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ORIGINAL RESEARCH

Factors Predicting Hemorrhagic Complications after Multimodal Reperfusion Therapy for Acute Ischemic Stroke

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BACKGROUND AND PURPOSE: We sought to find predictors for hemorrhagic complications in patients with acute ischemic stroke treated with multimodal endovascular therapy.

MATERIALS AND METHODS: We retrospectively reviewed patients with acute ischemic stroke treated with multimodal endovascular therapy from May 1999 to March 2006. We reviewed clinical and angiographic data, admission CT Alberta Stroke Programme Early CT Score (ASPECTS), and the therapeutic endovascular interventions used. Posttreatment CT scans were reviewed for the presence of a parenchymal hematoma or hemorrhagic infarction based on defined criteria. Predictors for these types of hemorrhages were determined by logistic regression analysis.

RESULTS: We identified 185 patients with a mean age of 65 ± 13 years and mean National Institutes of Health Stroke Scale score of 17 ± 4. Sixty-nine patients (37%) developed postprocedural hemorrhages: 24 (13%) parenchymal hematomas and 45 (24%) hemorrhagic infarctions. Patients with tandem occlusions (odds ratio [OR] 4.6 [1.4–6.5], $P < .016$), hyperglycemia (OR 2.8 [1.1–7.7], $P < .043$), or treated concomitantly with intravenous (IV) tissue plasminogen activator (tPA) and intra-arterial (IA) urokinase (OR 5.1 [1.1–25.0], $P < .041$) were at a significant risk for a parenchymal hematoma. Hemorrhagic infarction occurred significantly more in patients presenting with an ASPECTS ≤7 (OR 1.9 [1.3–2.7], $P < .01$).

CONCLUSIONS: Hemorrhagic infarctions are related to the extent of infarct based on presentation CT, whereas parenchymal hematomas are associated with the presence of tandem occlusions, hyperglycemia, and treatment with both IV tPA and IA urokinase in patients with acute stroke treated with multimodal endovascular therapy.

Acute ischemic stroke with persistent large-vessel extra- or intracranial occlusion is increasingly being treated with multimodal endovascular therapy combining pharmacologic and mechanical strategies.[1] However, the risk for intracerebral hemorrhage (ICH), a major concern, is poorly established. We sought to review our institutional cohort of patients treated with multimodal endovascular therapy to identify which clinical parameters and treatment modalities increase the risk of ICH.

Materials and Methods

With institutional approval, we retrospectively reviewed all patients presenting to our center with an acute ischemic stroke and treated with endovascular therapy from May 1999 to March 2006. We collected admission National Institutes of Health Stroke Scale score (NIHSS), risk factors, time from stroke onset to angiography and procedure completion, and admission CT Alberta Stroke Programme Early CT Score (ASPECTS).[2] Two authors unaware of patient histories or treatments tabulated ASPECTS as >7 or ≤7 with significant inter-rater agreement (kappa value of 0.82). Patients were also screened for hyperglycemia, defined as any glucose measurement ≥200 mg/dL within 24 hours after presentation.

Details of our treatment protocol, including which vessels we have treated, have been published previously[1] and are included in Table 1. Intravenous (IV) tissue plasminogen activator (tPA) was administered at the standard dose of 0.9 mg/kg according to the National Institute of Neurological Disorders and Stroke protocol.[3] As part of our endovascular protocol, patients received a 2000-U bolus of unfractionated heparin. For patients undergoing stent placement, IV eptifibatide (180 mcg/kg) was given during the procedure, followed by clopidogrel loading doses of 300–600 mg plus 325-mg aspirin immediately following intervention. Postintervention reperfusion success was based on Thrombolysis in Myocardial Infarction (TIMI) criteria described in our earlier report.[1]

CT scans were obtained within 24 hours of presentation and reviewed by 2 authors who classified the ICH as a parenchymal hematoma or hemorrhagic infarction based on defined criteria.[4] ICH was distinguished from poor contrast clearance if the initial postprocedure hyperattenuation was persistent on follow-up CT.[5] Evolving hyperattenuations were reclassified appropriately. End points were the presence of either hemorrhagic infarction or parenchymal hematoma and outcome was defined as in-hospital, death, or survival.

Statistics

Variables considered for univariate analysis have been provided in Table 1. Since our first report, we have grouped all patients with a concomitant extracranial and intracranial occlusion into a new category named "tandem occlusions" (Table 1). Also differing from our first report, our univariate analysis assessed separately the effects of intra-arterial (IA) tPA or IA urokinase, both with or without IV tPA, and time from stroke onset to procedure completion. Other new parameters for the univariate analysis included the risk of ICH in patients with successful reperfusion (TIMI ≥2), admission ASPECTS ≤7, and both. Baseline characteristics for patients with and without

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Table 1: Univariate analysis of predictors of PH and HI after multimodal endovascular therapy for acute ischemic stroke

Variable	PH (*N* = 24) *N* (%)	No PH (*N* = 161) *N* (%)	*P*	HI (*N* = 45) *N* (%)	No HI (*N* = 140) *N* (%)	*P*
Demographics						
Age (mean ± SD), years	68 ± 12	64 ± 13	.13	64 ± 14	64 ± 13	.96
NIHSS (mean ± SD)	18 ± 5	17 ± 4	.35	18 ± 04	17 ± 4	.20
Hypertension	13 (54)	100 (62)	.37	30 (67)	82 (59)	.59
Diabetes mellitus	4 (17)	38 (24)	.67	9 (20)	32 (23)	.69
Atrial fibrillation	8 (33)	44 (27)	.63	16 (36)	36 (26)	.34
Hyperlipidemia	8 (33)	61 (38)	.66	14 (31)	55 (39)	.29
Coronary artery disease	12 (50)	54 (34)	.18	12 (27)	54 (39)	.15
Hyperglycemia	**9 (38)**	**34 (21)**	**.04**	12 (27)	30 (21)	.30
Location of thrombus						
CCA bifurcation	0 (0)	8 (6)	.61	1 (2)	7 (5)	.68
ICA terminus	6 (25)	39 (24)	.89	10 (22)	35 (25)	.65
M1 MCA	10 (42)	68 (42)	.92	23 (51)	55 (39)	.22
M2 MCA	1 (4)	6 (4)	.83	3 (7)	4 (3)	.37
Vertebrobasilar system	1 (4)	26 (16)	.09	7 (16)	20 (14)	.38
Tandem occlusion	**6 (25)**	**15 (9)**	**.03**	4 (9)	17 (12)	.78
Type of intervention						
IV tPA	13 (54)	60 (37)	.09	20 (44)	53 (38)	.37
IV urokinase	7 (29)	27 (18)	.12	8 (18)	26 (19)	.87
IA tPA	11 (46)	84 (52)	.66	22 (49)	73 (52)	.61
IV IIb/IIIa	8 (33)	63 (39)	.66	17 (38)	54 (39)	.87
IV IIb/IIIa + thrombolytic	5 (21)	36 (22)	.93	10 (22)	31 (22)	.93
Angioplasty	7 (29)	65 (40)	.37	18 (40)	54 (39)	.89
Snare/Merci	7 (29)	20 (12)	.06	6 (13)	21 (15)	.70
Extracranial stent	4 (17)	27 (17)	.96	5 (19)	26 (14)	.38
Intracranial stent	1 (4)	25 (16)	.11	6 (13)	20 (14)	.88
IV tPA + IA urokinase	**4 (17)**	**8 (5)**	**.045**	3 (7)	9 (6)	.69
IV tPA + IA tPA	6 (25)	32 (20)	.59	9 (20)	29 (21)	.97
IV tPA + any IA thrombolytic	**10 (42)**	**40 (25)**	**.05**	12 (27)	38 (27)	.91
Postintervention						
TIMI 2 or 3 flow	14 (58)	102 (63)	.63	26 (58)	90 (64)	.48
CT imaging preprocedure ASPECTS	1 (4)	16 (10)	.47	**10 (22)**	**7 (5)**	**.002**
Neuroimaging postprocedure						
TIMI 2 or 3 flow + ASPECTS ≤7	1 (4)	8 (5)	.64	**5 (11)**	**4 (1)**	**.05**

Note:—PH indicates parenchymal hematoma; HI, hemorrhagic transformation; CCA, common carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery; IIb/IIA, glycoprotein receptor IIb/IIa antagonist; NIHSS, National Institutes of Health Stroke Scale; TIMI, Thrombolysis in Myocardial Infarction; ASPECTS, Alberta Stroke Programme Early CT Score. Boldfaced numbers indicate which parameters from the univariate analysis were entered into the multiple logistic analysis.

hemorrhagic complications were compared by using the chi-square test for categoric variables and the Student *t* test for continuous normal variables. Univariate analyses were performed with the clinical and radiologic parameters of interest to determine their association with parenchymal hematoma and hemorrhagic infarction separately. A logistic regression model to assess independent predictors of these hemorrhage types was constructed, analyzing variables with a *P* value < .10 from the univariate analyses. Additionally, a univariate analysis was performed to determine if parenchymal hematoma or hemorrhagic infarction was associated with a higher rate of in-hospital death.

Results

We identified 185 patients with a mean age of 65 ± 13 years and a mean NIHSS of 17 ± 4. A total of 69 (37%) patients had an ICH, with 24 (13%) parenchymal hematomas and 45 (24%) hemorrhagic infarctions. Mean time to angiography in our cohort was 333 ± 276 minutes, and mean time from stroke onset to procedural completion was 405 ± 225 minutes.

In the univariate analysis (Table 1), hemorrhagic infarction was more likely when the patient had radiographic evidence of a large hemispheric infarction (ASPECTS ≤7) before endovascular therapy. TIMI 2 or greater reperfusion in a hemisphere with a pretreatment ASPECTS ≤7 also predicted a hemorrhagic infarction. Parenchymal hematomas were associated with tandem occlusions, hyperglycemia, and the combined use of IV tPA and IA thrombolytics; particularly when urokinase was used for IA therapy. Patient age, NIHSS, and time from stroke onset to angiography or procedure completion did not influence the development any ICH in any statistically significant way.

Table 2 presents the multivariate predictors for parenchymal hematomas and hemorrhagic infarctions. Patients developing a parenchymal hematoma are at a significantly higher risk of in-hospital death (odds ratio [OR] 10.8 [4.1–29.0], $P <$ .0001). Hemorrhagic infarctions did not significantly increase the risk of mortality.

Combining different treatment modalities did not translate into a statistically higher rate of hemorrhagic complications or mortality. For patients receiving 1, 2, or ≥3 treatment modalities, the percentage of patients developing a parenchymal hematoma was 13%, 14%, and 12% respectively, a statistically nonsignificant difference. The same was true for hem-

Table 2: Independent predictors of parenchymal hematoma after multimodal treatment of acute ischemic stroke

Variable	OR	95%CI	*P*
Parenchymal hematoma			
Hyperglycemia	2.8	1.05–7.7	.043
Tandem occlusion	4.6	1.35–6.5	.016
IV tPA + IA urokinase	5.1	1.07–25.0	.041
Hemorrhagic infarction			
Admission ASPECTS ≤7	1.9	1.3–2.7	.01

Note:—CI indicates confidence interval; OR, odds ratio.

orrhagic infarctions, which occurred in 20%, 28%, and 21% of patients treated with 1, 2, and ≥3 treatment modalities, respectively.

Discussion

Patients with acute ischemic stroke treated with multimodal endovascular therapy are at a higher risk for parenchymal hematomas when they are treated with IV tPA and IA urokinase, present with tandem occlusions, and have hyperglycemia. Hemorrhagic infarction is associated with ASPECTS ≤7 on admission CT.

Given our retrospective design, we considered mortality and radiographic patterns of hemorrhage as objective outcome measures because clinical deterioration from ICH or cerebral edema in large infarcts can be difficult to differentiate. Parenchymal hematomas have correlated with poor outcomes in prior thrombolysis trials, whereas hemorrhagic infarctions have not.[4,6] Our findings are consistent with this in that we found a statistically increased mortality in our cohort with parenchymal hematomas versus those with hemorrhagic infarctions.

In our protocol, patients were treated with various combinations of IV and IA agents. Our univariate findings suggested that IV tPA with any IA thrombolytic increased the risk of a parenchymal hematoma. This finding was largely driven by the increased number of parenchymal hematomas when IA urokinase was used and was confirmed in the multivariate analysis. The risk from IA urokinase may be due to a higher drug dosage (average IA urokinase dose of 870,000 ± 425,000 U). Higher doses of thrombolytic can increase fibrinogen degradation products, which has been correlated with higher risks for bleeding.[7] Fewer hemorrhagic complications in prior retrospective studies with low-dose IA urokinase does substantiate a more conservative protocol when implementing this drug.[8]

Significant hemorrhagic complications during endovascular treatment of tandem extracranial and intracranial occlusions have not been reported previously, largely because this subgroup of patients has not been included in trials of IA prourokinase, IA tPA, or mechanical embolectomy.[9-11] However, in our cohort, 21 patients with acute stroke with tandem occlusions were treated, with 6 patients sustaining a parenchymal hematoma. We were unable to determine a reperfusion strategy, which may have increased the risk of hemorrhagic complications in this population. In 15 of the 21 patients with tandem occlusions, occlusions were revascularized with an extracranial stent, of which 2 developed a parenchymal hematoma. Six patients with tandem occlusion were treated without any stent placement, and 4 of these patients developed a parenchymal hematoma. Furthermore, the risk for parenchymal hematomas in patients with tandem occlusion interventions did not increase with the number of treatment modalities implemented. Of the 21 patients with tandem occlusion in our cohort, 3 patients were treated with 1 modality, 9 with 2 modalities, and 12 with 3 or more modalities. We found no significant increase in either parenchymal hematomas or hemorrhagic infarctions with more aggressive treatment.

The reason for parenchymal hematoma formation in the setting of a tandem occlusion may be due to significant reductions in cerebral blood flow from loss of collateral blood supply rather than from a particular endovascular treatment. Patients with tandem occlusions have lower cerebral blood flow via single-photon emission tomography and xenon-enhanced CT and have a high risk for hemorrhagic complications with IA thrombolysis.[12,13] Potentially, hemorrhagic complications may occur more in the setting of tandem occlusion because of reperfusion into larger infarctions or larger territories of significantly hypoperfused brain.

Hemorrhagic infarction represents petechial hemorrhage without mass effect and clinical deterioration, and it correlates with the size of the infarct.[4,6] Our study is consistent with prior observations in that hemorrhagic infarction did not affect mortality and was linked to ASPECTS ≤7, an objective measure of infarct size. However, ASPECTS ≤7 has been associated with parenchymal hematomas in an analysis of patients receiving IV tPA,[14] which differs from our results. This discrepancy may have been due to less aggressive treatment in patients presenting with larger infarcts particularly with the use of thrombolytics.

The findings are limited by the retrospective design but do give a framework in determining which patients may be at a higher risk for hemorrhagic complications from aggressive endovascular stroke therapies. Our cohort consists of mixed intracranial occlusions with combinations of treatment modalities that have evolved during 6–7 years. Aside from combined IV tPA and IA urokinase, we were unable to identify any treatment regimen that increases the risk for ICH. Also our retrospective design was unable to study specific maneuvers, such as microcatheter injections during intervention, which increase the risk of hemorrhagic complications.[15] Also because treatment was individualized for each patient and vessel occlusion, we were unable to eliminate bias in which patients were treated aggressively with more modalities versus a conservative approach.

As reported in our earlier report, our multimodal cohort has achieved TIMI 2 or greater reperfusion in 63% of patients treated. This compares favorably with IA prourokinase, combined IV and IA tPA, and mechanical embolectomy trials.[1,9-11] Not surprisingly, aggressive multimodal therapy has also translated into a numerically higher rate of symptomatic hemorrhagic complications. However, comparisons between multimodal therapy and these other treatments are difficult if not done directly in a consecutive cohort of patients. Multimodal therapy may still have a role in patients who are ineligible for embolectomy devices due to proximal occlusions or in those who fail to recanalize with single-technique treatment. Combined with our prior report, our present findings may offer direction for endovascular management and postprocedure care.

In conclusion, patients undergoing multimodal reperfusion strategies are at an increased risk of hemorrhagic infarction if they have an ASPECTS ≤7 on initial head CT. The development of a parenchymal hematoma is associated with hyperglycemia, tandem occlusion, and combination therapy with IV tPA and IA urokinase.

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