Low Albumin Levels in serum are associated with Cerebral Hemorrhage in Post-Intravenous Thrombolytic Therapy for Acute Stroke

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Background

There remains a 6% risk of hemorrhage with the use of IV thrombolytic therapy in acute stroke. There is currently no reliable method to determine which patients will bleed into the brain after receiving intravenous tissue plasminogen activator (IV tPA). Currently, large strokes or very severe strokes are excluded from receiving IV tPa as these patients are felt to have a higher risk of bleeding. Albumin has been proposed as being protective to the blood brain barrier. However, it is unclear if normal serum albumin is protective or at least associated with a decreased risk of bleeding after stroke.

Methods

Retrospective review study to investigate stroke patients albumin levels upon arrival to the ED. Demographic, co-morbity data, and medication information were collected in order to determine any additional associations. MRI/CT data reviewed to determine whether these patients had hemorrhage during the acute period (< 1 week) of their stroke care. Continuous demographic variables were compared between stroke patients with & without intracranial hemorrhage using two-tailed t-tests. Categorical demographic variables were compared between groups using chi-square analysis. The effect of albumin level on presence of intracranial hemorrhage after stroke was examined using a two-tailed t-test with serum albumin as a continuous variable. Patients were divided into groups for high and low albumin levels using a cut point of 3.3 grams/dl. The relationship between high & low albumin levels as categorical variables and presence of intracranial hemorrhage after stroke was then compared using chi-square analysis. A logistic regression model was constructed using intracranial hemorrhage as the outcome variable & serum albumin level as the predictor variable, correcting for effects of serum creatinine and INR.

Demographic Characteristic	Low Albumin (n = 30)	High Albumin (n = 214)	Significance
Age in years mean (S.D.)	70.00 (14.727)	70.10 (14.561)	0.972
Gender (% female)	43.3%	43.0%	0.972
NIH stroke scale score mean (S.D.)	11.20 (6.506)	11.46 (6.381)	0.854
Co-morbid Diabetes (% yes)	43.3%	20.6%	**0.006**
Co-morbid Hypertension (% yes)	66.7%	73.8%	0.408
Co-morbid Dyslipidemia (% yes)	36.7%	36.0%	0.942
Co-morbid Heart Failure (% yes)	26.7%	9.3%	**0.005**
Treated with Antiplatelet Agent (% yes)	36.7%	26.2%	0.261
Treated with Anticoagulant (% yes)	20.0%	5.1%	**0.011**
Smoker (% yes)	6.7%	16.4%	0.166
Creatinine mean (S.D.)	1.36 (0.9353)	1.13 (0.7117)	0.300
INR mean (S.D.)	1.20 (0.2325))	1.08 (0.1041)	**0.015**

Results

A total of 244 patients, 85 with ICH after ischemic stroke and 195 without ICH after ischemic stroke, were included in this study. Compared to patients without ICH after ischemic stroke, those with ICH were slightly older (mean = 72.74, S.D. = 15.14; mean = 68.67, S.D. = 14.07), and displayed a higher NIH stroke scale score at presentation (mean = 13.12, S.D. = 6.26; mean = 10.47, S.D. = 6.27). Additionally, trends towards increased likelihood to have co-morbid heart failure (16.5% vs. 8.8%, significance = 0.073) and to be treated with an antiplatelet agent (34.1% vs. 23.9%, significance = 0.083) were also noted. Compared to patients without ICH after ischemic stroke, those with ICH had significantly lower serum albumin (mean = 3.64, S.D. = 0.39; mean = 3.85, S.D. = 0.42; significance < 0.001), and higher INR (mean = 1.12, S.D. = 0.15; mean = 1.08, S.D. = 0.12; significance = 0.031). No difference in mean serum creatinine was identified.

A logistic regression model was then constructed, using presence of ICH after ischemic stroke as the dependent variable and including serum albumin, serum creatinine, and INR as potential predictor variables. The overall model was significant (-2 Log likelihood = 272.22; $p < 0.001$) and the estimated R-square was 0.106. With all three predictor variables included in the model, only serum albumin remained significant with a calculated odds ratio of 0.166, indicating that every 1.0 g/dl decrease in serum albumin resulted in a 0.166 greater odds of developing ICH after ischemic stroke.

Table 1: Demographic Characteristics of Patients with and without Intracranial Hemorrhage after Ischemic Stroke.

Demographic Characteristic	With Intracranial Hemorrhage	Without Intracranial Hemorrhage	Significance
Age in years (mean/S.D.)	72.74 (15.14)	68.67 (14.07)	**0.042**
Gender (% female)	47.1%	40.9%	0.353
NIH stroke scale score mean (S.D.)	13.12 (6.26)	10.47 (6.27)	**0.003**
Co-morbid Diabetes (% yes)	28.2%	20.8%	0.188
Co-morbid Hypertension (% yes)	72.9%	73.0%	0.998
Co-morbid Dyslipidemia (% yes)	42.4%	32.7%	0.135
Co-morbid Heart Failure (% yes)	16.5%	8.8%	**0.073**
Treated with Antiplatelet Agent (% yes)	34.1%	23.9%	**0.083**
Treated with Anticoagulant (% yes)	7.1%	6.9%	0.190
Smoker (% yes)	11.8%	17.0%	0.279

Table 2: Serum Albumin, Serum Creatinine and INR in Patients with and without Intracranial Hemorrhage after Ischemic Stroke.

	With Intracranial Hemorrhage	Without Intracranial Hemorrhage	Significance
Serum Albumin (g/dl) mean (S.D.)	3.64 (0.39)	3.85 (0.42)	**< 0.001**
Serum Creatinine mean (S.D.)	1.28 (1.01)	1.10 (0.54)	0.124
INR mean (S.D.)	1.12 (0.15)	1.08 (0.12)	**0.031**

Table 3: Logistic Regression Model of Serum Albumin and Intracranial Hemorrhage after Ischemic Stroke.

Variable	B	S.E.	Significance	Exp(B)
Albumin g/dl	-1.795	0.439	**< 0.001**	**0.166**

Discussion

A previous double blind clinical trial (ALIAS) of 25% normal saline was recently published which did not show a benefit to stroke outcome in patients given a 25% solution of albumin. Although they did not show a decrease in hemorrhage in the patients that received albumin, their data included both patients who received thrombolytics and those that did not. Our study included only patients who only received tPa.

There have been several animal model studies showing that albumin is involved in maintaining the integrity of the blood brain barrier (BBB). Loss of cell to cell adhension molecules associated with endothelium and other associated cells of the BBB are disrupted during acute ischemic stroke and this loss of connections results in breakdown of the BBB, resulting in intracerebral hemorrhage.

Serum albumin may interact the endothelium via yet to be determined mechanism to allow the endothelial cell-cell adhension molecules to remain intact or even up regulate them to strengthen them.

Further prospective study is needed to determine:

1. Do higher serum albumin levels decrease the risk of hemorrhagic conversion of acute ischemic stroke after administering thromblytics.
2. How albumin effects the tight junctions and adhesion elements and cell to cell interactions at the endothelial level of the blood brain barrier.
3. Whether supplemental albumin can protect ischemic stroke patients from “symptomatic” hemorrhage after thrombolytic therapy.

References

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