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Role of heparin during endovascular therapy for acute ischemic stroke

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ABSTRACT

Objectives: Systemic heparinization has become the mainstay anticoagulant in neurointerventional procedures to prevent thromboembolic complications. Its benefit during endovascular therapy for acute stroke however has not been established. The purpose of this study is to retrospectively evaluate the impact of heparin during endovascular therapy for acute ischemic stroke (AIS).
Patients and methods: We performed a retrospective review of our interventional stroke database from February 2009 to September 2012 for patients with anterior circulation AIS with ICA-T or MCA M1 occlusions. 76 patients were categorized into 2 groups: intraprocedural vs. no intraprocedural heparin use. Outcomes measured included reperfusion (modified TICI scale), cerebral hemorrhages (ECASS criteria), and 90-day outcomes (modified Rankin scale).
Results: Baseline characteristics were similar between heparin and non-heparin treated patients, except for presence of CAD (6% vs. 30%, $p = 0.01$), Coumadin (0% vs. 11%, $p = 0.04$), and NIHSS (15.6 ± 5.0 vs. 18.1 ± 4.6, $p = 0.03$). There was a nonsignificantly higher reperfusion rate achieved in heparin-treated patients compared to non heparin-treated patients (63% vs. 50%, $p = 0.35$). Patients who received heparin had significantly lower rates of hemorrhage ($p = 0.02$). Multivariate logistic regression for good outcome revealed only age (OR 0.86; 95% CI 0.78–0.95; $p < 0.01$), ASPECTS (OR 2.14; 95% CI 1.01–4.50; $p = 0.04$), and successful reperfusion (OR 19.25; 95% CI 2.37-155.95; $p < 0.01$) independently associated with mRS 0–2 at 90 days.
Conclusion: The use of intraprocedural heparin in patients with AIS from MCA M1 or ICA-T occlusion was found safe. The impact of heparinization is unclear and warrants further evaluation.

1. Introduction

The widespread adoption of systemic heparinization in the neurointerventional setting has resulted in a dramatic drop in thromboembolic complications [1,2]. Mechanical thrombectomy for acute ischemic stroke has been demonstrated to benefit patients with large vessel occlusions [3–6]. However, the role of heparin in the acute intervention for ischemic stroke in endovascular therapy is unclear. The benefits of heparin use, particularly during intra-arterial therapy for acute ischemic stroke, are counterbalanced by the increased potential for intracranial hemorrhage and other major bleeding events [7,8]. Even before the advent of endovascular therapy, the data regarding the use of heparin and its dosing have been heterogeneous among studies and inconclusive [2,9–13]. Therefore, the administration of heparin during endovascular procedures is controversial. We conducted a retrospective study evaluating the safety and potential benefits of intraprocedural heparin during intra-arterial therapy (IAT) in patients suffering acute ischemic stroke (AIS).

2. Patient and methods

2.1. Design and participants

We performed a retrospective review of the interventional stroke database from February 2009 to September 2012. Consecutive patients with middle cerebral artery (MCA) first division (M1) or internal carotid artery (ICA)-T occlusions were identified. Patients who were categorized under MCA M2, isolated cervical occlusions, or vertebrobasilar occlusions were excluded in order to sample a homogeneous population. Patients with coagulopathies

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(defined as INR >2 or with a documented history of a coagulative disorder) were also excluded from analysis.

Patients were categorized into 2 mutually exclusive groups, defined as intraprocedural heparin use and no intraprocedural heparin use. We recorded demographics (age, gender, medical history), use of antithrombotics (coumadin, antiplatelets), vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease (CAD), smoking, history of TIA or stroke), and NIH Stroke Scale (NIHSS). Patients were typically selected for IAT based on MRI diffusion weighted imaging or CT perfusion (core <70 cc, mismatch >1.2, and absolute mismatch >15 cc). Patients with last-known-normal time beyond 8 h had to have a favorable imaging profile (small core and significant clinical-core or perfusion-core mismatch). Heparin was used as per individual operator's discretion, typically being administered as a bolus intra-procedurally and not systematically controlled by ACT (activated clotting time). Alberta Stroke Program Early CT Score (ASPECTS) was utilized to grade baseline NCCT (or Magnetic Resonance Imaging [MRI] Diffusion-weighted Imaging [DWI]) examination [14].

2.2. Outcomes

Reperfusion was evaluated with modified Treatment in Cerebral Infarction (mTICI) scale [15,16]. Cerebral hemorrhages were assessed by the European Cooperative Acute Stroke Study (ECASS) criteria, which classifies hemorrhagic infarcts (HI) and parenchymal hematomas (PH) [17]. Good outcome was defined by modified Rankin scale (mRS) 0–2 at 90 days [18].

2.3. Statistical analysis

Continuous variables are reported as mean ± SD. Categorical variables are reported as proportions. Between groups, comparisons for continuous/ordinal variables were made with Student *t*-test, Mann-Whitney U or ANOVA, as appropriate. Categorical variables were compared by Chi-square or Fisher exact test as appropriate. Normality was tested by Kolgoromov–Smirnov. Significance was set at $P < 0.05$. Multivariate logistic regression analysis for predictors of good outcome was performed for variables at the 0.1 level of significance on univariate analysis, using a variable selection method.

3. Results

Out of 140 consecutive stroke patients that were screened, 76 patients fit the inclusion criteria. Heparin was used in 32 of 76 patients (42%), and the mean intraprocedural dose of heparin was 2787 ± 1309 units (median 2475 [IQR 2000–4000]).

The baseline characteristics of both groups were similar (Table 1) with the exception of CAD (6% in heparin-treated vs. 30% non-heparin treated; p = 0.01), Coumadin use (0% vs. 11%; p = 0.04), and NIHSS (15.6 ± 5.0 vs. 18.1 ± 4.6; p = 0.03). The heparin group also more commonly had tandem lesions (38% vs. 9%, p < 0.01), leading to a higher frequency of carotid stents and glycoprotein IIb/IIIa inhibitors (GPI) (Table 2). Although reperfusion was achieved in 63% of heparin-treated patients vs. 50% in the non heparin-treated cohort, the finding was not significant (p = 0.35). In univariate analysis, the overall rates of hemorrhage were found to be lower in patients who received intraprocedural heparin compared to those who did not (p = 0.02). Parameters for multivariate logistic regression at the p = 0.1 level of significance on univariate analysis included hypertension, tandem occlusion, reperfusion, age, NIHSS, ASPECTS, and heparin use. Multivariate logistic regression for good outcome revealed age (OR 0.86; 95% CI 0.78–0.95; p < 0.01), ASPECTS (OR 2.14; 95% CI 1.01–4.50; p = 0.045), and successful reperfusion (OR 19.25; 95% CI 2.37–155.95; p < 0.01) are independently associated with mRS 0–2 at 90 days. Sensitivity analysis was performed forcing heparin use into the multivariate model. Heparin use was not found to be independently associated with good outcomes (OR 1.14; 95% CI 0.27–4.69; p = 0.85).

Table 1
Baseline and demographic characteristics.

Demographics	Heparin n = 32	No Heparin n = 44	p-Value
Age	63.9 ± 15.9	67.8 ± 16.3	0.29
Gender (male)	17 (53%)	26 (59%)	0.64
Atrial fibrillation	9 (28%)	17 (39%)	0.46
Hypertension	23 (72%)	38 (86%)	0.14
Diabetes Mellitus	6 (19%)	13 (30%)	0.42
CAD	2 (6%)	13 (30%)	0.01
Prior TIA/stroke	5 (16%)	12 (27%)	0.22
Hyperlipidemia	10 (31%)	14 (32%)	1.00
Smoking	12 (38%)	7 (16%)	1.00
Coumadin	0 (0%)	5 (11%)	0.04
Antiplatelets	6 (19%)	9 (20%)	0.89
NIHSS	15.6 ± 5.0	18.1 ± 4.6	0.03
Last normal to ET (hs)	6.5 ± 2.6	6.3 ± 2.9	0.92
ASPECTS	7.5 ± 1.5	7.3 ± 1.6	0.63
CTP or DWI (selection)	31 (97%)	38 (86%)	0.12

CAD = coronary artery disease; TIA = transient ischemia attack; ET = endovascular therapy; ASPECTS = Alberta Stroke Program Early CT Score; CTP = Computed Tomographic Perfusion; DWI = Diffusion-Weighted Imaging.

Table 2
Treatment and Outcome.

	Heparin n = 32	No Heparin n = 44	p-Value
TREATMENT			
Intravenous Thrombolysis	20 (62%)	29 (66%)	0.81
GPIIb/IIIa	10 (31%)	0 (0%)	<0.01
General Anesthesia	2 (6%)	0 (0%)	0.08
MCA M1	21 (66%)	33 (75%)	0.43
ICA-T	11 (34%)	11 (25%)	0.44
Tandem Lesion	12 (38%)	4 (9%)	<0.01
Carotid Stent	10 (31%)	3 (7%)	<0.01
Intracranial Stent	1 (3%)	2 (5%)	0.75
Device			
Old Generation	28 (88%)	35 (80%)	0.36
Stentretriever	6 (19%)	6 (14%)	0.75
IA t-PA	17 (53%)	28 (64%)	0.33
Procedure Length (hrs)	1.6 ± 0.4	1.7 ± 0.7	0.09
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OUTCOMES			
Reperfusion			
TICI 2b-3	20 (63%)	22 (50%)	0.35
TICI3	4 (13%)	6 (14%)	0.85
Vessel Rupture	2 (6%)	4 (9%)	0.70
Hemorrhage (ECASS)			0.02
HI1	0 (0%)	7 (16%)	–
HI2	5 (16%)	4 (9%)	–
PH1	2 (6%)	9 (20%)	–
PH2	3 (9%)	3 (7%)	–
mRS ≤ 2 at 90days	12 (38%)	9 (20%)	0.12

GPI = glycoprotein IIb/IIIa inhibitor; MCA M1 = middle cerebral artery, division 1; ICA-T = internal carotid artery-T; IA t-PA = intra-arterial tissue plasminogen activator; TICI = Thrombolysis in Cerebral Infarction; ECASS = European Cooperative Acute Stroke Study; HI = hemorrhagic infarction; PH = parenchymal hematoma; mRS = modified Rankin scale HI1 = hemorrhagic infarction type 1 (small hyperdense petechiae) HI2 = hemorrhagic infarction type 2 (more confluent hyperdensity throughout infarct zone; without mass effect) PH1 = parenchymal hematoma type 1 (homogeneous hyperdensity occupying <30% of infarct zone; some mass effect) PH2 = parenchymal hematoma type 2 (homogeneous hyperdensity occupying >30% of infarct zone; significant mass effect)[23].