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Intravenous tPA (Tissue-Type Plasminogen Activator) in Patients With Acute Ischemic Stroke Taking Non–Vitamin K Antagonist Oral Anticoagulants Preceding Stroke

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Abstract

Background and Purpose——Although there are no trials or large cohorts to inform clinical care, current guidelines caution against giving intravenous tPA (tissue-type plasminogen activator) to patients with acute ischemic stroke who are taking non–vitamin K antagonist oral anticoagulants (NOACs). We performed a literature review of intravenous tPA in patients treated with NOACs preceding stroke.

Methods——A literature search of PubMed was performed encompassing January 2010 to March 2018. Patient characteristics, timing of last medication intake, laboratory testing, use of reversal, and outcomes ≤3 months after discharge were summarized.

Results——We identified 55 studies with 492 NOAC patients receiving tPA (dabigatran, 181; rivaroxaban, 215; apixaban, 40; and unspecified NOAC, 56). Among patients with complete data, the median time from the last NOAC intake to symptom onset was 8 hours (interquartile range, 2.5–14.5), with 55.2% (80/145) within 12 hours. Few patients underwent sensitive laboratory tests, such as thrombin time, diluted thrombin time, or anti-Xa assays before tPA administration. The overall observed rates of symptomatic intracranial hemorrhage, mortality, and favorable outcomes (National Institutes of Health Stroke Scale score, ≤1; modified Rankin Scale score, 0–2; or neurological improvement in the National Institutes of Health Stroke Scale score, ≥8 points) were 4.3% (20/462), 11.3% (48/423), and 43.7% (164/375), respectively. Among dabigatran-treated

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patients, reversal with idarucizumab was associated with fewer symptomatic intracranial hemorrhage (4.5% [2/44] versus 7.4% [8/108]; unadjusted odds ratio, 0.60; 95% CI, 0.12–2.92), death (4.5% [2/44] versus 12.0% [13/108]; unadjusted odds ratio, 0.35; 95% CI, 0.08–1.61), and more favorable outcomes (79.1% [34/43] versus 39.2% [29/74]; unadjusted odds ratio, 5.86; 95% CI, 2.45–14.00), although the differences were not statistically significant for symptomatic intracranial hemorrhage and death.

Conclusions——These preliminary observations suggest that tPA may be reasonably well tolerated without prohibitive risks of bleeding complications in selected patients on NOACs. Reversal of anticoagulant effects by idarucizumab for dabigatran-treated patients before tPA is an emerging strategy that was associated with more favorable outcomes.

Keywords

apixaban; dabigatran; humans; intracranial hemorrhages; rivaroxaban

Non–vitamin K antagonist oral anticoagulants (NOACs) are increasingly used for stroke prevention in high-risk patients with atrial fibrillation. However, increasing NOAC adoption also challenges clinicians when treating patients who experience an acute ischemic stroke while taking these medications. Although successful thrombolysis has been reported, the safety of intravenous tPA (tissue-type plasminogen activator) in NOAC patients has not been firmly established and may be harmful (class III: harm; level of evidence C-expert opinion).[1] In the absence of confirmatory research, we summarized all evidence from the literature and provided an up-to-date understanding of intravenous tPA in patients taking NOACs preceding stroke.

Methods

The authors declare that all supporting data are available within the article and its online-only Data Supplement. A literature review was conducted according to PRISMA guidelines and performed between June 2015 and March 2018 using PubMed with the term stroke and thrombolysis/thrombolytic therapy/recombinant tissue plasminogen activator/tissue plasminogen activator/alteplase/r-tPA/tPA/recanalization, combined with names of individual NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban), novel oral anticoagulant, non–vitamin K antagonist oral anticoagulant, direct oral anticoagulant, direct thrombin inhibitor, factor Xa inhibitor, or idarucizumab as title words or key words. The study flow diagram is shown in Figure I in the online-only Data Supplement. We limited to studies in humans, published in English. Because indications of endovascular treatment may not be generalizable to intravenous approach, we focused on intravenous tPA when data on route were available. A standard form was developed to extract patient demographics, key time intervals, laboratory tests, initial National Institutes of Health Stroke Scale, use of idarucizumab, symptomatic intracranial hemorrhage (sICH), and outcomes ≤3-month follow-up. Based on the NINDS trial criteria and data availability,[2] National Institutes of Health Stroke Scale score ≤1, modified Rankin Scale score 0 to 2, or neurological improvement in National Institutes of Health Stroke Scale score ≥8 points were considered as favorable outcome.

Except for 2 large multicenter cohorts,[3,4] most studies were case reports or case series. Because of potential publication bias, treatment selection, small sample size, lack of control, or lack of adjusted results, we did not perform a meta-analysis by pooling study odds ratios. Instead, we summarized characteristics and reported outcomes in the entire sample. Because the results of each NOAC are not comparable in this type of review, individual NOAC outcomes were not reported separately, except for dabigatran with idarucizumab because it represents an up-to-date information. The Institutional Review Board of Duke University approved the study.

Results

Baseline Characteristics

We identified 55 studies with a total of 492 NOAC patients (181 dabigatran, 215 rivaroxaban, 40 apixaban, and 56 unspecified NOAC agent) receiving stroke recanalization therapy (Table I in the online-only Data Supplement). Among patients with complete individual-level data, the median age was 77 years (interquartile range, 68–83; n=73), the median National Institutes of Health Stroke Scale score was 10 (interquartile range, 6–16; n=75), and the median time from last NOAC intake to stroke onset was 8 hours (interquartile range, 2.5–14.5; n=39; Table 1). Based on descriptions of the case presentation, 55.2% (80/145) took NOAC within 12 hours preceding stroke onset, 33.9% (43/127) within 13 to 24 hours, and 7.7% (10/130) >24 hours. The most commonly used coagulation test was aPTT, with 27.4% (34/124) of patients with prolonged aPTT. Fewer patients underwent sensitive tests, such as thrombin time (85.2% [23/27] with prolonged thrombin time), diluted thrombin time, dabigatran concentration for dabigatran (39.4%; 37/94), or anti-Xa assays for rivaroxaban and apixaban (47.3%; 43/91). No study reported using ecarin clotting time to detect the presence of dabigatran.

Clinical Outcomes

The overall observed rates of sICH, mortality, and favorable outcomes were 4.3% (20/462), 11.3% (48/423), and 43.7% (164/375), respectively (Table 2). Among dabigatran-treated patients, reversal with idarucizumab was associated with fewer sICH (4.5% [2/44] versus 7.4% [8/108]; unadjusted odds ratio, 0.60; 95% CI, 0.12–2.92), death (4.5% [2/44] versus 12.0% [13/108]; undjusted odds ratio, 0.35; 95% CI, 0.08–1.61), and more favorable outcomes (79.1% [34/43] versus 39.2% [29/74]; unadjusted odds ratio, 5.86; 95% CI, 2.45–14.00), although the differences were not statistically significant for sICH and death.

Discussion

The current guidelines caution against administrating intravenous tPA to patients taking NOACs unless sensitive laboratory tests are normal or the last intake of NOACs is >48 hours before stroke.[1] However, this recommendation is complex to implement because of the lack of rapidly available sensitive tests. Global coagulation tests, such as PT, aPTT, and INR are not specific for NOACs.[5] Indeed, few patients in this review received tPA based on sensitive test results, such as thrombin time or anti-Xa assays. Interestingly, most patients with last NOAC intake documented had NOAC within 24 hours before stroke (55.2% within 12 hours

and 33.9% between 13 and 24 hours), which was shorter than the recommended 48-hour window. Although few cases in this review were treated with tPA according to guideline recommendations, the observed sICH rates seem to be comparable with those reported in non-anticoagulated patients in clinical trials. Therefore, this review contributes to the growing body of evidence that patients taking NOACs may not have an increased bleeding risk after tPA adminstration.[6]

With the introduction of idarucizumab in 2015 and andexanet alfa in 2018, patients taking NOACs may undergo reversal of anticoagulation, potentially reducing bleeding risk. In our review of 152 cases with dabigatran, those reversed with idarucizumab appeared less likely to bleed (4.5% versus 7.4%) and die (4.5% versus 12.0%) and more likely to have favorable outcomes (79.1% versus 39.2%) than those not. These findings suggest that intravenous tPA after idarucizumab reversal is a reasonable option to consider in patients on dabigatran even though a prothrombotic effect cannot be completed excluded.[7] Further studies are needed to evaluate the safety and efficacy of anticoagulation reversal before tPA administration.

Our study has limitations. First, this review is based mostly on case reports or case series. Publication bias and treatment selection are likely significant and potentially overestimate or underestimate the true bleeding risk. Second, small sample size, lack of control groups, and only aggregate data in some studies prevent us from doing risk adjustment or running suitable meta-analyses. Third, owing to the nature of case reports and word limits imposed by various journals, patient-level details are often incomplete. Therefore, a direct comparison between NOAC versus no oral anticoagulants, NOAC versus warfarin, or between each individual NOAC agent cannot be made.

In conclusion, this present review suggests that use of intravenous tPA in selected patients with acute ischemic stroke treated with NOACs is feasible and appears to be well tolerated without prohibitive risks for bleeding complications. Reversal of anticoagulant effects by idarucizumab is an emerging strategy that was associated with more favorable outcomes. Further prospective studies and clinical trials are needed to evaluate the safety and efficacy of tPA in patients with ischemic stroke who are taking NOACs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures

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Table 1.

Baseline Characteristics

	Measures
NOACs	492 *
Dabigatran	181/492 (36.8%)
Reversal with idarucizumab	44/181 (24.2%)
Rivaroxaban	215/492 (43.7%)
Apixaban	40/492 (8.1%)
NOACs not specified	56/492 (11.4%)
Age, y †	Median, 77 (IQR, 68–83)
Women	233/492 (47.4%)
NOAC last intake before stroke, h †	Median, 8 (IQR, 2.5–14.5)
≤12	80/145 (55.2%)
13–24	43/127 (33.9%)
>24	10/130 (7.7%)
Precise time/range not reported	347/492 (70.5%)
Laboratory †	
Prolonged PT	7/16 (43.8%)
Prolonged aPTT	34/124 (27.4%)
Prolonged TT in dabigatran	23/27 (85.2%)
TT, dTT, or dabigatran concentration in dabigatran	37/94 (39.4%)
Anti-Xa assay in rivaroxaban or apixaban	43/91 (47.3%)
NIHSS on admission	Median, 10 (IQR, 6–16) †

dTT indicates diluted thrombin time; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; NOAC, non–vitamin K antagonist oral anticoagulants; and TT, thrombin time.

* Includes 30 patients receiving intra-arterial treatment.

† Among patients with complete individual-level data.

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Table 2.

Clinical Outcomes

NOACs	sICH	Death*	Favorable Outcomes*†
Overall	20/462 (4.3% [2.7–6.4])	48/423 (11.3% [8.6–14.6])	164/375 (43.7% [38.8–48.8])
Dabigatran			
Reversal with idarucizumab	2/44 (4.5% [0.8–13.4])	2/44 (4.5% [0.8–13.4])	34/43 (79.1% [65.4–89.3])
Without idarucizumab	8/108 (7.4% [3.5–13.4])	13/108 (12.0% [6.8–19.0])	29/74 (39.2% [28.6–50.5])

mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, non–vitamin K antagonist oral anticoagulants; and sICH, symptomatic intracranial hemorrhage.

*At discharge or ≤3-month follow-up.

†NIHSS, ≤1; mRS, 0–2; or improvement in NIHSS score, ≥8 points.