



Laboratory factors associated with symptomatic hemorrhagic conversion of acute stroke after systemic thrombolysis

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ABSTRACT

Background: Laboratory factors associated with hemorrhagic conversion (HC) after Intravenous thrombolysis with rtPA (IVT) for Acute Ischemic Stroke (AIS) remain nebulous despite advances in our knowledge of AIS. This study aimed to investigate the laboratory factors predisposing to HC in AIS patients receiving IVT.

Methods: We retrospectively reviewed the medical records of patients who received IV tPA for AIS at our comprehensive stroke center over a 9.6-year period. Besides age, gender, NIHSS, history of diabetes mellitus (DM), history of atrial fibrillation (Afib), we gathered their laboratory data including International Normalized Ratio (INR), lipid panel, serum albumin, serum creatinine, hemoglobin A1c (HbA1c), and admission blood glucose. Post-thrombolysis brain imaging were reviewed to evaluate for symptomatic ICH (sICH). The mean values of above mentioned laboratory data were compared between the group with sICH and patients with no sICH. Univariate and multivariate logistic regression were performed to evaluate the association of the laboratory findings with presence of sICH. sICH was defined as ICH causing an increase in NIHSS ≥ 4 .

Results: Of the 794 subjects in this study 51 (6.4%) had sICH. In the univariate analysis, patients who developed sICH had significantly higher NIHSS on admission (14.2 ± 5.4 vs 11.2 ± 6.5 , $p < .001$), LDL-cholesterol ($113.3 \text{ mg/dl} \pm 36.9$ vs $101.8 \text{ mg/dl} \pm 38.2$, $p = .032$), HbA1c ($6.9\% \pm 2.3$ vs 6.1 ± 1.3 , $p = .003$) and lower levels of Albumin ($3.5 \text{ g/dl} \pm 0.4$ vs $3.9 \text{ g/dl} \pm 0.5$, $p < .001$). Furthermore, a higher prevalence of history of DM (45% vs. 21.6%, $p = .020$) and Afib (25.4% vs. 10.4%, $p = .028$) was found in subjects who developed sICH. There were no significant group differences regarding age, sex, total cholesterol, blood glucose on admission, serum creatinine or INR levels ($p > .05$). After adjusting for multiple covariates, lower Albumin level and higher HbA1c were significantly associated with an increased risk for sICH development ($p < .05$). Chances of sICH increased by 33% for every 1 g/dl below a normal albumin level of 4.0 g/dl ($p < .05$).

Conclusion: Lower endogenous albumin level and higher HbA1c have shown to predispose to a higher risk of sICH after IVT for AIS and might be good predictors of sICH post IVT.

1. Introduction

Acute ischemic stroke (AIS) management has transformed with recent developments in Intravenous thrombolysis (IVT) and Intra-

arterial treatments (IAT). While the initial randomized clinical trials (RCT) [1–5] proved the efficacy and safety of IAT up to 6 h after symptom onset for large vessel occlusion (LVO) strokes, DAWN and DEFUSE 3 trials [6,7] further extended the time window of IAT for LVO

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strokes. Along similar lines, using advanced imaging namely CT Perfusion [8] and MR [9] based imaging, extending the time window and eligibility [10–15] for IVT has been looked at in various studies, and is now part of the AHA/ASA guidelines [16]. Symptomatic Intracranial Hemorrhage (sICH) however remains the most devastating and feared complication leading to high mortality and morbidity post IVT or IAT for AIS [17–19].

Aside from the clinical and radiological factors including advanced age, history of diabetes mellitus (DM), atrial fibrillation (Afib), higher National Institutes of Health Stroke Scale (NIHSS) score on presentation, extent of hypoattenuation on head CT being known factors predisposing to higher risks of sICH post IVT, animal models [20,21] of stroke have shown that an early disruption or loss of integrity of blood brain barrier (BBB) leads to sICH.

The blood brain barrier consists of endothelial cells joined together by tight junctions which are composed of smaller sub units, frequently biochemical dimers, which are transmembrane proteins such as occludins, claudins, junctional adhesion molecules, etc. Each of these transmembrane proteins is anchored into the endothelial cells with another protein complex that includes ZO-1 and other proteins [22].

It has been postulated that endogenous albumin has a neuroprotective role in maintaining microvascular integrity at the blood brain barrier (BBB) [23,24]. Additionally low-density lipoprotein (LDL-cholesterol), Serum Creatinine, blood glucose and hemoglobin A1c (HbA1c) levels have been studied in correlation to sICH post IVT [26–36, 39].

We aimed to analyze various laboratory data which may help to predict sICH post IVT in our large prospectively collected database at our comprehensive stroke center. This study is particularly important with the growing use and interest in tenecteplase (TNKase) [40] as well as the ongoing debate in combining IVT and IAT, knowing the risk factors for sICH may help in decision making for clinicians in future management of AIS.

2. Patients and methods

We studied all consecutive patients with AIS who were treated with IVT using intravenous recombinant tissue plasminogen activator (IV rtPA) with or without IAT at our high volume comprehensive stroke center over a period of 9.6-years. Data were entered into our prospective stroke database, including age, sex, medical history, cardiovascular risk factors, home medications, time of symptom onset, time of start of IV rtPA treatment, NIHSS score on admission and discharge, laboratory data (including platelet count, creatinine, albumin, lipid panel, HbA1c, International Normalized Ratio (INR) and liver function test).

2.1.1. Outcome parameters

Our primary outcome was the occurrence of sICH. Follow-up brain CT or MRI within 24–36 h of IV rtPA administration and medical records were reviewed to determine the number of patients with ICH and sICH. sICH was defined as ICH with an increase NIHSS of at least 4 points. All head CTs and brain MRIs were interpreted by board certified Neuroradiologists and clinical evaluations were done by our team of board certified Vascular Neurologists.

2.2. Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics 23 (IBM Corp, Armonk, New York). To investigate any possible group differences, Chi-square tests were utilized for categorical variables, while the Independent-samples *t*-tests were used for continuous variables. Mann-Whitney *U* tests were used for data not following a normal distribution. All relevant values were presented as frequency counts with percentages for categorical data and means with standard deviations

(SD) for continuous variables. Univariate logistic regression was performed with presence or absence of sICH as the dependent variable. To investigate the association between albumin level, LDL-cholesterol, total cholesterol, HbA1c, admission blood glucose level, serum creatinine and INR with sICH, logistic regression models were carried out. Because of the potential confounding effects of age, NIHSS, Afib status and history of DM, these variables were entered as covariates in multivariable logistic regression models.

A value of $P \leq .05$ was considered statistically significant. The study protocol was approved by the local institutional review board at our institution.

3. Results

We studied a total of 794 patients who were treated with IVT within 4½ hours after symptom onset of AIS. Of the 794 subjects in this study, 51 (6.4%) had sICH. Patients who had a sICH had significantly higher NIHSS on admission (14.2 ± 5.4 vs. 11.2 ± 6.5 , $p < .001$), LDL-cholesterol (113.3 ± 36.9 vs. 101.8 ± 38.2 , $p = .032$), HbA1c (6.9 ± 2.3 vs. 6.1 ± 1.3 , $p = .003$), and lower levels of Albumin (3.5 ± 0.4 vs. 3.9 ± 0.5 , $p < .001$) compared to the subjects with no sICH. Furthermore, a higher prevalence of history of DM (45% vs. 21.6%, $p = .020$) and Afib (25.4% vs. 10.4%, $p = .028$) were found in subjects with sICH. There were no significant group differences regarding age, sex, total cholesterol, blood glucose, serum creatinine or INR levels (all $p > .05$).

Table 1 represents the demographic and clinical characteristics of patients with sICH versus those without sICH. Table 2 provides the results of both univariate and multivariate logistic regression analysis of the laboratory data for sICH. Lower Albumin level and higher HbA1c were significantly associated with an increased risk for sICH, even after adjusting for covariates. Admission blood glucose, LDL-cholesterol, total cholesterol or serum creatinine level did not have any association with increasing the risk of sICH post IVT.

4. Discussion

In this study, we evaluated factors that predispose to sICH post treatment with IVT with or without IAT. Similar to the study by Che et al. [23], we found that lower endogenous serum albumin levels predisposed the patients to an increased risk of sICH post treatment with IVT. For every 1 g/dl decrease in albumin levels below a normal level of 4.0 g/dl, we found the risk of sICH increased by 33%. These results are consistent with the presumed role of albumin in maintaining normal astrocytic function as well as having a neuroprotective effect for the BBB²⁴.

Both acute and chronic hyperglycemia have been linked to poor

Table 1

Demographic and clinical characteristics of patients with sICH versus those without sICH.

Characteristics	sICH <i>n</i> = 51	No sICH <i>n</i> = 743	<i>p</i> -value
Age	74.1 (± 14.0)	71.2 (± 14.9)	0.123
Sex (Male)	30 (58.8%)	379 (51%)	0.273
NIHSS at admission	14.2 (± 5.4)	11.2 (± 6.5)	<0.001
History of diabetes mellitus	23 (45%)	161 (21.6%)	0.020
Atrial fibrillation	13 (25.4%)	78 (10.4%)	0.028
Serum albumin(g/dl)	3.5 (± 0.4)	3.9 (± 0.5)	<0.001
LDL-cholesterol(mg/dl)	113.3 (± 36.9)	101.8 (± 38.2)	0.032
Total cholesterol(mg/dl)	174.4 (± 40.1)	163.1 (± 43.3)	0.061
HbA1c (%)	6.9 (± 2.3)	6.1 (± 1.3)	0.003
Blood glucose on admission(mg/dl)	147.3 (± 74.9)	131.5 (± 47.7)	0.109
Serum creatinine(mg/dl)	1.1 (± 0.2)	1.1 (± 0.6)	0.662
INR	1.1 (± 0.2)	1.1 (± 0.1)	0.824

NIHSS = National Institutes of Health Stroke Scale, INR: International Normalized Ratio.

Bold indicates P-Values which are statistically significant.

Table 2

Logistic regression models showing odds of sICH with different variables.

Variable	Univariate			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Serum albumin (g/dl)	0.28	0.17–0.47	<0.001	0.31	0.19–0.52	<0.001
LDL-cholesterol (mg/dl)	1.0	1.0–1.0	0.033	1.0	1.0–1.0	0.015
HbA1c (%)	1.3	1.1–1.6	0.001	1.3	1.0–1.6	0.017
Admission blood glucose (mg/dl)	1.0	1.0–1.0	0.018	1.0	1.0–1.0	0.155
Total cholesterol (mg/dl)	1.0	1.0–1.0	0.062	1.0	1.0–1.0	0.024
Serum creatinine (mg/dl)	0.63	0.31–1.3	0.216	0.48	0.22–1.1	0.077
Age ^a	1.0	0.99–1.0	0.124			
Admission NIHSS ^a	1.1	1.0–1.1	<0.001			
History of DM ^a	1.9	1.1–3.2	0.022			
Atrial fibrillation ^a	2.0	1.1–3.9	0.031			

LDL = Low-density lipoprotein, DM = Diabetes Mellitus, OR: odds ratio, CI: confidence interval, NIHSS: National Institutes of Health Stroke Scale.

Bold indicates P-Values which are statistically significant.

^a Variables that were adjusted for in multivariable analyses.

outcomes in AIS including patients undergoing IVT. In patients treated with IVT in AIS, lower recanalization rates and poor outcomes were observed in prior studies [25,26]. A previous large multi-center study found higher rates of sICH in patients with elevated blood glucose levels on presentation [27]. We observed a significance for higher admission blood glucose levels portending to a higher risk of sICH in our study sample; however, those values lost significance in the multivariate analysis once we adjusted for other known risk factors. We did find that elevated HbA1c levels led to higher risk of sICH post IVT similar to what has been reported in earlier studies [27]. These findings are explained by the hypothesis that chronically elevated blood glucose levels indicated by HbA1c levels leads to microvascular damage.

The data on the role of LDL-cholesterol and total cholesterol levels and risk of sICH remains with mixed results with some studies [28,29] reporting no association with higher risk of sICH while others [30] observing lower LDL levels to portend to higher rates of sICH post IVT in AIS. We found no association of LDL levels with sICH. Elevated cholesterol levels also did not seem to increase odds of sICH.

We further evaluated the role of chronic kidney disease (CKD) and risk of increase in sICH rate post IVT in AIS patients. Patients with CKD are known to have abnormalities in coagulation and

platelet function as well as a higher risk of atherosclerosis and thrombotic vascular complications [31,32]. There exists conflicting data on CKD and risk of sICH with IVT in retrospective clinical studies, while some reported higher rates of sICH with more severe CKD based on GFR [33,34] and Serum Creatinine [35]. A large multicenter cohort study [] with >44,000 AIS patients reported no significant association of CKD with sICH post IVT. We analyzed serum creatinine levels as a surrogate for renal function and did not find a significant association of sICH with CKD in our cohort of patients.

Although our study included a relatively large sample for a single center study, it has several limitations. The unequal distribution of the number of patients between the two groups was a limitation; however, careful examination of the data distribution led us to believe that both groups were representative as spread of data and standard deviations were equal regardless of the group size. We also did not account for the asymptomatic ICHs since they are clinically insignificant and the goal of the study was to evaluate for devastating sICH with IVT. Although our data were collected in a prospective fashion, and outcome parameters

were assessed blinded to the baseline and imaging parameters, data analysis has been done retrospectively, including all known possible bias of such an approach. Additionally there might have been associated factors such as transient elevations in blood pressure which led to the sICH which we could not adjust for. However, all patients were treated according to current post IV rtPA guidelines [16].

In conclusion, in this relatively large sample single center study, we observed that lower serum albumin levels and higher baseline HbA1c levels predisposed to higher odds of sICH post IVT for AIS. LDL-cholesterol, total cholesterol, admission blood glucose and serum creatinine levels did not portend any significantly higher risk in our study population. Additional large scale studies may help elucidate the clinical significance of these findings further.

Statement of ethics

Subjects (or their parents or guardians) have given their written informed consent for being treated for IV tPA. The paper is exempt from ethical committee approval since IV tPA is considered the standard of care for treating acute ischemic stroke and there has been no disclosure of the patients' information in this paper.

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None.

Author contributions

All authors have contributed to the theoretical formalism, designing the study, data collection, data analysis and writing the manuscript.

Declaration of Competing Interest

Authors have no relevant financial disclosure to report.

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