may improve outcomes. More specifically, mono-aminergic agents (such as amantadine) may have a more pronounced effect in improving outcomes after TBI.[1] Several medications have been searched following a severe TBI as well as into the acute neuro-rehabilitation course. The goal of these medications is to improve arousal through modulation of the dopaminergic or noradrenergic pathways damaged during the injury or prevention of neuronal injury.[2] Improvement of dopamine receptors make better cognitive outcomes.[3] In TBI for cognitive functions, drugs can be used for proper treatment.[4]

Amantadine is known to increase release and reuptake of dopamine, causing increased concentration of dopamine in the synaptic cleft of neurotransmitters. Amantadine infusion in rats with TBI has been shown to increase striatal release and reuptake of dopamine while improving behavioral deficits. Furthermore, amantadine may act as an N-methyl-d-aspartate antagonist resulting in neuroprotective effects. In patients with TBI, amantadine may enhance cognitive function, concentration, processing time, psychomotor speed, and decreased fatigue.[4]

Amantadine infusion accelerates alertness and concentration and reduces irritability and aggression in individuals with TBI. Many studies showed that amantadine infusion can help the improvement of clinical and neurological status in TBI patients.[5] The Coma Recovery Scale-Revised (CRS-R) is one of the scores that can evaluate the neurological recovery of symptoms. It contains six measures: composed of auditory, visual, motor, oromotor–verbal function, communication, and arousal.[2] These scores are used for patients with disorders of consciousness.[6]

We suggested that, amantadine infusion treatment effects positively neurological recovery and neurocognitive function in patients with a severe head injury on the recovery of conscious with CRS-R in this study.

MATERYALS AND METHODS

This study was certified by the Kanuni Sultan Suleyman Education and Training Hospital ethical committee (Date: 16/04/2018 Decision no: 2018-16).

The inclusion criteria of the study were aged >18, had brain trauma, using amantadine infusion with the first day of ICU admission, GCS ≥ 3. Exclusion criteria of the study were patients aged <18, non-traumatic brain injury, who had more than two co-morbid diseases.

In this study, patient files between June 2016-December 2016 retrospectively scanned. The patients with TBI were classified into two groups: Patients receiving amantadine infusion group was Group I (n=40) and patients receiving standard ICU treatment group was Group group II (n=40). Amantadine infusion was given 200 mg/12 hours for 5 days to TBI patients with loss of consciousness in Group I.

Patients' age, gender, days of hospitalization, Glasgow Coma Score (GCS), education level, day of amantadine infusion, intubated or non-intubated in Intensive Care Unit (ICU), the recovery time of conscious, discharge time, recovery of CT or MR scan were retrospectively recorded. Recovery of Key Behavioral Benchmarks on the CRS-R was also recorded from the patient's files. The CRS-R included Consistent command, Object recognition, Functional Object Use, Intelligible Verbalization, Reliable Yes-or-No communication and Sustained attention parts.

Statistical methods: The SPSS statistical package, version 15.0 (SPSS Inc, Chicago, IL, USA) was used to analyze the statistics. Data were checked for a normal distribution using the SPSS® statistical package. Numerical variables were checked for normal distribution. The Student t-test was used for normally distributed numerical variables and the Mann-Whitney U test was used for non-normally distributed numerical variables. Chi-square test and Fisher exact test were used to compare categorical variables. $p < 0.05$ was considered statistically significant.

RESULTS

A total of 85 patients using amantadine infusion were reviewed in the study. Two patients excluded because of <18 age and 3 patients had missing data. So 80 patients included the study: amantadine infusion group; Group I (n=40) (3 females (7.5%), and 37 males (92.5)), Receiving standard ICU treatment group: Group II (n=40) (10 females (25%) and 30 males (75%)) (Figure 1).

Group I used amantadine infusion initially by intravenous infusion twice a day 200 mg (500 ml) first 5 days admission to ICU. After infusion, continued

with 100 mg tablet once a day if the consciousness did not improve. A total of 7 patients continued the therapy with oral form in Group I. The mean starting time to the oral form was 20.73 (± 15.2) days.

The median value of the starting day of amantadine infusion was found 5 (1-40). Arrhythmia in ECG was seen in only 1 patient (3.7%) in Group I in the context of side effects of amantadine infusion.

Educational status and demographic and clinical characteristics of patients were shown in Table 1 and Table 2.

There were no statistically significant differences between the educational status of patients ($p>0.05$). (Table 1)

The GCS of patients, when admitted to ICU, was lower in Group I, and this was statistically significant ($p <0.05$) (Table 2).

The frequency of recovery of key behavioral benchmarks on the Coma Recovery Scale-Revised and consciousness level after 4 weeks were shown in Table 3 and Table 4.

Functional object use and long-term attention had higher scores in Group I when compared to CRS-R (Table 3).

In Group 1, 17 patients (42.5%), in Group 2 10 patients (25%), totally 27 patients (33.75%) received full scores from all 6 parts of CRS-R (Table 4).

DISCUSSION AND CONCLUSION

In this present study, amantadine infusion affects positively neurological recovery and neurocognitive function for TBI compared to patients who did not receive amantadine infusion treatment. We think that the routine use of amantadine infusion in TBI patients will contribute to neurological healing and cognitive functions. We wanted to emphasize that new studies will contribute to the literature in order to increase the frequency of using this treatment.

Early times of TBI, a lot of neurotransmitters run out and the mechanism of injury differs metabolism of neurotransmitters.[7,8] Amantadine likes N-methyl-D-aspartate (NMDA) receptor antagonist, blocking glutamate, an NMDA channel activator and norepinephrine changes GCS and improve the outcome of TBI.[9,10] In this present study, when we investigated the GCS status, the patients when admitted to ICU had lower GCS in Group I and this was statistically significant. But compared to the treatment GCS status, there was no statistical difference. Because the admission ICU GCS was lower and the number of intubated patients during admission of ICU was more in Group I. Nevertheless, GCS status after treatment, time to recovery in consciousness was shorter in Group I and this was a statistically significant difference. In a study, they found that improvement of GCS and lower mortality rates who did not receive amantadine treatment.[5] When we compared the mortality rates between groups there were no statistically significant differences.

In many studies, in TBI, amantadine accelerate cognitive and neurological recovery.[9,11,12]

Also, we found that GCS increases significantly at the beginning of the intensive care unit admission. Moreover, we found that time to recovery in consciousness was shorter in Group I and this was statistically significant. It shows that in Group I patients came with lower GCS scores so bad clinical status but even so a recovery in consciousness was shorter with treatment, so clinical status was better.

Some studies showed that, in stroke patients, comatose patients or after cardiac arrest amantadine infusion treatment can be used as a conventional treatment after several days.[13-15]A multicenter study suggested amantadine can speed up recovery several weeks after injury.[3] However, in our intensive care unit, amantadine is generally begun earlier after TBI. In this study, amantadine infusion was usually started on the first day of ICU and the median value of the starting time of amantadine infusion was found 5 days (1-40). Although admission to GCS status in Group I was lower, no statistically significant differences were found between mean extubation time. When the groups were compared in terms of discharge time, it was found that the average discharge time of patients was longer in Group I. Because it was determined that Group 1 had more intubated patients, lower GCS status. In our knowledge, amantadine infusion was started in clinically worsening patients but better results were obtained in the improvement of consciousness.

Some studies suggested in severe brain injury, administration of amantadine occurs a low rate of complications and improves neurological recovery.[16,17] Although improvement in consciousness was better in Group I, there was no statistically significant difference in clinical improvement and CT or MRI findings in our study. In this present study, 60% of patients have good clinical recovery.

The CRS-R is a standardized neuro-behavioral evaluation tool comprising six organized subscales (i.e., auditory, visual, motor, oromotor–verbal, communication, and arousal).[18] CRS-R is a qualitative measure for understanding vegetative state, minimally conscious state or emergence from the mini-

mally conscious state. Functional object use and long-term attention had higher scores in Group I when compared to CRS-R. In Group I, 17 patients (42.5%), in Group II, 10 patients (25%), totally 27 patients (33.75%) received full scores from all 6 parts of CRS-R after 4 weeks. In our study, % 41.25of patients graduated from high school so we think that they answered the questions correctly on high rates and there were no statistical differences between the educational status of patients.

There are a lot of trauma scores that use in emergency departments. They usually include hemodynamical parameters. Jeong et al suggested New Trauma Scores (NTS) will be used in triage in trauma patients.[19] In that score, only systolic blood pressure and oxygen saturation were used. In our patients, there were no significant differences between groups. So both of the groups had homogeneous distribution between trauma severity.

In conclusion, amantadine treatment speeds up neurological recovery and ameliorate neurocognitive function with CRS-R and clinical recovery in TBI. Limitations: Because of the retrospective design of the study some important clinical characteristics were not recorded and the sample size is small. Randomized-controlled prospective studies with larger groups can be more significant.

Ethics Committee Approval: Our study was approved by the SBU Kanuni Sultan Suleyman Education and Training Hospiatl Ethics Committee (Date: 16/04/2018, Decision no: 2018.04).

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – A.S.Ş.; Supervision – A.S.Ş.; Materials – S.Ö., A.S.Ş.; Data Collection and/or Processing – S.Ö.; Analysis and/ or Interpretation – S.Ö. Writing – A.S.Ş.

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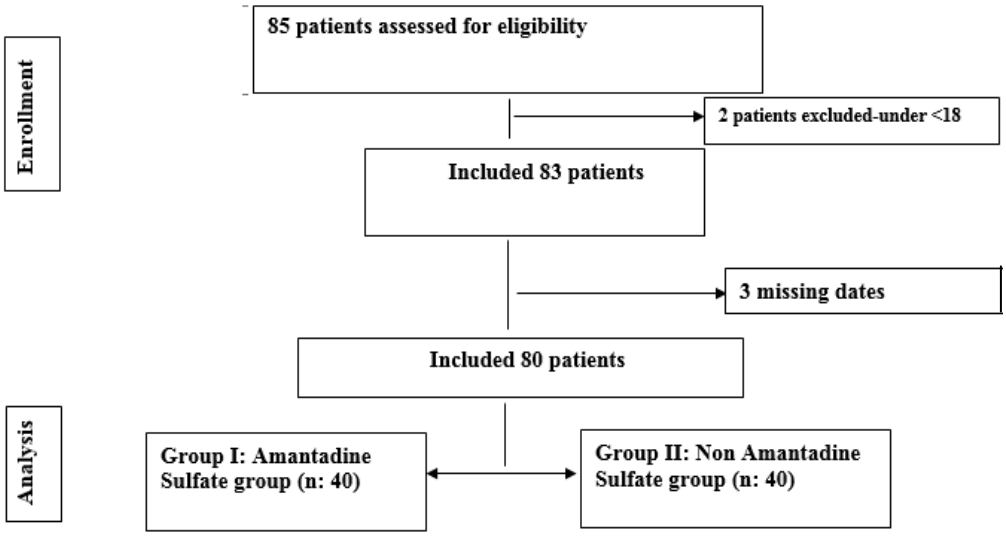

Figure 1. Flow diagram of the study (Flow chart).

Table 1. Educational status of patients.

Educational status	**Group I (n=40)**	**Group II (n=40)**
1(Elementary school)	10 (25%)	11 (27.5%)
2 (Secondary school)	10 (25%)	12 (30%)
3 (High school)	17 (42.5%)	16 (40%)
4 (University)	3 (7.5%)	1 (2.5%)

Table 2. Demographic and Clinical Characteristics.

	Group I (n=40)	**Group II (n=40)**	**p**
Age	34 (18-81)	40 (18-87)	0.60
Admission GCS	3 (3-15)	6 (3-15)	**0.02***
Treatment GCS	11.5 (3-15)	12.5 (3-15)	0.82
Extubation time (day)	11 (2-40)	10 (4-20)	0.60
Mortality	32.50%	40%	0.48
Intubated when admission to ICU	87.5%	57.5%	**0.003***
Extubation time(days)	11(2-40)	10(4-20)	0.6
Recovery in consciousness time (days)	4(1-22)	9(2-40)	**0.03***
Discharge time (days)	30(4-230)	14.5(2-150)	**0.004***
CT and MRI findings	21 (52.5%)	17(42.5%)	0.50
Bad clinical recovery	16 (40%)	23(57.5%)	0.11
Good clinical recovery	24 (60%)	17(42.5%)	0.11

**p <0.05, statistically significant; GCS =Glasgow Coma Score, ICU: Intensive Care Unit*

Table 3. Frequency of Recovery of Key Behavioral Benchmarks on the Coma Recovery Scale–Revised.

Clinical status	**Group I (n=40)**	**Group II(n=40)**	**p**
Consistent command	24 (100%)	23 (95.8%)	1
Object recognition	24 (100%)	23 (95.8%)	1
Functional Object Use	23 (95.8%)	**15 (62.5%)***	0.01
Intelligible Verbalization	17 (70.8%)	12 (50%)	0.23
Reliable Yes-or-No communication	24 (100%)	21 (87.5%)	0.23
Sustained attention	24 (100%)	**11 (45.8%)***	0.01

**p <0.05, statistically significant*

Table 4. Consciousness level after 4 weeks.

	Group I-n (%)	**Group II-n (%)**
0 part of CRS-R	16 (40)	17 (42.5)
4 parts CRS-R	2 (5)	10 (25)
5 parts CRS-R	5 (12.5)	3 (7.5)
6 parts CRS-R	17 (42.5)	10 (25)
Total	40 (100)	40 (100)

CRS-R=Coma Recovery Scale–Revised