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Low-dose IV Heparin Infusion Preserves Cognitive Function in aSAH Patients when Controlling for Covariates that Negatively Influence Cognition including Age, ACoA Aneurysm Location and Fever.

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Introduction

Cognitive dysfunction occurs in up to 70% of aneurysmal subarachnoid hemorrhage (aSAH) survivors preventing return to previous activities and quality of life.(1) Age, anterior communicating artery (ACoA) aneurysm location, and fever are associated with poor cognition following aSAH.(2) aSAH patients administered the Maryland low-dose intravenous heparin (LDIVH) infusion protocol recently demonstrated significant reductions in clinical vasospasm and vasospasm-related infarction.(3) We administered the Montreal Cognitive Assessment (MoCA, 0-30; normal >= 26) comparing cognition in aSAH patients treated with the Maryland LDIVH protocol vs. controls while controlling for predictors of cognitive dysfunction.(4)

Methods

Retrospective analysis was performed on all aSAH patients with MoCAs (aneurysms treated July 2009-April 2014). In 2012, patients began receiving LDIVH (10-12 u/kg/hr; ~14 days; FDA off-label). MoCA was scored by blinded non-study personnel. ANCOVA was performed for age and variables with significant Spearman's correlations to MoCA.

Table 1. Baseline Characteristics.

Characteristic	Control (n=22)	Heparin (n=25)	p value
Age (Mean ± SEM)	51.2 ±2.3	50.9 ±2.5	0.92
Fisher Grade 3	8	14	0.24
WFNS Scale (I/II/III/IV/V)	13/3/1/3/2	16/6/1/3/0	0.42
WFNS ≥ 4	5	3	0.56
Gender (Female)	17	17	0.70
Clipping	2	6	0.33
Anterior Circulation Aneurysm	19	23	0.88
Anterior Communicating Aneurysm (ACoA Aneurysm)	10	5	0.12
Premorbid Disability (Reported)	2	1	0.91
History of Dementia	2	2	1.0
Hypertension	13	19	0.35
Tobacco Use	15	14	1.0
Marijuana Use	1	7	0.08
Cocaine Use	1	3	0.70
Alcohol Use	5	8	0.70
Heroin Use	1	0	0.95

Results

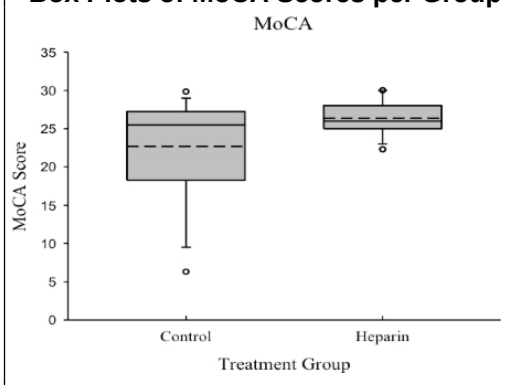
No significant differences in baseline characteristics were seen between groups (Table 1). Mean MoCA for the LDIVH group (n=25) was 26.2 vs. 22.7 in controls (n=22); (p=0.013). Serious cognitive impairment (MoCA <= 20) was observed in 32% of controls vs. 0% for heparin patients (p=0.008). MoCA means between groups remained significantly different when controlling for covariates negatively influencing cognition (Adjusted MoCA p-value for: age, p=0.009; ACoA aneurysm,p=0.038; and fever, p=0.006). There were no treatment complications.

Table 2. Results.

Results	Control (n=22)	Heparin (n=25)	p value
MoCA (Mean ± SEM)	22.7 ± 1.5	26.2 ± 0.5	p=.013*[1]
MoCA ≤ 20	7	0	p=.008*
Months to follow-up MoCA testing (Mean ± SEM)	25.4 ± 2.7	7.0 ± 1.5	p<.001[1]
Modified Rankin Scale (mRS) (Mean ± SEM)	1.4 ± 0.2	1.1 ± 0.2	p=.25
Modified Rankin Scale (mRS) ≤ 1	13	20	p=.21
Days from ictus to admission (Mean ± SEM)	1.6 ± 0.8	0.8 ± 0.4	p=.37
Length of hospital stay (Mean ± SEM)	16.4 ± 1.7	16.2 ± 1.0	p=.92
Days on continuous IV Heparin drip (Mean ± SEM)	N/A	11.9 ± 0.7	N/A
SubQ Heparin DVT prophylaxis (5000 units bid or tid)	11	11	p=.91
Total units of Heparin per patient post-securement (Mean ± SD), Control n=11	98,636 ± 43,880	248,644 ± 128,696	p<.001[1]
Hydrocephalus requiring external ventricular drain	7	8	p=1.0
Hydrocephalus requiring ventriculoperitoneal shunt	6	2	p=.17
Any fever episodes (>101.6°F)	4	4	p=1.0
Multiple fever episodes (>101.6°F)	2	4	p=.79
Packed Red Blood Cell (PRBC) transfusion	5	7	p=.94
Units PRBC transfused (Mean ± SEM)	0.68 ± 0.3	0.68 ± 0.3	p=1.0
Any Thrombocytopenia	3	1	p=.51
Deep Vein Thrombosis	1	0	p=.95
Anti-seizure medications	21	24	p=1.0
Discharge to rehab or skilled nursing facility	6	5	p=.81

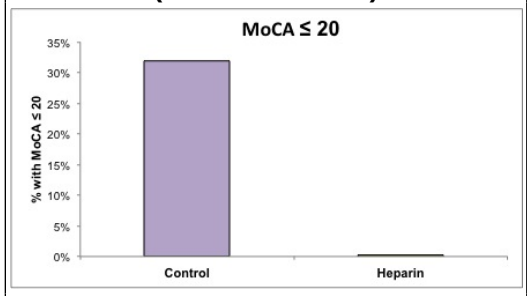
*1-tailed
[1]Independent t-test between means with unequal variance

Box Plots of MoCA Scores per Group

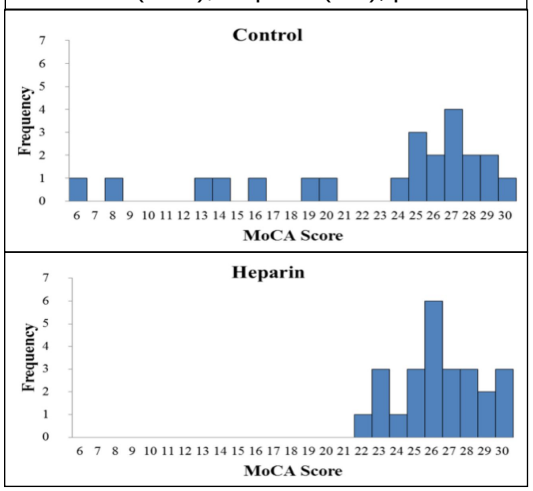


Median (Solid Line), Mean (Dashed Line), IQR (Box), 95th Percentile Confidence Interval (Whiskers), Min / Max (Circles)

Percent Severe Cognitive Dysfunction (MoCA 20 or less)



Control (32%), Heparin (0%); p=0.008



Conclusions

Heparin is a potent anti-inflammatory agent that reduces neuroinflammation following experimental SAH.(5,6) This study suggests that the Maryland LDIVH protocol safely improves cognitive outcomes in aSAH patients. These data support calls for a randomized trial of heparin.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Discuss the relationship between poor cognitive function and aSAH, 2) Describe data supporting the LDIVH protocol's effect on preservation of cognitive function in aSAH patients.

References

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