Amantadine for Severe Traumatic Brain Injury: Impact on Pre-Rehabilitation Acute Hospitalization Recovery. A Retrospective Analysis

Daniel D. Kim BS; Kimberly Sue Meyer MSN, ACNP; Warren W. Boling MD, FRACS, FRCS(C)
Department of Neurosurgery, University of Louisville School of Medicine
Louisville, KY

Introduction

Amantadine Hydrochloride (AH), a safe, inexpensive NMDA antagonist with dopamine agonist effects, is one treatment considered to have potential therapeutic value in impvoing cognitive and functional outcome for patients who have suffered Traumatic Brain Injury (TBI), a leading cause of death and disability(1). A 2012 prospective and placebo controlled trial of AH for TBI administered during the post-acute rehabilitation phase provided the first rigorous evidence that AH therapy accelerated functional recovery, particularly in patients who were enrolled earlier in the study (28-70 days vs 71-112 days) and in those who were in a minimally conscious state rather than in a vegetative state (2). In this retrospective study, the authors investigated outcome variables in the acute hospitalization phase of severe TBI treated with AH. Various acute hospitalization outcome parameters were assesed, and patients were compared with a control that did not receive AH matched for variables that are known to impact outcomes.

Methods

Patients were retrospectively identified from University of Louisville Hospital's (ULH) trauma data base who sustained a traumatic brain injury in 2010-2012. Inclusion Criteria: Individuals ages 18-65 and severe TBI (Glasgow Coma Score (GCS) 3 to 8). Exclusion criteria: missile-type penetrating brain injury, premorbid major CNS/developmental abnormality (e.g., mental retardation, prior significant brain injury, etc.). Injury severity measures were On-Scene GCS and Injury Severity Score (ISS). Outcome Measures were Disability Rating Scale (DRS) score assessed at day of discharge from hospital, total ICU length of stay, total hospital length of stay defined as the date treating physician determined patient was ready for discharge, and discharge destination (to home, subacute (outpatient) rehabilitation, acute rehabilitation, or skilled nursing).

Methods (continued)

Over the years, AH has been administered by a few providers at ULH to this severe TBI population that constituted the study cohort. Matched controls who did not receive AH were compared with the study group. Propensity score matching criteria were ISS (difference within 3), GCS (diff within 2), and age (diff withing 10 yrs) resulting in 22 with AH treatment (AH Group) and 22 with no AH treatment (Controls). Propensity scores were computed using a multivariate logistic regression model. In univariate analysis, non-parametric rank sum test was used to compare continuous outcomes (total hospital days, ICU days, and discharge DRS) and chi-square test was used to compare categorical outcomes (discharge destination and discharge DRS). In multivariate analysis, log-linear model was used for continuous outcomes and logistic regression was used for categorical variables.
All tests were two sided and were statistically significant if p-value < 0.05. SAS 9.3 (SAS Institute, Inc, Cary, NC) was used for data processing and data analysis.

Results

Results of unmatched data analysis can be seen on Tables 1 and 2.
After propensity score matching (tables 1 and 2), AH Group and Control group had similar ages (median 33 and 32, respectively, p=0.359), gender compositions (75% and 79% males, respectively, p=0.505). ISS were similar in both groups (median 29 and 29, respectively, p=0.991). Patients given amantadine still had longer hospital stay (median days 25 vs. 18.5, p-value: 0.0129), which, in multivariate analysis controlling for all considered patient characteristics, translated into a 64% longer stay (estimate ratio: 1.64, 95% CI: 1.28 – 2.10), (Fig.1). Total ICU Days were not different in AH group vs Control (median 13.5 vs 8.5, respectively, p=0.1304), (Fig.1). Discharge DRS overall and subcategories were not different in AH group vs Control (median 14 vs 11, respectively, p=0.139), (Fig.2 and Fig.3). Disposition was not different in AH Group and Controls for outpatient rehabilitation (42% vs 46%, p=0.771), acute rehab (29% vs 29%, p=1.00), or subacute rehab (4% vs 1%, p=0.157), (Fig.4).

Table 1: Patient Demographics and Injury Measures

	All patients			Propensity Score Matched Patients		
	Control (n=39)	Amantadine (n=38)	*p*-value	Control (n=24)	Amantadine (n=24)	*p*-value
Age						
Mean (STD)	37.2 (11.6)	38.2 (12.1)		34.9 (12.5)	37.8 (13.1)	
Median (Q1 – Q3)	38 (27 – 45)	38 (29 - 48)	0.7988	33.0 (26 – 42)	32 (28 – 49)	0.3585
Gender			0.1654			0.7313
Female	7 (17.95)	12 (31.58)		5 (20.83)	6 (25.00)	
Male	32 (82.05)	26 (68.42)		19 (79.17)	18 (75.00)	
Injury Severity Score						
Mean (STD)	26.7 (8.1)	32.0 (11.8)		27.9 (83.7)	27.9 (9.8)	
Median (Q1 – Q3)	25 (22 – 33)	30 (22 – 38)	0.0446*	29 (21 – 33)	29 (19.5–35.5)	0.9917
On-scene 1st GCS			0.1449			0.7204
3	21 (53.85)	11 (28.95)		12 (50.00)	10 (41.67)	
4	3 (7.69)	5 (13.16)		3 (12.50)	3 (12.50)	
5	5 (12.82)	7 (18.42)		2 (8.33)	5 (20.83)	
6	6 (15.38)	9 (23.68)		6 (25.00)	4 (16.67)	
7	1 (2.56)	5 (13.16)		1 (4.17)	1 (4.17)	
8	3 (7.69)	1 (2.63)		0 (0.00)	1 (4.17)	

Table 2: Univariate and Multivariate Comparison of Outcomes

	All patients			Propensity Score Matched Patients		
	Control (n=39)	Amantadine (n=38)	*p*-value	Control (n=24)	Amantadine (n=24)	*p*-value
Total Hospital Days						
Mean (SD)	17.9 (9.6)	27.8 (12.5)		18.5 ± 10.4	27.6 ± 14.0	
Median (Q1 – Q3)	16 (10 - 24)	25 (18 - 34)	0.0004*	18.5 (9.5 - 26)	25 (18 – 32.5)	0.0129*
Estimate ratio, 95% CI	Reference	1.50 (1.21 – 1.85)		Reference	1.63 (1.20 – 2.22)	
Total ICU Days						
Mean (SD)	9.8 (6.8)	17.0 (11.8)		10.4 ± 6.9	14.3 ± 6.8	
Median (Q1 – Q3)	8.5 (4 - 15)	13.5 (10 - 18)	0.0007*	8.5 (4 - 15)	13.5 (10 – 16.5)	0.1304
Estimate ratio, 95% CI	Reference	1.66 (1.22 – 2.24)				
Discharge location, n (%)						
Home	7 (17.95)	4 (10.53)	0.3521	5 (20.83)	3 (12.50)	0.4386
Outpatient/Home Rehab	17 (43.59)	14 (36.84)	0.5461	11 (45.83)	10 (41.67)	0.7711
Acute Rehab	12 (30.77)	13 (34.21)	0.7471	7 (29.17)	7 (29.17)	1
Skilled Nursing	3 (7.69)	7 (18.42)	0.1615	1 (4.17)	4 (16.67)	0.1563
Discharge DRS						
Mean (SD)	10.2 (5.2)	15.1 (6.6)		10.2 ± 5.2	15.2 ± 6.6	
Median (Q1 – Q3)	11 (7 - 13)	14 (12 - 22)	0.0006*	11 (7 - 13)	14 (12 - 22)	0.139
Estimate ratio (95% CI)	Reference	1.32 (1.06 – 1.64)				
DRS categories, n (%)						
1 – 6: Mild/Partial/Moderate	9 (23.08)	3 (7.98)	0.0663	5 (20.83)	3 (12.50)	0.4386
7 – 21: Severe	29 (74.36)	25 (65.79)	0.4114	18 (75.00)	17 (70.83)	0.7453
22 – 29: Vegetative	1 (2.56)	10 (26.32)	0.0029*	1 (4.17)	4 (16.67)	0.1563
Vegetative, OR (95% CI)	Reference	7.41 (1.09 – 50.3)				

Figure 1.

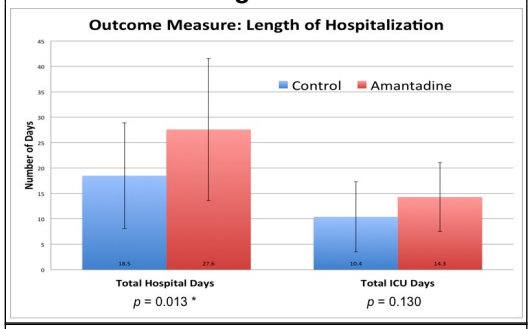
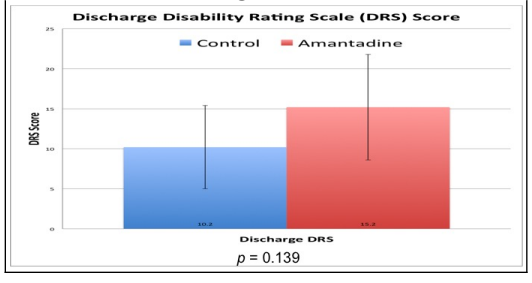


Figure 2.



Learning Objectives

Participants should be able to discuss outcomes of acute hospitalization after Amantadine Hydrochloride administration in patients with severe TBI.

Figure 3.

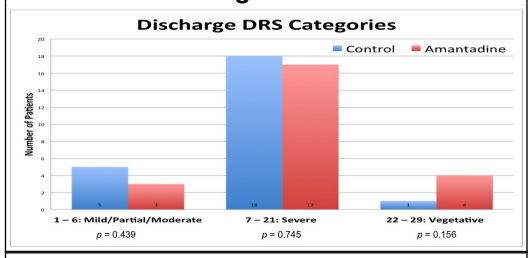
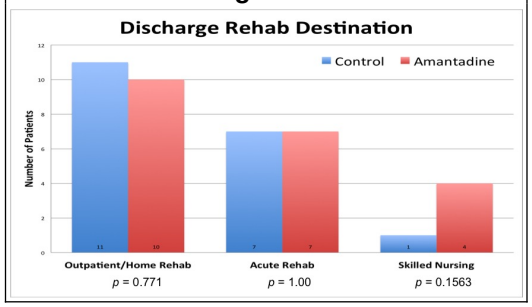


Figure 4.



Conclusions

Matched for injury severity, GCS, and age, Amantadine administration in the acute hospitalization phase demonstrated no significant difference compared with controls in DRS and was associated with longer hospital stay. In a recent randomized controled study amantadine showed considerable benefit for TBI in the post acute rehabilitation setting. This outcome was not demonstrated in our investigation. Additional investigation into confounding variables such as socioeconomic status effect on hospital length of stay will be valuable to better define the role of AH for TBI in the acute hospitaization. Further prospective studies will be needed to fully evaluate AH use in acute hospitalization.

References

1. Spritzer S D, et al. Amantadine for patients with severe traumatic brain injury: a critically appraised topic. The Neurologist 2015;19(2):61-4.
2. Giacino J T, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. The New England journal of medicine 2012;366(9):819-26.