



Can Amantadine Ameliorate Neurocognitive Functions After Subarachnoid Haemorrhage? A Preliminary Study

Amantadin Subaraknoid Kanamalarda Nörokognitif Fonksiyonları İyileştiriyor mu? Bir Ön Çalışma

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Cite this article as: Akçıl EF, Dilmen ÖK, Vehid H, Tunalı Y. Can Amantadine Ameliorate Neurocognitive Functions After Subarachnoid Haemorrhage? A Preliminary Study. Turk J Anaesthesiol Reanim 2018; 46: 100-7

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Objective: Aneurysmal subarachnoid haemorrhage (SAH) may have devastating effects on patients. Motor and neurocognitive impairments may arise depending on the location and grade of the SAH. Although the effects of amantadine on neurocognitive function after traumatic brain injury have been widely studied to the best of our knowledge, their effects on recovery from SAH in humans have not been studied. The present study aimed to evaluate how amantadine influences improvement in neurocognitive function in patients with aneurysmal SAH over a period of six months.

Methods: This preliminary study included 12 patients with aneurysmal SAH who were admitted to the neurointensive care unit of Cerrahpaşa Faculty of Medicine. Patients in Group A (n=5) received the standard treatment for SAH and amantadine for 30 days after admission, and those in Group C (n=7) received only the standard treatment. Neurocognitive function was evaluated using the Coma Recovery Scale-Revised and Disability Rating Scale on the first and fifth days and at the third and sixth months after admission. The primary endpoint of the present study was to compare the effects of amantadine in combination with the standard treatment to those of the standard treatment alone on the neurocognitive function of patients with SAH for over 6 months.

Results: Compared to the standard treatment alone, amantadine administration with the standard treatment during the early period of SAH may improve recovery.

Conclusion: Amantadine along with the standard treatment can ameliorate neurocognitive function after SAH.

Keywords: Amantadine, subarachnoid haemorrhage, neurocognitive functions

Amaç: Aneurizmalara bağlı subaraknoid kanamalarda, kanamanın yeri ve derecesine göre motor ve nörokognitif fonksiyonlar değişik derecelerde etkilenebilmektedir. Travmatik beyin hasarı sonrası amantadinin nörokognitif fonksiyonlar üzerine etkisi geniş olarak çalışılmış olsa da, bildiğimiz kadarıyla insanlarda sunaraknoid kanama sonrası iyileşmeye etkisi çalışılmamıştır. Bu çalışmanın amacı, amantadinin aneurizmaya bağlı subaraknoid kanamalarda kanamadan sonraki 6 ay süresince nörokognitif fonksiyonları nasıl etkilediğini değerlendirmektir.

Yöntemler: Bu ön çalışma aneurizmal sunaraknoid kanama tanısıyla Cerrahpaşa Tıp Fakültesi nöroyoğun bakım ünitesine kabul edilen 12 hastayı içermektedir. Grup A'da (n=5) standart subaraknoid kanama tedavisinin yanında 30 gün boyunca amantadin verilirken, Grup C'de sadece standart tedavi uygulandı (n=7). Nörokognitif fonksiyonlar; amantadin başlandığında, beşinci günde, üçüncü ve altıncı ayda "coma recovery scale-revisited" ve "disability rating scale" ile değerlendirildi. Bu çalışmanın primer sonlanım noktası, aneurizmaya bağlı subaraknoid kanaması olan hastalarda, standart tedaviye amantadin eklenmesinin kanama sonrası 6 ay süresince nörokognitif fonksiyonlardaki iyileşme üzerine olan etkilerini standart tedaviyle karşılaştırmaktır.

Bulgular: Bu çalışma, aneurizmaya bağlı subaraknoid kanaması olan hastalarda, standart tedaviye amantadin eklendiğinde, kanama sonrası 6 ay süresince nörokognitif fonksiyonlardaki iyileşmenin, standart tedaviye göre daha iyi olabileceğini gösterdi.

Sonuç: Subaraknoid kanamalarda standart tedaviye amantadin eklenmesinin nörokognitif fonksiyonlarda iyileşmeye olumlu katkısı bulunmaktadır.

Anahtar sözcükler: Amantadin, subaraknoid kanama, nörokognitif fonksiyonlar

Introduction

Aneurysmal subarachnoid haemorrhage (SAH) is associated with high morbidity and mortality rates. Two main factors determining the morbidity and mortality rates due to SAH are re-bleeding and vasospasms. Therefore, the prevention of re-bleeding and management of vasospasms are essential in patient management (1). The main purpose of the current treatment is to maintain cerebral perfusion while preventing and controlling raised intracranial pressure (ICP) to evade secondary brain injury (2).

This study is presented in 51. Turkish Anesthesiology and Reanimation Congress in the form of oral presentation (25-29 October 2017 Antalya/Turkey).

Bu çalışma 51. Türk Anesteziyoloji ve Reanimasyon Kongresi'nde (25-29 ekim 2017 Antalya/Türkiye) sözlü olarak sunulmuştur.

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Received / Geliş Tarihi : 20.09.2017

Accepted / Kabul Tarihi : 28.02.2018

Subarachnoid haemorrhage causes excessive glutamate release associated with SAH-induced brain injury (3, 4). Glutamate release and glutamate N-methyl-D-aspartate (NMDA) receptor activation may be responsible for early and late ischemia as well as brain swelling in patients with SAH (4, 5).

Amantadine, a NMDA receptor antagonist, has been widely studied in patients with traumatic brain injury (TBI), and its efficacy on neurocognitive improvement after TBI has been demonstrated (6-10).

Memantine, which is a derivate of amantadine, is also a NMDA receptor antagonist, and its neuroprotective effects in SAH have been demonstrated in experimental animal studies (11-13). Memantine has also been found to have protective effects against SAH-induced vasospasms (14).

To the best of our knowledge, there is no human study that has evaluated the effects of the NMDA receptor antagonists on SAH-related neurocognitive damage.

Thus, the main aim of the present study was to evaluate the effects of amantadine on improvement in neurocognitive function in patients with aneurysmal SAH.

Methods

This prospective, randomised controlled study was performed between July 2014 and February 2017. After approval from the Ethics Committee of University of Istanbul, Cerrahpasa School of Medicine (Ethical Committee No: 83045809/604/01.01-114346; 4 July 2014) and written informed consent from the relatives of patients were received, 12 patients who were admitted to the neurointensive care unit with SAH due to cerebral artery aneurysm, who had Glasgow Coma Scale (GCS) scores of below 8/15 and who were aged between 18 and 70 years old were included in the study.

Patients presenting with heart failure, myocardial dysfunction, second- and third-degree atrioventricular blocks, bradycardia ($<55 \text{ min}^{-1}$), prolonged QT interval, arrhythmia, hypokalemia and hypomagnesemia were excluded from the study.

Patients were randomised to one of two groups using the sequentially numbered, opaque, sealed envelope technique. Amantadine was administered along with the standard SAH treatment protocol (Group A) in patients following neurointensive care unit admission, and only the standard treatment was administered to patients in the control group (Group C) (Figure 1).

The standard SAH treatment protocol included initial surgical clipping or endovascular coil embolisation of the ruptured aneurysm. Before aneurysm repair with surgical clipping or coil embolisation, the systolic arterial pressure was kept below 160 mmHg (1, 15). If the systolic arterial pressure was above

160 mmHg, intravenous (IV) esmolol infusion was administered (loading dose of 0.5 mg kg^{-1} over 1 min, then $0.05 \text{ mg kg min}^{-1}$ for 4 min, in inadequate response in 5 min; $0.1 \text{ mg kg min}^{-1}$ IV infusion).

Patients who had GCS scores below 8/15 on admission were mechanically ventilated in the volume-controlled mode with a tidal volume of 8 mL kg^{-1} (ideal body weight), inspiration: expiration ratio of 1:2, positive end-expiratory pressure (PEEP) of $5 \text{ cmH}_2\text{O}$ and respiratory rate (9-12 per min) adjusted to maintain PaCO_2 in the range of 33-35 mmHg. After the acute phase, depending to the level of consciousness, extubation or tracheostomy was performed.

An external ventricular drainage (EVD) (Medtronic Neurosurgery®, USA) catheter was placed in patients who presented with hydrocephalus and/or who had Fisher grade IV SAH. Subsequently, the ICP and cerebral perfusion pressure (CPP) were monitored. Cerebrospinal fluid was drained via the EVD catheter to maintain the ICP below 20 mmHg. Osmotic diuresis with 20% mannitol or 3% sodium chloride was administered in case of an increased ICP despite the drainage, and in case of persistently increased ICPs, sedation was initiated (16). Between the 5th and 15th days after the initial SAH event, in the presence of a newly developed focal neurological deficit or decreased level of consciousness with or without fever, leukocytosis and hyponatremia were evaluated as symptoms of vasospasm. If vasospasm was suspected, digital subtraction angiography was performed to determine the diagnosis while euolemia and hypertension were maintained. Noradrenalin infusion was administered to induce hypertension, and mean arterial pressures were adjusted to

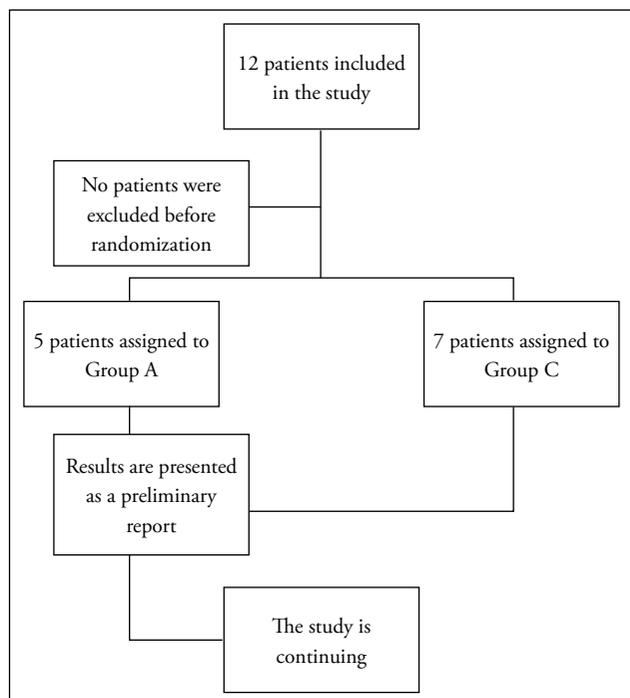


Figure 1. Study flowchart

Table 1. Coma recovery scale-revised

Auditory Function Scale
4- Consistent movement to command
3- Reproducible movement to command
2- Localization to sound
1- Auditory startle
0- None
Visual Function Scale
5- Object recognition*
4- Object Localization: Reaching*
3- Visual pursuit*
2- Fixation*
1- Visual startle
0- None
Motor Function Scale
6- Functional object use ^β
5- Automatic motor response*
4- Object manipulation*
3- Localization to noxious stimulation*
2- Flexion withdrawal
1- Abnormal posturing
0- None/Flaccid
Oromotor Function Scale
3- Intelligible verbalization*
2- Vocalization/Oral movement
1- Oral reflexive movement
0- None
Communication Scale
2- Functional: Accurate ^β
1- Non-functional: Intentional*
0- None
Arousal Scale
3- Attention
2- Eye opening with/without stimulation
1- Unarousable
Total Score
^β Denotes emergence from the minimally conscious state
* Denotes minimally conscious state

reach an individual CPP that improved the neurological deficit or level of consciousness. If the vasospasm continued despite euvolemia and hypertension, intra-arterial vasodilator use or angioplasty was planned.

Anticonvulsant prophylaxis with levetiracetam was administered to all patients and continued for 3-7 days. Long-term anticonvulsant therapy was continued in patients who had seizures.

Totally, 200 mg of IV amantadine was administered daily to Group A patients for five days after admission; then, 100 mg of amantadine was administered via the peroral/enteral route twice a day for 25 days.

The localisation of the ruptured aneurysm, the GCS score and the Fisher grades of the patients on admission and whether vasospasm or hydrocephalus developed were also recorded.

Neurocognitive function was recorded on admission to the neurointensive care unit (before amantadine administration for Group A; baseline), on the fifth day after admission and at the third and sixth months after admission date using the Coma Recovery Scale-Revised (CRS-R) (Table 1) and disability rating scale (DRS) (Table 2).

The primary endpoint of the present study was to evaluate whether adding amantadine to the standard treatment improves neurocognitive function of patients with SAH over the initial 6 month period.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) for Windows 15.0. All results are expressed as mean±SD and median.

Pearson's chi-square test was used for the comparison of qualitative variables between the groups (such as gender, ASA physical status, localisation of the ruptured aneurysm, GCS scores and Fisher grades on admission, development of vasospasm and hydrocephalus) which showed binary change. The determination of normality and homogeneity of data distribution was performed using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare non-normally distributed variables between the groups. The Wilcoxon signedrank test was used to compare non-normally distributed variables within the groups. Differences between the groups were analysed using independent samples t-test for age, body weight, height, CRS-R scores and DRS scores. Differences within the groups were analysed using the paired sample t-test. $p \leq 0.05$ were considered statistically significant.

Results

Twelve patients were included in this study. All patients survived during the six-month study period.

The patients in the study groups were similar in terms of gender, age, body weight, height and ASA physical status ($p > 0.05$) (Table 3).

All patients underwent surgical clipping, had an EVD catheter placed and received anticonvulsant therapy. Two patients in Group A and three in Group C developed vasospasms. Three patients in Groups A and C developed hydrocephalus.

The patients in the study groups were similar in terms of the localisation of the ruptured aneurysms, GCS scores and Fisher grades on admission and the development of vasospasm

and hydrocephalus ($p=0.8$, $p=0.2$, $p=0.4$, $p=0.9$ and $p=0.9$, respectively) (Table 4).

The CRS-R scores on the fifth day and at the third and sixth months were significantly higher in Group A than in Group C ($p=0.005$, $p=0.003$ and $p=0.003$ respectively) (Figure 2).

The fifth-day and third- and sixth-month CRS-R scores were significantly higher than those at baseline in Group A ($p=0.01$, $p=0.001$, and $p=0.04$, respectively) and in Group C ($p=0.017$, $p=0.001$, and $p=0.001$, respectively) (Figure 2).

The DRS scores on the fifth day and at the third and sixth months were significantly lower in Group A than in Group C ($p=0.031$, $p=0.001$ and $p=0.001$, respectively) (Figure 3).

The fifth-day and third- and sixth-month DRS scores were significantly lower than those at baseline in Group A ($p=0.043$) and Group C ($p=0.018$) (Figure 3).

Discussion

This study showed that the NMDA receptor antagonist amantadine administered with the standard treatment may better ameliorate neurocognitive function after aneurysmal SAH than the standard treatment only.

Approximately a quarter of patients with SAH die, and half of the survivors live with varying degrees of disability and neurocognitive impairment. Early repair of aneurysms and management of SAH-related complications, such as hydrocephalus and delayed cerebral ischemia, are thought to improve the functional outcome (15). Several studies on neuroprotection in SAH are being conducted (17). The drug memantine has been studied for this purpose, and its efficacy on neuroprotection in experimental SAH models has been demonstrated before (13). It was also found to be protective against SAH-induced vasospasm (14).

Glutamate is the major excitatory neurotransmitter in the brain. Excessive activation of NMDA-type glutamate receptors causes Ca^{2+} transport into the neurons, thereby causing neuronal excitotoxicity (18). Memantine is an NMDA-type glutamate receptor antagonist, and this counteraction has been shown to be neuroprotective in many experimental studies (19, 20). Memantine is a derivative of amantadine (11). Both of them increase dopamine release in the central nervous system by affecting striatal neurons; furthermore NMDA-type glutamate receptor antagonism also enhances dopaminergic activity (21, 22). TBI is associated with reduction in the levels of catecholamines such as dopamine. The dopaminergic pathway is thought to regulate cognition and awareness (6, 8). Amantadine has been found to improve neurocognitive function and arousal after TBI due to its dopaminergic effect (7, 23).

Studies conducted with amantadine were conducted in patients with moderate-to-severe TBI (GCS=3-10/15) (7, 8).

Table 2. Disability rating scale

A. Eye Opening
0- Spontaneous
1- To speech
2- To pain
3- None
B. Communication Ability
0- Oriented
1- Confused
2- Inappropriate
3- Incomprehensible
4- None
C. Motor Response
0- Obeying
1- Localizing
2- Withdrawing
3- Flexing
4- Extending
5- None
D. Feeding (Cognitive Ability Only)
0. Complete
1- Partial
2- Minimal
3- None
E. Toileting (Cognitive Ability Only)
0. Complete
1- Partial
2- Minimal
3- None
F. Grooming (Cognitive Ability Only)
0. Complete
1- Partial
2- Minimal
3- None
G. Level of Functioning (Physical, Mental, Emotional or Social Function)
0- Completely independent
1- Independent in social environment
2- Mildly dependent-Limited assistance (non-resid – helper)
3- Moderately dependent-Moderate assist (person in home)
4- Markedly dependent-Assist all major activities, all times
5- Totally dependent-24 hour nursing care
H. “Employability” (As a Full Time Worker, Homemaker or Student)
0- Not restricted
1- Selective jobs, competitive
2- Sheltered workshop, non-competitive
3- Not employable
Total Score; 0 – None, 1 – Mild disability, 2 to 3 – Partial disability, 4 to 6 – Moderate disability, 7 to 11 – Moderately severe disability, 12 to 16 – Severe disability, 17 to 21 – Extremely severe disability, 22 to 24 – Vegetative state, 25 to 29 – Extreme vegetative state

The patients in our study also had SAH at Fisher grade III-IV, and their GCS scores were below 8/15.

In the study conducted by Huang et al. (14), memantine was found to be protective against SAH-induced vasospasm in rats. The incidence of vasospasm was similar between the groups in our study.

Giacino et al. (7) compared amantadine with placebo in 184 patients with TBI and found that DRS scores indicated faster recovery rate with amantadine than with placebo. They administered amantadine 4-16 weeks after injury for four weeks. During the evaluation at six weeks, they concluded that recovery slowed

after the discontinuation of amantadine. In our study, we initiated amantadine treatment on admission and continued treatment for a 30-day period. In the fifth-day and at the third-month evaluations, we found that adding amantadine for patient management better improved neurocognitive and behavioural function. Compared to the third-month evaluation, we did not observe any improvement or regression at the sixth-month evaluation. This difference might be due to our longer period of observation and the larger sample size in the other study.

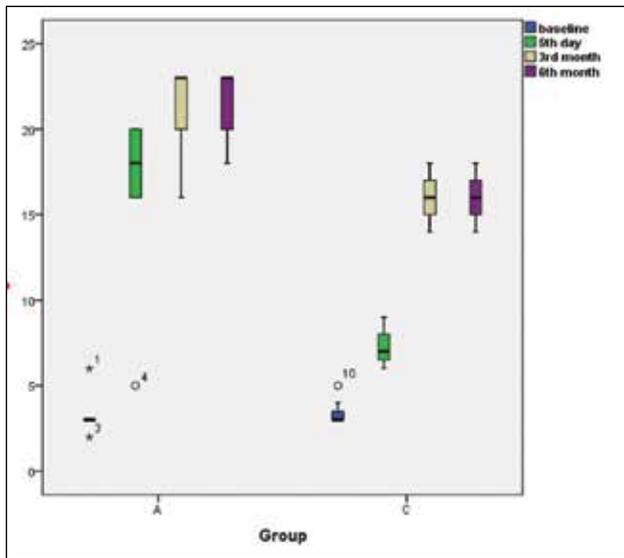


Figure 2 . CRS-R scores at the indicated time intervals. Results are expressed as median (IQR). Outlier results were marked with symbols.
CRS-R: Coma Recovery Scale-Revised

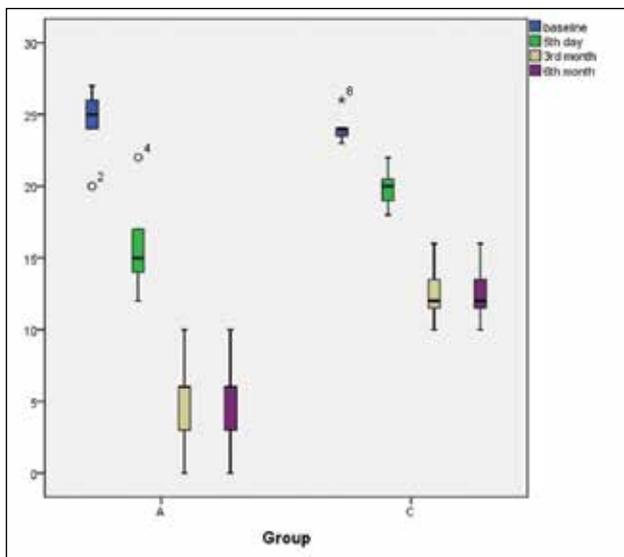


Figure 3. DRS scores at the indicated time intervals. Results are expressed as median (IQR). Outlier results were marked with symbols.
DRS: disability rating scale

Table 3. Patient characteristics

	Group A n=5	Group C n=7	p
Female gender n (%)	2 (40%)	3 (42.9%)	0.92
Age (years) (mean±SD)	50.6±11.86	54.57±8.44	0.51
Body weight (kg) (mean±SD)	73±12.92	68.14±5.49	0.38
Height (cm) (mean±SD)	169.2±10.91	168.71±4.34	0.91
ASA physical status (I/II/III) (n)	3/2/0	3/4/0	0.46
The patients in the study groups were similar in terms of gender, age, body weight, height and ASA physical status (p>0.05). n: number of patients; ASA: American Society of Anesthesiologists			

Table 4. Localisation of the aneurysm, GCS scores and Fisher grades on admission, and frequency of development of vasospasm and hydrocephalus

	Group A n=5	Group C n=7	p
Localisation of the aneurysm n (%)			0.8
MCA	3 (60%)	3 (42.8%)	
ACoMA	2 (40%)	2 (28.5%)	
ICA	0	2 (28.5%)	
Basilar	0	0	
GCS score on admission n (%)			0.3
3-4	0	0	0.2
5	1 (20%)	2 (28.5%)	
6	2 (40%)	2 (28.5%)	
7	2 (40%)	3 (42.8)	
Fisher grades I/II/III/IV (n)	0/0/3/2	0/0/4/3	0.4
Vasospasm n (%)	2 (40%)	3 (42.8%)	0.9
Hydrocephalus n (%)	3 (60%)	3 (42.8%)	0.9
The patients in the study groups were similar in terms of the localisation of the ruptured aneurysms, GCS and Fisher grades on admission, and frequency of the development of vasospasm and hydrocephalus (p>0.05). n: number of patients; MCA: Middle cerebral artery; ACoMA: Anterior communicating artery; ICA: Internal carotid artery; GCS: Glasgow Coma Scale			

Meythaler et al. (8) compared early administration (<6 weeks after TBI) to late administration (>6 weeks after TBI) of 200 mg of amantadine daily during 6 weeks in patients with TBI presenting with GCS scores below 10. They concluded that amantadine accelerates recovery, but they could not demonstrate the difference between the early and late initiation of amantadine administration. There is no consensus regarding the initiation time of amantadine administration in patients with TBI (6). Our patients were admitted to the neurointensive care unit in the first two days after SAH, and we initiated amantadine administration immediately after admission. We hypothesise that amantadine can block excitatory NMDA-type glutamate receptors during the acute period the injury, thus decreasing the severity of the insult.

Saniova et al. (24) compared standard therapy (mechanical ventilation with normocapnia, head position, sedation, temperature control, seizure control, euvoemia with CPP above 70 mm Hg, ICP below 20 mmHg, SjvO₂ at 60-80%, and parenteral and enteral feeding) and amantadine to standard therapy alone in patients with TBI. They found that GCS scores were higher and mortality rates were lower in the amantadine group. In our study, we used the CRS-R and DRS scores to assess neurocognitive and behavioural status. The CRS-R scale give a summary of six measures including auditory, visual, motor, oromotor functions as well as communication and arousal (25). The DRS score evaluates the level of arousal, cognitive abilities, physical dependence on others and employability (26). These scoring systems are recommended for patients with disorders of consciousness because the distinction between the minimally conscious state and vegetative state are well recognised, particularly with the CRS-R (25, 26).

To the best of our knowledge, this study is the first that evaluated the effects of amantadine on neurocognitive recovery after SAH in humans. The results were impressive; therefore, we had a desire to share them as a preliminary report. For these reasons, the present study has a small sample size and is underpowered.

Conclusion

Amantadine can ameliorate neurocognitive function in patients with SAH. More studies with larger sample sizes should be conducted.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University Cerrahpaşa School of Medicine (No: 83045809/604/01.01-114346; 4 July 2014).

Informed Consent: Written informed consent was obtained from relatives of patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.T.; Design - Ö.K.D., Y.T.; Supervision - Ö.K.D., Y.T.; Resources - E.F.A.; Materials - E.F.A., Ö.K.D., Y.T.; Data Collection and/or Processing - E.F.A., Ö.K.D., Y.T.; Analysis and/or Interpretation - E.F.A., Ö.K.D., H.V., Y.T.; Literature Search - E.F.A.; Writing Manuscript - E.F.A., Ö.K.D., H.V., Y.T.; Critical Review - Ö.K.D., Y.T.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi'nden (No: 83045809/604/01.01-114346; 4 Temmuz 2014) alınmıştır.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastaların akrabalarından alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - Y.T.; Tasarım - Ö.K.D., Y.T.; Denetleme - Ö.K.D., Y.T.; Kaynaklar - E.F.A.; Malzemeler - E.F.A., Ö.K.D., Y.T.; Veri Toplanması ve/veya İşlemesi - E.F.A., Ö.K.D., Y.T.; Analiz ve/veya Yorum - E.F.A., Ö.K.D., H.V., Y.T.; Literatür Taraması - E.F.A.; Yazıyı Yazan - E.F.A., Ö.K.D., H.V., Y.T.; Eleştirel İnceleme - Ö.K.D., Y.T.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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