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Original research

Amantadine treatment is associated with improved consciousness in patients with non-traumatic brain injury

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ABSTRACT

Objective This study determined the effect of amantadine treatment on consciousness in patients with non-traumatic brain injury.

Methods We pooled individual patient data of five single-centre observational studies to determine the effect of amantadine treatment among patients with ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, community-acquired bacterial meningitis and status epilepticus, admitted between January 2012 and December 2015 and ventilated ≥ 7 days. Patient selection and multivariable regression modelling were used to adjust for differences in intergroup comparison and for parameters associated with consciousness. Improvement of consciousness 5 days after treatment initiation was defined as primary outcome. Secondary outcomes included Glasgow Coma Scale (GCS) at day 5 and GCS at day 10, rate of ICU delirium, epileptic seizures and all-cause mortality at 90 days.

Results Overall, 84 of 294 (28.6%) eligible patients received amantadine. Amantadine treatment was associated with improvement of consciousness at day 5 (amantadine: 86.9% vs control: 54.0%; absolute difference: 32.9 (20.0–44.2); adjusted OR (aOR): 5.71 (2.50–13.05), $p < 0.001$). Secondary outcomes showed differences in GCS 5 days (9 (8–11) vs 6 (3–9), $p < 0.001$) and GCS 10 days (10 (8–11) vs 9 (6–11), $p = 0.003$) after treatment initiation. There were no significant differences regarding all-cause mortality (aOR: 0.89 (0.44–1.82), $p = 0.758$) and ICU delirium (aOR: 1.39 (0.58–3.31), $p = 0.462$). Rate of epileptic seizures after initiation of amantadine treatment was numerically higher in the amantadine group (amantadine: 10.7% vs control: 3.0%; absolute difference: 7.7 (0.3–16.4); aOR: 3.68 (0.86–15.71), $p = 0.079$).

Conclusions Amantadine treatment is associated with improved consciousness among patients with different types of non-traumatic brain injury in this observational cohort analysis. Epileptic seizures should be considered as potential side effects and randomised controlled trials are needed to confirm these findings.

INTRODUCTION

Globally, there are approximately 55 million people living with disability related to traumatic brain injury (TBI) and 80 million with disability related

to stroke.^{1,2} Rehabilitation should be initiated early after brain injury to ensure recovery and prevent long-term disability.^{3–5} However, patients with severe brain injury frequently suffer from impaired consciousness undermining rehabilitation and functional recovery.^{3,6} Moreover, prolonged impairment of consciousness may result in unjustified care limitation and worse patient outcome by self-fulfilling prophecy.^{7–10}

Amantadine, an N-methyl-D-aspartate receptor antagonist and indirect dopamine agonist, exerts effects on multiple neurotransmitters and is used as neurostimulant in patients with prolonged disorders of consciousness.^{11,12} A randomised controlled trial and several observational studies showed that amantadine accelerated functional recovery in TBI.^{13,14} Regarding non-TBI (NTBI), amantadine is frequently administered in patients with impaired consciousness, but its effect in the acute care setting remains to be verified and evidence is based on case reports and cohort studies with limited patient numbers ($n \leq 12$) or lack of a control group.^{12,14–18} Seizures have been reported as side effect of amantadine administration, why amantadine may also exert detrimental effects in patients with NTBI.¹⁹

The present study pooled individual patient data (IPD) of five observational studies to investigate the effect of amantadine treatment on (1) consciousness, rate of (2) mortality, (3) ICU delirium and (4) epileptic seizures.

METHODS

Study design and patient selection

The present study pooled IPD of five observational studies conducted at the university hospital Erlangen, a tertiary care centre in Germany. Patients with primary spontaneous intracerebral haemorrhage (ICH) from the prospective University of Erlangen Cohort of Patients With Spontaneous Intracerebral Haemorrhage study,^{20,21} patients with ischaemic stroke (IS) from a prospective stroke registry,²² patients with subarachnoid haemorrhage (SAH) from a prospective institutional SAH registry,²³ patients with community-acquired bacterial meningitis (CABM) from a prospective institutional registry,²⁴ and patients with status epilepticus (SE) from a retrospectively established institutional SE database²⁵; admitted to the

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neurological intensive care unit (ICU) between 1 January 2012 and 31 December 2015 and ventilated ≥ 7 days were included. All studies were approved by the local institutional review board and patients or legal representatives provided informed consent unless waived by the review board.^{20 22–25}

Definitions and data acquisition

Data on demographics, clinical admission status and in-hospital parameters were assessed as previously published.^{20 22–27} Diagnosis of ICH, IS and SAH was established based on clinical findings and first cranial imaging scans after symptom onset.^{23 28} Diagnosis of CABM was confirmed by cerebrospinal fluid, laboratory and clinical findings.^{24 29} SE was defined as clinically or electroencephalographically persisting seizure ≥ 5 min or as a series of seizures without interictal recovery.^{25 30} Glasgow Coma Scale (GCS; at hospital admission and thereafter assessed daily at the ICU bedside at 10:00 am (± 4 hours)), ventilation parameters and amantadine treatment (ie, dosage, time, duration and route of administration) were recorded as noted in medical charts and prospective databases. ICU delirium was defined as delirium diagnosed by attending physicians based on the Confusion Assessment Method for the Intensive Care Unit.³¹ Epileptic seizures were defined as electrographic evidence of ictal activity on electroencephalography (EEG) with or without

corresponding clinical symptoms or signs, or witnessed clinical symptoms or signs diagnosed as epileptic seizure by the attending neurologist.³² Amantadine treatment was defined as intravenous and/or oral administration of at least a single dose of at least 100mg amantadine with the intention to improve patients' consciousness. Amantadine treatment was considered in patients with GCS score of 6 or less by standard clinical practice at the institution, but initiation and timing of amantadine were at the discretion of the attending physician. Amantadine administered for other indications such as Parkinson's disease was not considered as amantadine treatment. Amantadine treatment was categorised according to timing of treatment initiation as early (ie, administration of the first dose within 3 ± 2 days after weaning initiation), delayed (within 8 ± 2 days) and late (within 13 ± 2 days) treatment.

Outcome measures

Primary outcome

Improvement of consciousness at day 5 was defined as primary outcome characterised as increase in GCS score of at least 3 points within 5 days after initiation (treatment group) or consideration (control group) of amantadine treatment.¹⁶

Figure 1 Flow chart of study participants. Overall, 302 patients with different NTBI and mechanical ventilation ≥ 7 days were recruited between 1 January 2012 until 31 December 2015; 102 with IS, 113 patients with ICH, 42 with SAH, 16 with CABM and 29 with SE. After exclusion of eight patients because of missing data on amantadine treatment, the study sample consisted of 294 patients. In the control group, patients were randomised (1:1:1) to one of the three categories of treatment initiation (early, delayed and late) and patients who were not eligible for amantadine treatment at respective time points (GCS >6 at each day of the corresponding categories of treatment initiation: day 1 until day 5 for early treatment initiation group, day 6 until day 10 for delayed group and day 11 until day 15 for late group) were excluded. Afterwards, there were 84 patients in the amantadine group and 100 patients in the control group. Patients in the SE registry could be included repeatedly for separate episodes of SE, but patients included in outcome analysis of amantadine treatment were all different individual patients. CABM, community-acquired bacterial meningitis; ICH, intracerebral haemorrhage; IS, ischaemic stroke; NTBI, non-traumatic brain injury; SAH, subarachnoid haemorrhage; SE, status epilepticus; UKER, Universitätsklinikum Erlangen;.

Table 1 Clinical characteristics of the study cohort

	Amantadine group (n=84)	Control group (n=100)	P value
Age, years (IQR)	76 (69–80)	65 (57–74)	<0.001
Female sex, number (%)	36 (42.9)	42 (42.0)	0.907
Type of disease, number (%)			
Ischaemic stroke	34 (40.5)	30 (30.0)	0.137
Intracerebral haemorrhage	33 (39.3)	34 (34.0)	0.458
Subarachnoid haemorrhage	8 (9.5)	16 (16.0)	0.194
Community-acquired bacterial meningitis	4 (4.8)	6 (6.0)	0.757
Status epilepticus	5 (6.0)	14 (14.0)	0.074
Amantadine treatment initiation/consideration, number (%)			
Early treatment*	32 (38.1)	50 (50.0)	0.106
Delayed treatment†	40 (47.6)	37 (37.0)	0.146
Late treatment‡	12 (14.3)	13 (13.0)	0.800
Hospital parameters (IQR)			
GCS on admission	10 (3–13)	9 (9–13)	0.947
GCS at treatment initiation	5 (4–5)	4 (3–6)	0.367
Duration of ventilation until weaning initiation, days	2.61 (1.28–4.85)	3.92 (2.56–8.53)	0.001
Time from symptom onset to amantadine treatment/consideration, days	10.74 (7.87–14.09)	12.41 (7.70–15.84)	0.200

*Early treatment was defined as administration of the first dose of amantadine within 3±2 days after weaning initiation.

†Delayed treatment was defined as treatment initiation within 8±2 days.

‡Late treatment was defined as treatment initiation within 13±2 days.

GCS, Glasgow Coma Scale.

Secondary outcomes

Secondary efficacy outcomes comprised (1) improvement of consciousness at day 10 defined as increase in GCS score of at least 3 points within 10 days after initiation of amantadine treatment, (2) GCS at day 5, (3) GCS at day 10 after initiation of amantadine treatment, (4) emergence from unconsciousness at day 5 defined as demonstration of localisation or command following or confused communication or better within 5 days after initiation of amantadine treatment, (5) emergence from unconsciousness at day 10 and (6) all-cause mortality rate at day 90 after hospital admission. Secondary safety outcomes were (7) rate of ICU delirium and (8) rate of epileptic seizures after initiation of amantadine treatment. GCS at day 5 and GCS at day 10 were defined as GCS assessed at day 5 and, respectively, at

day 10 after initiation of amantadine treatment or at hospital discharge, whichever came first.

Statistical analyses

SPSS V.21.0 and Excel V.16.0 were used for statistical analyses, Excel V.16.0 and Adobe Illustrator V.24.3 for graphical illustration. Results are presented as mean (±SD) or median (IQR) or number of events (percentage). Categorical variables were compared by the Pearson's χ^2 test or the Fisher's exact test, respectively.^{5 28} Ordinal variables and non-normally distributed continuous variables were compared by the Mann-Whitney U-test, normally distributed continuous variables by the Student's t-test.^{5 28}

To minimise bias by timing of treatment initiation, we randomised (1:1:1) patients in the control group to one of the three categories of treatment initiation (early, delayed and late) and afterwards excluded patients who were not eligible for amantadine treatment at respective time points (GCS >6 at each day of the corresponding categories of treatment initiation: day 1 until day 5 for early treatment initiation group, day 6 until day 10 for delayed group and day 11 until day 15 for late group). Multivariable regression analyses were adjusted for parameters showing significant differences in intergroup comparison and for parameters associated with consciousness (GCS at day 5 or day 10) after initiation of amantadine treatment in univariate analysis ($p < 0.05$). Significance levels of the secondary outcomes were adjusted for multiplicity using Bonferroni-Holm method.

Subgroup analyses were conducted for the primary outcome among the subgroups of patients according to age (≤ 70 years >70 years), sex (women, men), type of disease (IS, ICH, SAH, CABM, SE), timing of treatment initiation (early, delayed, late), treatment dosage (≤ 300 mg, >300 mg) and GCS at hospital admission.^{3–15} For exploratory analyses, the time course of GCS values before and after initiation of amantadine treatment was compared between treatment and control group.

RESULTS

Study population and clinical characteristics

IPD of 302 patients with different NTBI and mechanical ventilation ≥ 7 days were pooled. After exclusion of eight patients because of missing data on amantadine treatment, the study sample consisted of 294 patients (figure 1). Overall, 84 of 294

Table 2 Primary and secondary outcomes

Outcomes	Amantadine group (n=84)	Control group (n=100)	Absolute difference (95% CI)	Adjusted OR (95% CI)	P value
Primary					
Improvement of consciousness at day 5, number/total (%)	73/84 (86.9)	54/100 (54.0)	32.9 (20.0 to 44.2)	5.71 (2.50 to 13.05)	<0.001
Secondary efficacy					
Improvement of consciousness at day 10, number/total (%)	77/84 (91.7)	67/100 (67.0)	24.7 (13.1 to 35.3)	5.34 (2.03 to 14.04)	0.001*
GCS at day 5, median (IQR)	9 (8–11)	6 (3–9)			<0.001*
GCS at day 10, median (IQR)	10 (8–11)	9 (6–11)			0.003*
Emergence from unconsciousness at day 5, number/total (%)	66/84 (78.6)	49/100 (49.0)	29.6 (15.7 to 41.7)	4.04 (1.92 to 8.51)	<0.001*
Emergence from unconsciousness at day 10, number/total (%)	69/84 (82.1)	59/100 (59.0)	23.1 (9.9 to 35.0)	3.07 (1.42 to 6.63)	0.004*
All-cause mortality at 90 days, number/total (%)	32/80 (40.0)	29/94 (30.9)	9.2 (–5.0 to 23.0)	0.89 (0.44 to 1.82)	0.758
Secondary safety					
ICU delirium, number/total (%)	15/84 (17.9)	15/100 (15.0)	2.9 (–7.8 to 14.0)	1.39 (0.58 to 3.31)	0.462
Epileptic seizures, number/total (%)	9/84 (10.7)	3/100 (3.0)	7.7 (0.3 to 16.4)	3.68 (0.86 to 15.71)	0.079

*Significant after Bonferroni-Holm correction.

GCS, Glasgow Coma Scale; ICU, intensive care unit.

Figure 2 Subgroup analyses. Subgroup analyses were conducted for the primary outcome, improvement of consciousness at day 5, using multivariable regression analyses adjusted for age, GCS at treatment initiation and duration of ventilation until weaning initiation (without the subgroup-defining variable). Early treatment was defined as administration of the first dose of amantadine within 3 ± 2 days after weaning initiation; delayed treatment was defined as treatment initiation within 8 ± 2 days; late treatment was defined as treatment initiation within 13 ± 2 days. CABM, community-acquired bacterial meningitis; GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; IS, ischaemic stroke; SAH, subarachnoid haemorrhage; SE, status epilepticus.

patients (28.6%) received amantadine; 34/100 (34.0%) in IS, 33/108 (30.6%) in ICH, 8/41 (19.5%) in SAH, 4/16 (25.0%) in CABM and 5/29 (17.2%) in SE (see online supplemental table 1). Treatment was initiated early (ie, within 3 ± 2 days after weaning initiation) in 32 of 84 patients (38.1%), delayed (within 8 ± 2 days) in 40 (47.6%) and late (within 13 ± 2 days) in 12 (14.3%) patients (see online supplemental figure 1). To account for timing of treatment initiation, we randomised patients in the control group to one of the three groups of treatment initiation (early, delayed and late) and afterwards excluded patients who were not eligible for amantadine treatment at respective time points (figure 1).

The final study sample consisted of 184 patients, of which 84 (45.7%) received amantadine treatment (table 1). There were 42.4% women and the median (IQR) age at hospital admission was 71 (60–78) years. Data on all-cause mortality at 90 days were available for 174 of 184 (94.6%) patients and mortality at 3 months was 35.1%. One patient in the control group received amantadine for other indications. Patients in the amantadine group were older (amantadine: 76 (69–80) years vs control: 65 (57–74) years; $p<0.001$), whereas patients in the control group had longer duration of mechanical ventilation before weaning initiation (amantadine: 2.61 (1.28–4.85) days vs control: 3.92 (2.56–8.53) days; $p=0.001$). There were no statistically significant differences regarding time from symptom onset to amantadine treatment initiation/consideration (amantadine: 10.74 (7.87–14.09) days vs control: 12.41 (7.70–15.84) days; $p=0.200$). Outcome analyses were performed using multivariable regression analysis adjusted for age and duration of mechanical ventilation and additionally for GCS at treatment initiation as variable associated with consciousness ($p<0.05$ for

the association with improvement of consciousness at day 5 and at day 10 in univariate analysis).

Analysis of primary and secondary outcomes

Primary outcome

Regarding the primary outcome, amantadine treatment was associated with improvement of consciousness at day 5 (amantadine: 73/84 (86.9%) vs control: 54/100 (54.0%); absolute difference: 32.9 (20.0 to 44.2); adjusted OR (aOR): 5.71 (2.50–13.05), $p<0.001$; table 2).

Secondary outcomes

Regarding secondary efficacy outcomes, amantadine treatment was associated with improvement of consciousness at day 10 (amantadine: 77/84 (91.7%) vs control: 67/100 (67.0%); absolute difference: 24.7 (13.1–35.3); aOR: 5.34 (2.03–14.04), $p=0.001$; table 2). There were significant differences in GCS at day 5 (amantadine: 9 (8–11) vs control: 6 (3–9), $p<0.001$) and at day 10 (amantadine: 10 (8–11) vs control: 9 (6–11), $p=0.003$; table 2 and figure 2). Amantadine treatment was associated emergence from unconsciousness at day 5 (amantadine: 66/84 (78.6%) vs control: 49/100 (49.0%); absolute difference: 29.6 (15.7–41.7); aOR: 4.04 (1.92–8.51), $p<0.001$) and at day 10 (amantadine: 69/84 (82.1%) vs control: 59/100 (59.0%); absolute difference: 23.1 (9.9–35.0); aOR: 3.07 (1.42–6.63), $p=0.004$). Rate of all-cause mortality at 90 days (amantadine: 32/80 (40.0%) vs control: 29/94 (30.9%), aOR: 0.89 (0.44–1.82), $p=0.758$) was not different across treatment groups.

Regarding secondary safety outcomes, rate of ICU delirium (amantadine: 15/84 (17.9%) vs control: 15/100 (15.0%);

Figure 3 Exploratory analyses regarding the time course of consciousness. Illustration of the time course of consciousness from 5 days before amantadine treatment initiation (shown in light grey) until 10 days thereafter, d0 represents the day of amantadine treatment initiation. (A) For exploratory illustration, mean values of GCS were calculated for amantadine group (square) and control group (circle). Points represent the mean and thin lines the SD. (B) For exploratory illustration, mean differences of GCS values between amantadine group and control group were calculated. Points represent the mean difference and thin lines the 95% CI. Patients discharged from hospital before respective days of GCS assessment were not accounted for (secondary outcome analysis of GCS at day 5 and GCS at day 10 included GCS at hospital discharge for these patients). GCS, Glasgow Coma Scale; NTBI, non-traumatic brain injury.

absolute difference: 2.9 (−7.8 to 14.0); aOR: 1.39 (0.58–3.31), $p=0.462$) did not differ across treatment groups. There was a non-significant difference regarding the rate of epileptic seizures after initiation of amantadine treatment (amantadine: 9/84 (10.7%) vs control: 3/100 (3.0%); absolute difference: 7.7 (0.3–16.4); aOR: 3.68 (0.86–15.71), $p=0.079$). Continuous EEG monitoring was performed in 130 of 184 (70.7%) patients, 8 of 12 (66.7%) seizure events were non-convulsive seizures (first seizure event that occurred in patients with seizures after treatment initiation).

Subgroup and exploratory analyses

Subgroup analyses were performed for the primary outcome, improvement of consciousness at day 5 (figure 2). Treatment effects of amantadine were not significantly different among subgroups of patients according to age, GCS at hospital admission, timing of treatment initiation and treatment dosage (aOR: ≤ 600 mg: 4.80 (1.74–13.26), >600 mg: 9.64 (1.15–80.50); p value for interaction: 0.562). Treatment effects tended to be modified by type of disease (aOR: IS: 4.23 (0.89–20.10), ICH:

8.77 (1.96–39.34); SAH: 4.59 (0.31–67.90); CABM: 0.83 (0.02–35.25); SE: 1.55 (0.07–32.84); p value for interaction: 0.077).

Exploratory analyses regarding the time course of consciousness measured by the GCS are shown in figure 3. There were no relevant differences between amantadine and control group within 5 days before amantadine treatment initiation (figure 3A). After treatment initiation, consciousness of patients in the amantadine was improved compared with the control group (figure 3B).

DISCUSSION

To our knowledge, this study represents the first comprehensive analysis of amantadine treatment in NTBI. We found that amantadine treatment is associated with improved consciousness and may represent a viable treatment option for patients with prolonged disorders of consciousness, but epileptic seizures should be considered as potential side effect of amantadine.

Amantadine was reported to increase brain metabolism in the frontoparietal network and is widely used as neurostimulant to improve consciousness.^{11 12 15} However, sufficient level of clinical evidence is only available for patients with TBI.^{11 13} We here found that amantadine treatment is associated with improvement of consciousness within 5 and 10 days after weaning initiation among patients with NTBI. Treatment effects of amantadine are consistent among patient subgroups. However, amantadine might be more efficient among patients with IS, ICH and SAH, and future studies should focus on these patients.

Regarding clinical outcomes, amantadine was associated with 11% lower odds of mortality at 90 days compared with the control group. The difference was not statistically significant, but the study was underpowered to show effects on mortality. As improved consciousness facilitates rehabilitation, functional recovery and may prevent long-term disability, future studies should evaluate treatment effects of amantadine on mortality and functional outcomes.^{3 11}

Amantadine exerts different effects on multiple neurotransmitters, which may cause side effects, notably epileptic seizures and delirium.^{11 14 19} Regarding delirium, we here found that amantadine was not associated with a relevant risk of delirium in this observational cohort analysis. Regarding epileptic seizures, Nickels *et al* reported that generalised seizures occurred in 2 of 12 patients with TBI treated with amantadine.¹⁹ However, the study did not include a control group and these seizures may represent sequela of TBI, why epileptic seizures have been discussed as potential side effects of amantadine ever since the publication of this study.^{11 13 14 17} We, here, show that amantadine treatment was associated with a non-significant 7.7% absolute increase in the rate of epileptic seizures in this observational cohort analysis with routinely performed continuous EEG monitoring. Although these differences were not statistically significant, future studies should consider epileptic seizures as potential side effects of amantadine treatment.

This study has some shortcomings. Bias by indication and timing of treatment initiation may have confounded analyses, the single-centre approach could limit generalisability, and the study was underpowered to evaluate treatment effects of amantadine on mortality, seizures and delirium. Furthermore, assessment of consciousness was based on the GCS, resulting in practical limitations of assessment in intubated patients.

CONCLUSIONS

Amantadine treatment was associated with improved consciousness in this observational cohort analysis and may represent a viable treatment option for patients with NTBI with prolonged disorders of consciousness. Randomised controlled trials are needed to confirm these findings and evaluate treatment effects of amantadine on mortality and functional outcomes. Epileptic seizures should be considered as potential side effect of amantadine.

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