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INTRAVENOUS THROMBOLYSIS FOR PATIENTS WITH IN-HOSPITAL STROKE ONSET: PROPENSITY-MATCHED ANALYSIS FROM THE SITS-EAST REGISTRY

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Keywords: intravenous thrombolysis; acute ischemic stroke; in-hospital stroke; onset-to-treatment time; door-to-needle time; stroke awareness

ABSTRACT

Introduction: Recent cross-sectional study data suggest that intravenous thrombolysis (IVT) in patients with in-hospital (IHS) acute ischemic stroke (AIS) onset is associated with unfavourable functional outcomes at hospital discharge and in-hospital mortality compared to patients with out-of-hospital stroke onset (OHS) treated with IVT. We sought to compare outcomes between IVT treated IHS and OHS patients by analysing propensity score matched (PSM) data from the SITS-EAST registry.

Methods: We compared the following outcomes for all PSM patients: 1.symptomatic intracranial hemorrhage (sICH) defined with the SITS-MOST criteria, 2.favourable functional outcome

(FFO) defined as a modified Rankin Scale (mRS) score of 0-1 at three months, 3.Functional independence (FI) defined as a mRS score of 0-2 at three months, 4.3-month mortality.

Results: Out of total 19,077 IVT-treated AIS patients, 196 IHS patients were matched to 5124 OHS patients, with no differences in all baseline characteristics (p>0.1). IHS had longer door-to-needle [90 min (60-140) vs. 65 (47-95), p<0.001] and door-to-imaging times [40 min (20-90) vs 24 (15-35), p<0.001] compared to OHS. No differences were detected in the rates of sICH (1.6% vs 1.9%, p=0.756), FFO (46.4% vs 42.3%, p=0.257), FI (60.7% vs. 60.0%,p=0.447) and mortality (14.3% vs 15.1%,p=0.764). The distribution of 3-month mRS-scores was similar in the two groups (p=0.273).

Conclusions: Our findings underline the safety and efficacy of IVT for IHS. They also underscore the potential of reducing in-hospital delays for timely tPA delivery in patients with IHS.

Introduction

In-hospital stroke (IHS) is defined as an acute ischemic stroke (AIS) event occurring during hospitalization for another diagnosis or procedure [1,2]. IHS occur frequently and represent 2%-17% of all AIS [1,2]. IHS patients are reported to have higher vascular comorbidities, increased stroke severity and worse functional outcomes compared to patients with out-of-hospital stroke (OHS) onset [3,4]. Moreover, recent cross-sectional data suggest that intravenous thrombolysis (IVT) in IHS patients is associated with unfavourable functional outcomes at hospital discharge and higher in-hospital mortality compared to OHS patients [5,6].

We sought to compare outcomes between IHS and OHS AIS patients treated with IVT by analyzing unmatched and propensity score matched data from the Safe Implementation of Treatments in Stroke-East (SITS-EAST) registry.

Methods

We analyzed prospectively collected data from the SITS-EAST registry on consecutive AIS patients treated with IVT during a twelve-year period (October 2003- December 2015). SITS registry is an observational multinational cohort that has been previously described in detail [7]. SITS-EAST registry represents a subset of SITS-ISTR with its own steering committee and joint data ownership. The participating countries (Bulgaria, Croatia, Czech Republic, Estonia, Greece, Hungary, Lithuania, Poland, Russia, Slovakia, Slovenia and Turkey) in the SITS-EAST registry, represent approximately 30% of the population of SITS registry [8,9]. SITS-EAST Register data were collected on patients treated with IVT using the general SITS-ISTR register platform [8]. **Ethics approval for SITS-EAST and SITS-EAST registries was obtained in countries that required this, while other countries approved the register for conduct as an anonymized audit. The SITS-EAST is embedded within the SITS-ISTR, which was originally approved by the Ethics Committee of Karolinska Institutet, Stockholm [7]. The present study is a retrospective analysis from patients enrolled in the SITS-EAST registry, and therefore informed consents are not applicable.**

We included all AIS patients treated with intravenous tissue plasminogen activator (tPA) if they: 1. had available data on the place of stroke onset, 2. had no significant disability prior to stroke onset (modified Rankin Scale score, mRS ≤1) and 3. had available three-month functional outcome assessment using the mRS-score. Included patients were dichotomized according to place of AIS onset as IHS, if stroke onset occurred during hospitalization for any reason or OHS if the patient at stroke onset was not hospitalized. After dichotomization IHS patients were matched to OHS patients using a structured, iterative propensity score model with the primary objective to maximize the balance in the distribution of possible confounders between the two groups [9].

The outcome events of interest included: 1. symptomatic intracerebral hemorrhage (sICH) according to the SITS-MOST definition (local or remote parenchymatous hemorrhage type 2 combined with NIHSS-score increase ≥4 points or leading to death <22–36 hours) [7], 2. three-month favorable functional outcome (FFO; defined as mRS-score of 0 or 1), 3. Three-month functional independence (FI; defined as mRS-score of 0 **or 2**), 4. any cause mortality and 5. the distribution of the 3-month mRS scores between IHS and OHS groups at 3 months [8,9].

Statistical analyses

We used a propensity score matching algorithm, including all baseline characteristics except for those reporting time metrics, to calculate the propensity score of the variable IHS for each subject. A nearest neighbor matching algorithm was then used to match IHS patients to all eligible OHS patients within 0.2*SD of the logit of the propensity score distribution. To determine whether the propensity score approach achieved balance in all potential confounders, we compared all baseline characteristics of IHS patients to their propensity matched OHS patients.

Statistical comparisons were performed between matched and unmatched groups using the χ2-test (or the Fisher's exact test) and the unpaired t-test (or Mann-Whitney U-test), where appropriate. We also compared baseline characteristics between IHS and OHS patients to detect potential imbalances between the two populations, while the distribution on the mRS-scores at three months between IHS and OHS patients was compared with the Cochran Mantel-Haenszel test.

All statistical analyses were performed with the use of the Stata Statistical Software Release 13 for Windows (College Station, TX, StataCorp LP).

Results

A total of 19,077 AIS patients **(2% with IHS)** were treated with IVT in SITS-EAST registry from October 2003 to December 2015. **Compared to OHS patients, IHS patients had higher rates of hypertension (p=0.023), congestive heart failure (p=0.017), antiplatelet pretreatment (p<0.001), antihypertensive pretreatment (p=0.001) and statin pretreatment (p<0.001). On admission IHS patients had higher BMI (p=0.003), SBP (p=0.015) and DBP levels (p=0.008), while they were more likely to receive stroke unit care (p<0.001) and had significantly longer door-to-imaging (DTI; p<0.001) and door-to-needle (DTN; p<0.001) times. No significant differences were found for all outcomes of interest, except for a higher rate for all-cause mortality at 3 months in**

patients with IHS compared to OHS patients (20.1% vs. 13.8%; p=0.004; Supplemental Table I & Supplemental Figure II).

After excluding patients with disability prior to index event (n=1,907) or with missing data on the baseline functional status (n=1,579) or the 3-month functional outcome (n=5,152) we identified 196 IHS and 10243 OHS patients fulfilling the inclusion criteria (Supplemental Figure I). IHS patients had higher prevalence of congestive heart failure (p=0.023) and higher rates of pretreatment with antiplatelets (p=0.005), antihypertensives (p=0.002) and statins (p<0.001) at baseline. IHS patients also had higher rates of stroke unit care (p<0.001). IHS patients had longer **DTI** (p<0.001) and **DTN** times (p<0.001) compared to OHS patients**, while** no differences were detected for all outcomes of interest between groups **(Supplemental Table II & Supplemental Figure III)**.

Propensity score matching resulted in two groups of 196 IHS patients and 5124 OHS patients that were balanced (p>0.1) for all potential confounding variables (Table). IHS patients had longer DTI [40 **min** (20-90) vs 24 **min** (15-35), p<0.001] and DTN [126 **min** (80-150) vs. 65 **min** (47-95), p<0.001] compared to OHS patients. No significant differences were found between the two groups on the rates of sICH (1.6% vs 1.9%, p=0.756), FFO (46.4% vs 42.3%, p=0.257), FI (60.7% vs. 60.0%, p=0.447) and mortality (14.3% vs 15.1%, p=0.764). The distribution of three-month mRS scores were similar between groups [2 (0-4) vs. 2 (1-4), p=0.273; Figure].

Discussion

Our study showed that IVT treatment in IHS patients has comparable safety and efficacy outcomes compared to IVT administration in OHS patients, contradicting thus the results of previously published studies [6,7] and suggesting that eligible hospitalized patients with AIS should not be precluded from prompt IVT administration. In addition, we detected significant in-hospital delays on IVT administration for IHS patients, with longer DNT and DTI compared to OHS patients.

Our results are in accordance with a prospective cohort study from the Ontario Stroke Registry database, reporting that IHS patients not only have lower IVT administration rates, but also have significantly longer times from symptom recognition to neuroimaging and to subsequent IVT administration, compared to OHS patients [10]. Likewise, a cohort analysis from the Get With the Guidelines Stroke (GWTG-Stroke) registry suggests that IHS are under-recognized and under-reported. More specifically, evaluation times for IHS patients remain twice longer than the recommended 25-minute benchmark, while IHS patients are less likely to adhere to process-based quality measures compared to OHS patients [3,11]. The paradoxical effect between early stroke recognition and delayed treatment administration, due to the perception that there is sufficient time before the end of the thrombolytic window, is a known phenomenon in acute stroke care [12]. Additionally, according to the results of a stroke awareness questionnaire survey, even though physicians and nurses have adequate knowledge of stroke signs and symptoms, there is low awareness regarding swift tPA (tissue plasminogen activator) administration for stroke occurring during hospitalization for another medical condition, with only 52% of the staff on general wards reporting awareness of an in-hospital stroke protocol [13]. **Given that there is a clear benefit of endovascular reperfusion therapies (ERTs) in AIS patients with emergent large vessel occlusions (ELVOs), either with or without pretreatment with systemic thrombolysis [14], there is also an urge to increase in-hospital awareness regarding ERTs as highly relevant treatment options in the setting of ELVO and especially for IHS patients that due to prevalent comorbidities might be ineligible for IVT. Notably, a recent French study reported markedly high Mechanical Thrombectomy treatment rates (45%) in a series of 64 patients with IHS [15].**

Our experience contradicts the previous reports from National Inpatient Sample (NIS) [5,6] that represents the largest all-payer inpatient care database in the United States, containing data on more than seven million hospital stays. These discrepant results may be attributed to differences in design and data collection between the two registries. NIS does not document stroke severity and functional outcome using NIHSS and mRS scores respectively. Furthermore, patients are not followed up after discharge and three-month outcomes are unavailable. Also, NIS database lacks information regarding symptom onset. Therefore, the day of thrombolysis in relation to the day of admission are used to define IHS leading to potential misclassifications of IHS and OHS. Last and most important, outcomes reported in NIS were not adjusted for baseline stroke severity and secondary prevention therapies.

The results of the present manuscript derive from an international, multi-center registry with standardized protocol and from groups that are adequately balanced for numerous potential confounders after propensity matching. On the other hand, certain methodological shortcomings should be acknowledged. First, SITS-EAST registry is an observational multinational cohort with self-reported safety and effectiveness outcomes and no central adjudication for imaging or clinical outcomes. However, SITS-EAST registry reflects 'real-life' clinical experience from several countries and thus we consider our results to be independent from particular healthcare system features and thus directly generalizable. Second, it should be noted that neuroimaging parameters that could represent significant confounders (e.g. the presence of hyperdense cerebral artery sign or early ischemic changes on baseline CT scan) were unavailable. Third, data on neither the reason nor the department of hospitalization is collected in SITS registry and this crucial information for patients with IHS treated with tPA are lacking from the present report. Results from another cohort study suggest that more than 60% of IHS occur during hospitalization in the departments of cardiology and cardiovascular surgery, and are associated with cardiovascular surgery or other procedures [16]. Finally, the present manuscript is a retrospective analysis of prospectively collected data and thus potential selection bias cannot be excluded. For instance, the two groups could not be matched for time metrics (DTN & DTI time) in our propensity matched analyses.

In conclusion, our findings suggest that IVT treatment is both safe and effective in eligible IHS patients. They also highlight the presence of significant in-hospital delays for tPA delivery in this patient subgroup. Increased awareness among physicians and nurses and establishment of robust in-hospital stroke protocols and pathways are the cornerstones for prompt IVT administration in AIS occurring during hospitalization for another medical condition.

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Table. Baseline characteristics, time metrics and outcomes of patients with IHS and OHS (matched analysis).

Variable	IHS (n=196)	OHS (n=5124)	p-value
Baseline Characteristics			
Age (mean±SD), years	67.9±11.5	68.4±12.0	0.557
Males (%)	53.6%	55.8%	0.538
Admission NIHSS (median, IQR)	9 (6-15)	10 (7-16)	0.230
BMI (median, IQR)	27 (25-32)	27 (25-31)	0.167
Hypertension (%)	78.9%	78.0%	0.781
Diabetes (%)	20.1%	22.6%	0.409
Hyperlipidemia (%)	39.5%	37.2%	0.522
Current smoking (%)	21.6%	19.4%	0.455
Previous stroke (%)	3.1%	2.0%	0.299
Atrial fibrillation (%)	22.4%	23.9%	0.641
Congestive heart failure (%)	16.1%	18.8%	0.347
Antiplatelet pretreatment (%)	40.1%	35.0%	0.150
Antidiabetic pretreatment (%)	11.1%	14.4%	0.205
Antihypertensive pretreatment (%)	70.3%	64.5%	0.100
Statin pretreatment (%)	35.6%	31.0%	0.184
Admission SBP baseline (mean±SD), mmHg	152.8±21.6	155.4±22.3	0.109
Admission DBP (mean±SD), mmHg	83.8±12.6	85.4±13.6	0.117

Admission serum glucose (median, IQR), mg/dL	121 (107-142)	122 (106-149)	0.365
Cholesterol baseline (mean±SD)	178.5±44.3	191.8±50.3	0.116
Stroke Unit Care (%)	70.4%	65.2%	0.130
Endovascular reperfusion therapies (%)	**3.5%**	**3.1%**	**0.736**
Working hours (%)	34.7%	38.2%	0.314
Times from stroke onset to treatment			
Onset-to-door time (min, median, IQR)	-	76 (55-111)	-
Door-to-needle time (min, median, IQR)	90 (60-140)	65 (47-95)	<0.001
Door-to-imaging time (min, median, IQR)	40 (20-90)	24 (15-35)	<0.001
Outcomes			
sICH (%) – SITS MOST	1.6%	1.9%	0.756
mRS at 3-months (median, IQR)	2 (0-4)	2 (1-4)	0.273*
FFO (mRS:0-1) at 3-months (%)	46.4%	42.3%	0.257
FI (mRS:0-2) at 3-months (%)	60.7%	60.0%	0.447
Mortality at 3-months (%)	14.3%	15.1%	0.764

*by Cochran Mantel-Haenszel test

IHS: in-hospital stroke onset, OHS: out-of-hospital stroke onset, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure, IQR: interquartile range, LDL: low density lipoprotein, HDL: high density lipoprotein, TG: triglycerides, sICH: symptomatic intracerebral hemorrhage, mRS: modified Rankin Scale, FFO: favorable functional outcome

Figure. Distribution of thee-month modified Rankin Scale scores in propensity score matched groups of patients with in-hospital and out-of-hospital stroke onset.