Intravenous Thrombolysis For Ischemic Stroke Patients on Dual Antiplatelets

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Abstract

Objective: We assessed the outcomes of intravenous thrombolysis (IVT) in acute ischemic stroke (AIS) patients on dual antiplatelet therapy prior to stroke onset.

Methods: We analyzed prospectively collected data from the SITS International Stroke Thrombolysis Register (SITS-ISTR) on consecutive IVT-treated AIS patients during a seven-year period (2010-2017). In propensity-score matched groups of patients with dual antiplatelet pretreatment and no antiplatelet pretreatment we compared: 1) SICH, according to SITS-MOST, ECASS II and NINDS definitions, 2) 3-month mortality, 3) 3-month favorable functional outcome (FFO; mRS-scores:0-1), 4) 3-month functional independence (FI; mRS-scores:0-2) and 5) distribution of the 3-month mRS-scores. Dual antiplatelet pretreatment was defined as all possible combinations among aspirin, clopidogrel, dipyridamole or any other antiplatelet.

Results: Propensity-score matching resulted in two groups of 1043 patients each, balanced for all baseline characteristics. In the propensity-score matched analysis the two groups had comparable ($p>0.017$ using Bonferroni correction for multiple comparisons) SICH rates according to SITS-MOST (2.9% vs. 1.5%; 95%CI:-0.03,-0.01), ECASS II (5.2% vs. 4.4%; 95%CI:-0.03,0.01) and NINDS (7.7% vs. 6.6%; 95%CI:-0.03,0.01) definitions. No differences in the 3-month mortality (17.9% vs. 16.6%; 95%CI:-0.05,0.02), FFO (45.6% vs. 46.0%; 95%CI:-0.04,0.05), FI rates (59.2% vs. 60.7%; 95%CI:-0.03,0.06) or the distribution in 3-month mRS-scores [2 (1-4) vs. 2 (0-4); 95%CI:-0.29,0.09] were documented between the two groups.

Interpretation: Given that patients on dual antiplatelet pretreatment have similar SICH, 3-month mortality rates and functional outcomes compared to patients with no antiplatelet pretreatment, dual antiplatelet pretreatment history should not be used as a reason to withhold IVT in otherwise eligible AIS patients.

TEXT

Introduction

Even though, antiplatelet pretreatment is not considered a contraindication for intravenous thrombolysis (IVT) with tissue plasminogen activator (tPA) in eligible acute ischemic stroke (AIS) patients,[1] there are contradictory data regarding the association of antiplatelet pretreatment with safety and efficacy outcomes of AIS patients treated with systemic thrombolysis.[2]

A systematic review and meta-analysis of 19 observational studies on the safety and efficacy of IVT for AIS in patients receiving antiplatelet therapy prior to stroke onset reported higher odds of post-thrombolytic symptomatic intracerebral haemorrhage (SICH) in AIS patients receiving dual antiplatelet pretreatment, with combination of acetylsalicylic acid (ASA) and clopidogrel, when compared to patients without history of dual antiplatelet pretreatment intake (OR=1.88, 95% CI 1.18–3.00).[3] However, all included studies in the aforementioned meta-analysis were retrospective with patients taking long-term antiplatelet medications being significantly older and with more comorbidities.[3] Moreover, a recent pre-specified subgroup analysis of Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) has reported that antiplatelet adversely affects safety and efficacy outcomes of IVT for AIS.[4] Finally, a post-hoc analysis of the Virtual International Stroke Trials archives reported discouraging results with IVT compared to placebo in a small subgroup of AIS patients with dual antiplatelet pretreatment history.[5] Notably, the rate of SICH per ECASS II definition was the highest (8.5%) in this specific subgroup in comparison to all other AIS subgroups treated with alteplase despite contraindications and warnings.[5]

In view of the former considerations we sought to assess the impact of dual antiplatelet pretreatment on the safety and efficacy outcomes of AIS patients treated with IVT by analysing propensity score matched data from the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register (SITS-ISTR).

Methods

We analyzed prospectively collected data from the SITS-ISTR on consecutive AIS patients treated with IVT from January 1, 2010 to June 15, 2017. SITS-ISTR data were collected from participating centers treating AIS patients with IVT using the general register platform, as previously described.[6,7]

We included all AIS patients treated with tPA if they had: 1. available data regarding the history of antiplatelet intake prior to stroke onset 2. no significant disability prior to stroke onset (modified Rankin Scale score, mRS ≤1) 3. available 3-month functional outcome assessment using the mRS-score, 4. available follow-up neuroimaging with either computed tomography or magnetic resonance imaging after IVT administration. Patients with history of single antiplatelet intake were excluded from the present analysis since our aim was to compare safety and efficacy outcomes of IVT in AIS patients pretreated with dual antiplatelet in comparison to AIS without antiplatelet pretreatment. Dual antiplatelet pretreated patients had received at least any of the combinations of ASA, clopidogrel, dipyridamole or other antiplatelet.

After dichotomization according to the history of dual antiplatelet intake prior to stroke onset, patients in the treatment group (patients with history of dual antiplatelet pretreatment) were matched to control group patients without any prior antiplatelet treatment at stroke onset. For matching we used a structured, iterative propensity score model with inclusion of all baseline characteristics, except for the

history of dual antiplatelet pretreatment, and the primary objective to maximize the balance in the distribution of possible confounders between the two aforementioned groups.[8,9] The corresponding propensity score of the treatment variable (history of dual antiplatelet intake) was calculated for each subject and a nearest neighbor matching algorithm with a 1:1 allocation was subsequently implemented to match eligible patients in the treatment group (patients with history of dual antiplatelet preatreatment) to patients in the control group (patients without history of antiplatelet pretreatment). To determine whether the propensity score matching approach achieved balance in all potential confounders, we compared all baseline characteristics of patients in the treatment group to their control patients, before and after propensity score matching.[10]

In the propensity score matched groups we assessed the following safety outcome events of interest: 1. SICH rates according to the SITS-MOST definition [local or remote parenchymatous hemorrhage type 2 within 22–36 hours imaging scans combined with ≥4 points worsening on the National Institutes of Health Stroke Scale (NIHSS) score or leading to death within 24 hours],[11] ECASS II definition (any intracranial bleed with ≥4 points worsening on the NIHSS score)[12] and NINDS definition (any intracranial bleed with ≥1 point worsening on the NIHSS score),[13] 2. symptomatic remote parenchymal hemorrhage, defined as solitary or multiple hemorrhages appearing in brain regions without visible ischemic damage, remote from the area of ischemia causing the initial stroke symptoms, accompanied with early neurological deterioration as previously described.[14] 3. asymptomatic intracranial hemorrhage (aICH) defined as evidence of intracranial bleeding on brain CT without neurological worsening using NINDS definition (≥1 point increase in the NIHSS-score) 4. mortality rates at 3 months.

We also evaluated the following efficacy outcome events of interest: 1. favorable functional outcome (FFO) at 3 months rates (defined as mRS-score of 0 or 1),[10] 2. functional independence (FI) at 3 months rates (defined as mRS-score 0-2)[10] and 3. functional improvement at the months quantified by the distribution of 3-month mRS-scores between the two groups.[15] Finally, we performed subgroup analyses for all safety and efficacy outcomes between patients receiving dual antiplatelet pretreatment with the combination of ASA and clopidogrel and patients receiving dual antiplatelet pretreatment with other antiplatelet combinations or patients receiving dual antiplatelet pretreatment with the combination of ASA and dipyridamole.

Statistical analysis

Statistical comparisons between the aforementioned propensity score matched groups were performed s using the $\chi 2$-test (or the Fisher's exact test) and the unpaired t-test (or Mann-Whitney U-test), where appropriate, while the distribution of the mRS-scores at three months in propensity score matched dual antiplatelet pretreatment and no antiplatelet pretreatment groups was compared using the Cochran-Mantel-Haenszel test.[14] The differences in all clinical outcomes of interest between the two groups were tested under statistical significance hypotheses using an alpha value of 0.05. To avoid false positive findings due to multiple testing in the primary safety outcome of SICH, being assessed with three different definitions, we implemented a more conservative significance threshold of 0.05/3=0.017, using the Bonferroni correction for multiple testing. Statistical analyses were performed with RStudio: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria), with the use of the "MatchIt" package

(Matching software for causal inference) for matching patients across the two groups,[16] and the Stata Statistical Software Release 13 (College Station, TX, StataCorp LP).

Results

Out of a total 95,923 IVT-treated AIS patients we identified 28,112 eligible patients (Figure 1). The two groups had only comparable baseline stroke severity (Table 1), while patients with dual antiplatelet pretreatment (n=1,355) were older (95%CI: -6.00, -4.80; p<0.001) and had higher prevalence of all vascular risk factors (p<0.001), except for the history of current smoking, compared to patients without antiplatelet pretreatment history (n=26,757). Dual antiplatelet pretreated patients had also higher rates of statin pretreatment (95%CI: -0.59, -0.54; p<0.001), lower systolic (95%CI: 0.73, 3.27; p=0.002) and diastolic blood pressure (95%CI: 2.63, 4.16; p<0.001) on admission, higher baseline glucose levels (95%CI: -6.28, -0.52; p=0.023), shorter onset-to-treatment times (95%CI: 1.81, 7.99; p<0.001) and less endovascular reperfusion therapies (95%CI: 0.01, 0.03; p=0.004) following alteplase infusion compared to patients without antiplatelet pretreatment history (Table 1).

Propensity score matching resulted in two groups of 1043 patients each (Figure 2), balanced for all baseline characteristics (Table 2). Dual antiplatelet pretreated patients had received combinations of ASA with clopidogrel (n=617) or dipyridamole (n=324) or other antiplatelet (n=87), combinations of clopidogrel with dipyridamole (n=3) or other antiplatelet (n=11) and combination of dipyridamole with other antiplatelet (n=1). In propensity score matched analysis patients with dual antiplatelet pretreatment history had comparable SICH rates, according to the SITS-MOST (2.9% vs. 1.5%; 95%CI: -0.03, -0.01; p=0.037 - considered non-significant

taking into account the threshold of 0.017 due to Bonferroni adjustment), ECASS II; p=0.354) and NINDS definitions (7.7% vs. 6.6%; 95%CI: -0.03, 0.01; p=0.318), to patients with no antiplatelet pretreatment history. The two groups did not differ in terms of symptomatic remote parenchymal hemorrhage (1.1% vs. 0.6%; 95%CI: -0.01, 0.01; p=0.155) and aICH (6.9% vs. 6.2%; 95%CI: -0.03, 0.01; p=0.526). Additionally, no differences in the 3-month mortality (17.9% vs. 16.6%; 95%CI: -0.05, 0.02; p=0.417), FFO (45.6% vs. 46.0%; 95%CI: -0.04, 0.05; p=0.860) and FI rates (59.2% vs. 60.7%; 95%CI: -0.03, 0.06; p=0.503) were detected between the two groups (Table 3), while the distribution of the 3-month mRS-scores was comparable [2 (1-4) vs. 2 (0-4); 95%CI: -0.29, 0.09; p=0.683; Figure 3].

Subgroup analyses revealed no disparities in the outcomes of interest between patients receiving pretreatment with the combination of ASA and clopidogrel (n=617) and patients with history of pretreatment with other antiplatelet combinations (n=426; Figure 4A) or combination of ASA and dipyridamole (n=324; Figure 4B).

Discussion

Our study showed that dual antiplatelet pretreatment was not associated with higher risk of SICH, remote SICH and asymptomatic ICH in AIS patients treated with IVT. Likewise, 3-month mortality and functional outcomes were not affected by dual antiplatelet intake prior to stroke onset. Our findings are in accordance and provide further support to the recently published guidelines from the American Heart Association/ American Stroke Association recommending that the benefit of IVT treatment for eligible AIS patients with history of dual antiplatelet intake outweighs the probability of increased SICH risk (Class I; Level of Evidence B).[17]

An increased risk of SICH per SITS-MOST in patients with dual antiplatelet pretreatment history receiving IVT has previously been reported in a SITS-ISTR analysis of 31,627 patients during an eight year period (2002-2010), highlighting dual antiplatelet pretreatment history as the strongest predictor of SICH (according to the SITS-MOST definition).[18] Likewise, in another analysis from the SITS-ISTR registry that evaluated 11,865 AIS patients receiving IVT treatment during a 5-year period (2002-2007) the combination of ASA and clopidogrel was independently associated with an increased risk for SICH per NINDS and ECASS II definitions. However, no significant differences were found on the functional recovery and 3-months mortality rates between patients with dual antiplatelet pretreament history and patients without antiplatelet pretreatment history.[19]

Compared to the aforementioned reports from the SITS-ISTR, including only patients between 18 and 80 years of age receiving IVT treatment within the 3-hour time window,[18,19] the current study provides additional data on the impact of dual antiplatelet pretreatment in post-IVT outcomes by incorporating data from AIS patients over 80 years old (19.1%), receiving IVT treatment beyond 3 hours (28.9%) or treated with concomitant endovascular reperfusion therapies after IVT administration (3.3%). Finally, it should be noted that in the present analysis we included a significantly higher number of dual antiplatelet pretreated patients compared to both the VISTA archive (n=71)[5] and the previous SITS-ISTR report (n=326).[19] We have also implemented a propensity score matching algorithm that balanced the two groups for all available baseline characteristics, since patients with dual antiplatelet pretreatment history have a higher prevalence of vascular comorbidities (coronary artery disease, peripheral arterial disease, prior ischemic stroke) compared to patients without antiplatelet pretreatment.

Our findings further challenge the recent pre-specified subgroup analysis of Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) suggesting that the history of antiplatelet pretreatment adversely affects safety and efficacy outcomes of IVT for AIS,[20] highlighting further the confounding role of increasing age and co-existing vascular comorbidities that are more prevalent in AIS patients pretreated with antiplatelets.[20] These findings are also in line with a recent meta-analysis highlighting that pretreatment with single or dual antiplatelet therapies was not associated with a higher risk of SICH and worse 3-month functional outcomes in AIS treated with intravenous alteplase after adjustment for potential confounders.[21]

Several limitations of the present report need to be acknowledged. First, this is an observational study design with retrospective analysis of prospectively collected data and therefore selection bias cannot be excluded. Second, despite the fact that all our analyses were performed in propensity score matched groups that were balanced for all available baseline characteristics, the presence of potential imbalances in unmeasured confounders (e.g. neuroimaging parameters, cerebral microbleed presence prior to IVT administration) cannot be excluded. Third, SITS-ISTR is an observational multinational registry with self-reported safety and effectiveness outcomes and no central adjudication of imaging or clinical outcomes. Even though significant heterogeneity in acute stroke care may be present across different national systems and also within institutions from the same country, the SITS-ISTR 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. Fourth, missing data in SITS-ISTR may introduce another source of bias.[6] The differences in the SICH rates of AIS patients with and without dual

antiplatelet pretreatment history that were documented both in the current and previous SITS-ISTR analysis[19] reached different levels of statistical significance according to the varying SICH definitions. This disparity may be attributed not only to the inherent heterogeneity of available SICH definitions, but also to missing data for SICH-ECASS II (1.4% of study population) and SICH-NINDS (1.1% of study population) outcomes in the current analysis. Taking also into account the vast differences across the two groups (Table 1) and the large number of treated individuals, we performed a 1:1 nearest neighbor matching, considering that an increased matching ratio will not result in significant improvement of the overall precision and may increase the risk of bias due to the lower quality of the second matches compared to the first ones.[22] Finally, it should be noted that no information on the clinical indication or the duration of dual antiplatelet pretreatment were available and thus additional analyses evaluating the effect of clinical indication and dual antiplatelet treatment duration on safety and efficacy outcomes were not feasible.

In conclusion, our study provides reassurance to stroke clinicians that patients on dual antiplatelet therapies prior to index stroke onset have comparable 3-month survival and functional outcomes compared to patients without history of any antiplatelet intake. History of dual antiplatelet pretreatment should not be used as a sole reason to withhold IVT in otherwise eligible AIS patients.

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Author contributions

GT, AHK and NA contributed to the conception and design of the study; GT, AHK, DM and NA contributed to the acquisition and analysis of data; GT, AHK, DM, ZG, MK, MJM, DS and NA contributed to drafting the text; GT and AHK contributed to preparing the figures.

Potential Conflicts of Interest

All authors report no disclosures relevant to the current manuscript.

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Figure legends

Figure 1. Flowchart presenting the selection of eligible and propensity score matched patients.

Figure 2. Distribution of propensity scores between acute ischemic stroke patients with and without history of dual antiplatelet therapy before and after propensity score matching.

Figure 3. Distribution of the modified Rankin Scale scores at three months between acute ischemic stroke patients with and without history of dual antiplatelet therapy prior to the administration of intravenous thrombolysis.

Figure 4. Subgroup analyses on the safety and efficacy outcomes between patients receiving pretreatment with combination of acetylsalicylic acid and clopidogrel compared to (A) patients receiving pretreatment with other antiplatelet combinations and (B) patients receiving pretreatment with combination of acetylsalicylic acid and dipyridamole.

TABLES

Table 1. Baseline characteristics of unmatched groups

Variable	DAPP+ (n=1355)	AP- (n=26757)	95%CI	p-value
Age (mean±SD), years	71.6±10.8	66.2±13.8	-6.00, -4.80	<0.001
Males (%)	68.2%	56.1%	-0.15, -0.10	<0.001
Admission NIHSS (median, IQR)	9 (6-16)	9 (6-15)	-0.34, 0.34	0.918
Hypertension (%)	81.1%	56.6%	-0.27, -0.22	<0.001
Diabetes (%)	28.8%	14.2%	-0.17, -0.12	<0.001
Hyperlipidemia (%)	57.5%	21.3%	-0.39, -0.33	<0.001
Current smoking (%)	15.2%	21.1%	0.04, 0.08	<0.001
Atrial fibrillation (%)	18.8%	12.3%	-0.09, -0.04	<0.001
Congestive heart failure (%)	15.6%	4.2%	-0.13, -0.09	<0.001
History of previous stroke* (%)	30.1%	3.7%	-0.29, -0.24	<0.001
Statin pretreatment (%)	71.2%	14.7%	-0.59, -0.54	<0.001
Admission SBP baseline (mean±SD), mmHg	150.5±23.3	152.5±23.8	0.73, 3.27	0.002
Admission DBP (mean±SD), mmHg	80.5±14.0	83.9±14.4	2.63, 4.16	<0.001
Admission serum glucose (mean±SD), mg/dL	133.4±52.9	130.0±49.2	-6.28,-0.52	0.023
Onset-to-treatment time (mean±SD), min	153.5±56.6	158.4±56.3	1.81, 7.99	0.002
Endovascular reperfusion therapies (%)	3.1%	4.8%	0.01, 0.03	0.004

DAPP: dual antiplatelet pretreatment, AP-: No antiplatelet pretreatment, 95%CI: 95% confidence intervals for the differences between the two groups, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure, IQR: interquartile range

*earlier than 3 months before the index event

Table 2. Baseline characteristics of propensity score matched groups

Variable	DAPP+ (n=1043)	AP- (n=1043)	95%CI	p-value
Age (mean±SD), years	71.4±11.0	71.4±10.7	-0.93, 0.93	0.956
Males (%)	68.4%	67.9%	-0.04, 0.03	0.814
Admission NIHSS (median, IQR)	9 (6-15)	9 (6-15)	-0.57, 0.49	0.894
Hypertension (%)	81.3%	81.4%	-0.03, 0.03	0.963
Diabetes (%)	30.1%	31.0%	-0.03, 0.05	0.669
Hyperlipidemia (%)	57.4%	59.5%	-0.02, 0.06	0.334
Current smoking (%)	15.2%	14.9%	-0.03, 0.03	0.893
Atrial fibrillation (%)	20.6%	23.3%	-0.01, 0.06	0.135
Congestive heart failure (%)	14.9%	16.8%	-0.01, 0.05	0.223
History of previous stroke* (%)	29.7%	26.7%	-0.07, 0.01	0.134
Statin pretreatment (%)	71.3%	72.8%	-0.02, 0.05	0.451
Admission SBP baseline (mean±SD), mmHg	151.2±23.4	151.0±22.7	-2.18, 1.78	0.855
Admission DBP (mean±SD), mmHg	80.6±13.9	80.8±14.6	-1.02, 1.42	0.725
Admission serum glucose (mean±SD), mg/dL	134±53	135±49	-3.38, 5.38	0.667
Onset-to-treatment time (mean±SD), min	154±57	154±56	-4.85, 4.85	0.763
Endovascular reperfusion therapies (%)	3.0%	3.5%	-0.01, 0.02	0.459

DAPP: dual antiplatelet pretreatment, AP-: No antiplatelet pretreatment, 95%CI: 95% confidence intervals for the differences between the two groups, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure, IQR: interquartile range

*earlier than 3 months before the index event

Table 3. Outcomes of propensity score matched groups.

Variable	DAPP+	AP-	95%CI	p-value
SICH (%) – SITS MOST	2.9%	1.5%	-0.03, -0.01	0.037
SICH (%) – ECASS II	5.2%	4.4%	-0.03, 0.01	0.354
SICH (%) – NINDS	7.7%	6.6%	-0.03, 0.01	0.318
Symptomatic Remote Parenchymal Hemorrhage (%)	1.1%	0.6%	-0.01, 0.01	0.155
Asymptomatic Intracranial Hemorrhage (%)*	6.9%	6.2%	-0.03, 0.01	0.526
mRS at 3 months (median, IQR)	2 (1-4)	2 (0-4)	-0.29, 0.09	0.683**
FFO (mRS: 0-1) at 3 months (%)	45.6%	46.0%	-0.04, 0.05	0.860
FI (mRS: 0-2) at 3 months (%)	59.2%	60.7%	-0.03, 0.06	0.503
Mortality at 3 months (%)	17.9%	16.6%	-0.05, 0.02	0.417

DAPP: dual antiplatelet pretreatment, AP-: No antiplatelet pretreatment, 95%CI: 95% confidence intervals for the differences between the two groups, SICH: symptomatic intracerebral hemorrhage, mRS: modified Rankin Scale, FFO: favorable functional outcome, FI: functional independence

* according to NINDS criteria

**by Cochran Mantel-Haenszel test