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Persistent vegetative state after severe cerebral hemorrhage treated with amantadine

A retrospective controlled study

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Abstract

Amantadine is currently recommended for use in patients of posttraumatic brain injury with unconsciousness. However, the application of amantadine in consciousness disturbance after cerebral hemorrhage has only been rarely reported. This allows for a further exploration of the role of amantadine in the treatment of PVS resulting from severe cerebral hemorrhage.

Retrospective cohort study from 1/2015 to 7/2019 in Beijing Chaoyang hospital. We included adult patients treated with amantadine after severe cerebral hemorrhage in PVS. Primary outcome was time of consciousness recovery and Glasgow Out Scale scores after 5 months from onset. We compared characteristics and outcomes to a control cohort. matched on age, Coma Recovery Scale-Revised score, volume and location of hemorrhage.

Among the 12 patients who received amantadine treatment, 6 patients regained consciousness (50%) after 5 months of disease onset, but were still severely disabled. Besides, the time for regaining consciousness was within 3 months of disease onset. The remaining 6 patients were still in a PVS. Compared with the amantadine group, the consciousness recovery rate (50% vs 33.3%, $P = .68$) after 5 months in the nested control group was not significantly different. The awakening time for patients in the amantadine group was earlier than the control group (100% vs 25%, $P = .03$).

In this study, amantadine can accelerate the recovery of consciousness in patients following severe cerebral hemorrhage. We recommend further randomized controlled studies to determine the efficacy of amantadine.

Abbreviations: CRS-R = Coma Recovery Scale-Revised, GOS = Glasgow Out Scale, PVS = persistent vegetative state, VS = vegetative state.

Keywords: amantadine, cerebral hemorrhage, persistent vegetative state

1. Introduction

Stroke is one of the 3 leading causes of mortality and disability, with spontaneous cerebral hemorrhage accounting for 9% to 27% of stroke cases.[1] Due to neurological impairment caused by hemorrhage, increased cranial pressure, and cerebral edema, acute cerebral hemorrhage possesses relatively high morbidity and mortality: 35% of patients die within 3 months in the early stage, and 37% are in a state of moderate to severe disability.[2] Moreover, even with interventions such decompressive craniectomy and removal of hematoma, some patients fall into a vegetative state (VS) after initial coma owing to massive blood loss and tissue insult. VS is a condition in which there is wakefulness without behavioral evidence of conscious awareness, A VS lasting for more than 1 month is called persistent vegetative state (PVS).[3]

PVS treatment is an extended and complicated process, and to date there is no gold standard treatment. Current treatment methods include drugs, electrical stimulation, magnetic stimulation, and hyperbaric oxygen.[4] Neuropharmacologic therapies are commonly used off label to enhance arousal and behavioral responsiveness, on the premise that injury-induced derangements in dopaminergic and noradrenergic neurotransmitter systems can be improved through supplementation. Amantadine is one of the most commonly used drugs. There have been a multitude of studies analyzing the effects of amantadine in recent years. Amantadine is known to enhance neurotransmission, through the activation of dopamine-dependent brain circuits,[5] Amantadine acts at the presynaptic level by inhibiting dopamine reuptake, and at the postsynaptic level by increasing the number of dopamine receptors and altering their conformation.[6] At the same time, amantadine was an N-methyl-d-aspartic (NMDA) receptor antagonist, also possesses an anti-acetylcholine effect, further enhancing the effects of dopamine. Brain imaging has been carried out to evaluate the hypothesis that amantadine improves neurotransmission in dopaminergic circuits. ^{18}F-fluorodeoxyglucose-PET (positron emission tomography) revealed increased metabolism in the prefrontal cortex and slightly increased striatal D2 dopamine receptor availability.[7,8]

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The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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In clinical studies, amantadine was found to promote the recovery of neurological function in patients with disturbances of consciousness after severe brain trauma.[9–11] However, only a few studies have described a role for amantadine in alleviating disturbance of consciousness after cerebral hemorrhage. Avecillas-Chasín et al[12] reported a case applying amantadine in a patient with cerebral hemorrhage postoperatively in a minimally conscious state, with result indicating an obvious positive effect.

Here, we retrospectively analyzed 46 patients with PVS after severe cerebral hemorrhage during hospitalization in a hyperbaric oxygen department from 2015 to 2019, and evaluated the therapeutic effects of amantadine.

2. Methods

2.1. Study subjects

All patients included in this study were in PVS after cerebral hemorrhage. Diagnostic criteria from the American Academy of Neurology for PVS[3] were selected, and patients in a VS lasting for more than 1 month were diagnosed as PVS. Exclusion criteria: traumatic cerebral hemorrhage; complications affecting consciousness level, such as fever, pulmonary infection, severe hyponatremia, pregnancy, severe kidney diseases (creatinine clearance rate lower than 60 mL/min), or seizures; and hydrocephalus needing shunt surgery. According to the above criteria, 46 patients with severe cerebral hemorrhage admitted to the Department of Hyperbaric Oxygen from 2015 to 2019 in Beijing Chaoyang hospital were enrolled. All patients were hospitalized after 1 to 2 months of cerebral hemorrhage and received conventional hyperbaric oxygen therapy and rehabilitation. Among them, 12 patients were given amantadine orally based on conventional treatment, while 34 did not receive amantadine treatment.

2.2. Collection of medical history

Patient medical history, including sex, age, etiology, hemorrhage location, volume of hemorrhage, time of admission, Coma Recovery Scale-Revised (CRS-R) score[13] at admission, start time of amantadine administration, Glasgow Out Scale (GOS) score five months after onset, was recorded in detail.

2.3. Amantadine dose and time

After admission, 12 patients diagnosed with PVS started oral administration of amantadine at a dose of 100 mg twice daily. If there was no side effect, the dose of amantadine increased to 150 mg twice per day in the third week, and in the fourth week, the dose was further increased to a maximum dose of 200 mg twice per day. The neurological function was assessed 5 months after onset.

2.4. Hyperbaric oxygen therapy and rehabilitation

After admission, all patients received hyperbaric oxygen and rehabilitation therapies. Hyperbaric oxygen therapy: a total of 45 sessions were administered at a treatment pressure of 0.2 MPa, with increasing pressure for 25 minutes and with oxygen inhalation for 60 minutes under stable pressure (oxygen inhalation with mask at oxygen concentration of 99.5%). After the initial increase, the pressure was reduced for 35 minutes. Treatment session were once a day, and 1 treatment course was equal to 15 times session, with a 10 day of break before next course.

Rehabilitation therapy was mainly bedside rehabilitation, including anti-convulsive mode and maintenance of range of motion.

2.5. Evaluation of neurological function

CRS-R score: CRS-R score is a standard tool for neurobehavioral evaluation, including auditory, visual, motor, motor/verbal, communication, and arousal scales, with a range of 0 to 23. The higher the score, the stronger the neurobehavioral ability. Each patient was scored with a CRS-R score after admission.

GOS score: Efficacy was evaluated based on GOS score:

1. death;
2. VS, unconscious, but with a heartbeat and breathing, occasionally opening of eyes, yawning and other local motor reactions;
3. severely disabled and conscious, but cognitively, verbally, and physically disabled, needing to be cared by others full-time;
4. moderately disabled with cognitive, behavioral, and personality disorders; with mild hemiplegia, ataxia, dysphasia, and other disabilities; barely independent in daily life, family, and social activities;
5. good recovery and can resume most normal activities but may have minor residual problems.

GOS scores were given at 5 months after disease onset to determine prognosis. Two investigators who were blinded to amantadine usage completed the assessment of prognosis.

2.6. Research methods

We conducted a nested cohort study including 12 patients receiving amantadine treatment among all 46 patients after cerebral hemorrhage. The other 34 patients who did not receive amantadine were matched by age, CRS-R score and volume of hemorrhage, without significant difference. Twelve patients of 34 patients with matched hemorrhage location were enrolled in the nested cohort study.

2.7. Statistics

Patient demographics, clinical characteristics, and outcomes were tabulated and compared between the cohort receiving amantadine and each nested "control" cohort using a *t* test, chi-square test, or Fisher exact test.

3. Results

3.1. Demographics of amantadine group

Twelve among the 46 patients with cerebral hemorrhage were treated with amantadine, who were mostly men, accounting for 67.7% of the total patients, with an average age of 53 ± 7.98 years. Hemorrhage was mainly caused by hypertension, accounting for 91.6% of all hemorrhage. The hemorrhage location included: 5 cases in the frontal temporal parietal lobe (41.7%), 4 in the basal ganglia (33.3%), 2 in the thalamus (16.7%), and 1 in the brain stem (8.3%). The average hemorrhage volume was 51 ± 27.4 mL, and the CRS-R score at admission was 3.6 (2–7). Due to different admission time, time to start taking medicine of 12 patients was 30 to 90 days after onset.

Table 1

Clinical characteristics and outcomes of patients receiving amantadine.

Patient	Sex	Age	Etiology	Operation method	Hemorrhage location	Volume of hemorrhage (ml)	CRS - R score on admission	Time to start taking medicine after onset (d)	Amantadine dosage	Time (day) of starting to improve	GOS score 5 mo after disease onset
1	F	50	Hypertension	Bilateral external ventricular drainage	Left thalamus	24	2	30	200 mg bid	3	3
2	M	54	Hypertension	Decompressive craniectomy and removal of hematoma	Right basal ganglia	50	2	40	200 mg bid	3	3
3	M	45	Hypertension	Ventricle plus lumbar cistern drainage	Right thalamus, brain stem	24	6	30	200 mg bid	4	3
4	F	46	Hypertension	Decompressive craniectomy and removal of hematoma	Brain stem	16	6	65	200 mg bid	3	3
5	M	49	Hypertension	Decompressive craniectomy and removal of hematoma	Left basal ganglia	105	7	30	150 mg bid	7	3
6	F	66	Hypertension	Decompressive craniectomy and removal of hematoma	Left frontal parietal lobe	70	5	60	150 mg bid	4	2
7	M	49	Hypertension	Decompressive craniectomy and removal of hematoma	Left basal ganglia	32	5	30	200 mg bid	5	3
8	M	61	Hypertension	Decompressive craniectomy and removal of hematoma	Right temporal lobe	50	4	90	100 mg bid	No	2
9	M	42	Hypertension	Decompressive craniectomy and removal of hematoma plus cranioplasty	Right frontal parietal lobe	95	2	90	200 mg bid	No	2
10	M	53	Hypertension	Decompressive craniectomy and removal of hematoma	Right temporo-parietal lobe	45	2	90	100 mg bid	No	2
11	F	66	Unclear	Decompressive craniectomy and removal of hematoma	Right frontotemporal parietal lobe	56	3	75	200 mg bid	No	2
12	M	57	Hypertension	Lumbar cistern drainage	Right basal ganglia	50	2	72	200 mg bid	No	2

CRS–R = Coma Recovery Scale–Revised, F = female, GOS = Glasgow Out Scale, M = male.

The medication period was 2 to 4 months. During the medication, there were 4 patients with side effects: 1 case of sleep disturbance, 2 cases of diarrhea, 1 case of rash, so these 4 patients did not continue to increase the dose. The oral dose of 12 patients were 100 to 200 mg twice daily. See patients' baseline characteristics in Table 1.

3.2. Results of amantadine group

Among the 12 patients who received amantadine treatment, 6 patients regained consciousness (50%) 5 months after disease onset, but were still severely disabled. GOS score was 3. Importantly, the effects of amantadine usually became apparent 3 to 7 days after initial treatment, the time for regaining consciousness was within 3 months of disease onset. The remaining 6 patients were still in a PVS. GOS score was 2. See details of patients' outcome in Table 1.

3.3. Results of matched controls

A total of 34 patients received hyperbaric oxygen and rehabilitation therapy without amantadine treatment. Twelve patients in the nested control group showed no significant difference in age, location and volume of hemorrhage, and CRS-R score compared with the amantadine group. Compared with the amantadine group, the consciousness recovery rate (50% vs 33.3%, $P = .68$) in the nested control group was not significantly different 5 months after onset. The awakening time of the 6 patients who regained consciousness in the amantadine group was within 3 months after onset. In the nested control group, only 1 was within 3 months, and 3 were within 4 to 5 months. The awakening time for patients in the amantadine group was earlier than the nested control group (100% vs 25%, $P = .03$). There was no significant difference in the recovery rate of consciousness 5 months after onset between the amantadine group and 34 patients in the control group (50% vs 37.2%, $P = .513$). Besides, there was no significant difference in the awakening time between the amantadine group and the control group (100% vs 76.9%, $P = .517$). Comparisons between groups are shown in Table 2.

4. Discussion

The 2018 American practice guidelines for patients with disorders of consciousness[14] recommendation of amantadine for patients with unresponsive wakefulness syndrome and minimally conscious state 4 to 16 weeks after traumatic brain injury is based on one randomized controlled trial.[11] However, there are only a few cases reporting the use of amantadine in consciousness disturbance after severe cerebral hemorrhage.[12] In this retrospective control study, the effect of amantadine was proved. The arousal rate was not significantly different between the amantadine group and the nested control group. However, the time for regaining consciousness in the amantadine group was earlier than that in the nested control group, suggesting that amantadine could promote the awakening of PVS after cerebral hemorrhage. Compared with the whole control group, there was no statistically significant difference in the recovery rate and recovery time of the amantadine group, but the ratio was better

Table 2

Clinical features and outcomes of patients receiving amantadine and matched cohorts.

	Matched controls		
	Unadministered amantadine group n = 34	Unadministered amantadine and hemorrhage location matching group n = 12	Amantadine treatment group n = 12
Age (yrs)	51 ± 15.1	51 ± 12.8	53 ± 7.98
Sex			
Male	25 (73.5%)	8 (66.7%)	8 (67.7%)
Female	9 (26.4%)	4 (33.3%)	4 (33.3%)
Etiology of hemorrhage			
Hypertension	23 (67.6%)	10 (83.3%)	11 (91.6%)
Others	11 (32.4%)	2 (16.7%)	1 (8.4%)
Admission time			
1–2 mo	26 (76.5%)	9 (75%)	7 (58.3%)
2–3 mo	8 (23.5)	3 (25%)	5 (41.7%)
Hemorrhage location			
Frontotemporal parietal lobe	12 (35.3%)	5 (41.7%)	5 (41.7%)
Basal ganglia	13 (38.2%)	4 (33.3%)	4 (33.3%)
Thalamus	2 (5.9%)	2 (16.7%)	2 (16.7%)
Brain stem	1 (2.9%)	1 (8.3%)	1 (8.3%)
Ventricle	3 (8.8%)	0	0
Cerebellum	3 (8.8%)	0	0
Volume of hemorrhage (ml)	54 ± 23.1	53 ± 20.1	51 ± 27.4
CRS-R score on admission	3.5 (2–7)	3.4 (2–6)	3.6 (2–7)
GOS score 5 mo after onset			
2	21 (61.8%)	8 (66.7%)	6 (50%)
3	13 (38.2%)	4 (33.3%)	6 (50%)
Consciousness recovery time			
< 3 mo after onset	10 (76.9%)	1 (25%)*	6 (100%)
4–5 mo after onset	3 (23.1%)	3 (75%)*	0

* $P < .05$ vs amantadine treatment group.

than the control group. The recovery rate of consciousness (50% vs 37.2%), the recovery rate of consciousness within 3 months (100% vs 76.9%). Compared with the nested control group, the amantadine group also had a higher rate of consciousness recovery (50% vs 33.3%). Due to the small sample size, larger clinical trials are needed to confirm the effect of amantadine.

The awakening mechanism associated with amantadine in disturbance of consciousness is related to the enhancement of dopamine in the substantia nigra and in neurotransmission within the mesencephalic limbic and frontal striatum loop system, which are responsible for regulating awakening, activation and attention.[11] The above results have been confirmed by positron emitted tomography examination.[7] On the other hand, excessive release of excitatory amino acids, like glutamate, due to ischemia is thought to induced a sustained activation of NMDA receptors leading to an increase above toxic levels of free intracellular Ca^{2+}. This phenomenon is known as excitotoxicity. Acting as a noncompetitive inhibitor of NMDA receptor signaling, amantadine might be effective in attenuating NMDA receptor induced neurotoxicity,[15] this may help to reduce brain damage in patients with cerebral hemorrhage and promote patients' wakefulness.

Amantadine has been safely administered in doses of 100 to 400 mg/d, with 1 case report demonstrating a dose-dependent effect on cognitive improvement.[16] Amantadine has a half-life of 11 to 15 hours, and is generally administered twice a day. After oral administration, it is mainly metabolized by the kidney. Amantadine dosing must be adjusted in renal insufficiency and should not be used in patients taking dopamine antagonists (typical and atypical antipsychotics).[17] Adverse effects were reported in 1 trial; these included hallucinations, pedal edema, generalized seizure, and hypomania.[18] However, the adverse events of patients taking the amantadine group did not increase significantly compared with the control group in a randomized controlled study.[11] In this study, 4 patients experienced side effects: 1 case of sleep disturbance, 2 cases of diarrhea, 1 case of rash, but the symptoms were mild and improved after symptomatic treatment. Amantadine was used in the treatment of severe intracerebral hemorrhage without serious side effects, but a larger sample size is still required for verification due to the small sample size.

Six of the 12 patients treated with amantadine regained consciousness within 3 months, among which 2 had hemorrhage in the thalamus, 3 in the basal ganglia, and one in the brain stem. However, the other 6 patients did not regain consciousness after 5 months, among which 5 had hemorrhage in the frontal temporal parietal lobe and 1 in the basal ganglia. Amantadine treatment in patients with hemorrhage in the frontal temporal parietal lobe had poor efficacy, so which patients could gain more benefits from the treatment still needed further investigation.

Limitations: Our study has some limitations. This was a retrospective controlled study, and not a randomized controlled study. The sample size was small, so a strict randomized controlled study is still needed to further verify the results presented in this paper. Second, the effects of other adjuvant therapies (such as hyperbaric oxygen and rehabilitation) are unknown. Third, because the time of referral to our department was different, the starting time and duration of each patient's medication were inconsistent, and the results may be affected. Fourth, patients taking amantadine were randomly selected and obtained informed consent from their families. The family members of patients who agreed to use amantadine may have a

stronger willingness to help the patients to recover than those who did not use amantadine, and took care of patients more carefully. This raised the possibility of selection bias.

5. Conclusions

In this study, Amantadine has been shown to accelerate recovery following severe cerebral hemorrhage. We strongly recommend further randomized controlled studies to determine the efficacy of amantadine.

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