Intravenous Thrombolysis in Patients with Acute Ischemic Stroke after a Reversal of Dabigatran Anticoagulation with Idarucizumab: A Real-World Clinical Experience

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Background: Intravenous thrombolysis (IVT) is contraindicated in patients with acute ischemic stroke (AIS) using oral anticoagulants. A specific human monoclonal antibody was introduced to reverse immediately the anticoagulation effect of the direct inhibitor of thrombin, dabigatran. Until now, mostly individual cases presenting with successful IVT after a reversal of dabigatran anticoagulation in patients with AIS were published. Thus, we aimed to report real-world data from clinical practice. *Methods:* Patients with AIS on dabigatran treated with IVT after antidote reversal were enrolled in the retrospective nationwide study. Neurological deficit was scored using the National Institutes of Health Stroke Scale (NIHSS) and 90-day clinical outcome using modified Rankin scale (mRS) with a score 0-2 for a good outcome. Intracerebral hemorrhage (ICH) was defined as a presence of any sign of bleeding on control imaging after IVT, and symptomatic intracerebral hemorrhage (SICH) was assessed according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria. *Results:* In total, 13 patients (7 men, mean age 70.0 ± 9.1 years) with a median NIHSS admission score of 7 points were analyzed. Of these patients, 61.5% used 2 × 150 mg of dabigatran daily. Antidote was administrated 427 ± 235 minutes after the last intake of dabigatran, with a mean activated prothrombin time of 38.1 ± 27.8 seconds and a mean thrombin time of 72.2 ± 56.1 seconds. Of the 13 patients, 2 had ICH and 1 had SICH, and no other bleeding complications were observed after IVT. Of the total number of patients, 76.9% had a good 3-month clinical outcome and 3 patients (23.1%) died. Recurrent ischemic stroke occurred in 2 patients (15.4%). *Conclusion:* The data presented in the study support the safety and efficacy of IVT after the

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reversal of the anticoagulation effect of dabigatran with antidote in a real-world clinical practice. **Key Words:** Acute ischemic stroke—intravenous thrombolysis—anticoagulation—dabigatran—antidote—reversal.

Introduction

Patients with acute ischemic stroke (AIS) use often oral anticoagulants, mostly as a preventive treatment of embolic events for atrial fibrillation (AF). Intravenous thrombolysis (IVT) is generally contraindicated in these patients.[1] Nevertheless, in certain conditions, IVT may be considered; in patients using warfarin, the value of international normalised ratio should be less than 1.7. In patients using non–vitamin K oral anticoagulants (NOACs), IVT is recommended only if NOAC is not definitely taken within the last 48 hours or if specific laboratory detection tests for appropriate NOAC are normal.[1]

Since the end of 2015, idarucizumab, a specific human monoclonal antibody (Praxbind; Boehringer-Ingeheim, Ingelheim am Rhein, Germany), has been available, which binds dabigatran approximately 350 times more than dabigatran binds thrombin.[2] A standard dose of 2×2.5 g of idarucizumab completely reverses the biological effect of dabigatran within a few minutes.[3,4] In patients using dabigatran, IVT may now be performed after an immediate reversal of the anticoagulation effect of dabigatran by intravenously administering idarucizumab.[5] Up to now, mostly individual cases presenting with successful IVT after the reversal of the anticoagulation effect of dabigatran in patients with AIS were published.[5-8] Thus, we aimed to report real-world data from clinical practice in the form of a nationwide study.

Methods

Patients with AIS who were treated with IVT after the administration of idarucizumab for the reversal of the anticoagulation effect of dabigatran were enrolled in the retrospective nationwide study. All stroke centers were called to participate in the present study using an e-mail survey. Patient data were collected anonymously and included demographic and baseline stroke characteristics, laboratory parameters, imaging data, adverse events and complications, and clinical outcomes. None of all included patients participated in any clinical trial or prospective clinical study with predefined inclusion and exclusion criteria and with a prespecified management.

In all enrolled patients, admission clinical status was evaluated using the National Institutes of Health Stroke Scale (NIHSS) by a certified neurologist. The occurrence of intracerebral hemorrhage (ICH) was assessed on the control computed tomography (CT) or magnetic resonance imaging (MRI) after 24 hours, and ICH was defined as any sign of the presence of bleeding on control imaging. Symptomatic intracerebral hemorrhage (SICH) was defined as a local remote parenchymal hematoma (type 2) or a subarachnoid hemorrhage associated with at least a 4-point increase in the NIHSS score or leading to death.[9]

Neurological deficit was evaluated using the NIHSS after 24 hours and clinical outcome was obtained after 3 months using the modified Rankin Scale (mRS). A score 0-2 points was considered a good outcome.

The study protocol was in compliance with the Declaration of Helsinki (1975) and was approved by the ethical committee of the hospital the first author was affiliated with.

Results

In total, 13 patients with AIS (7 men, mean age 70.0 ± 9.1 years) were enrolled in the study. The patients were treated between September 2016 and October 2017. Demographic and baseline clinical characteristics are shown in Table 1. Eight patients (61.5%) used a daily dose of 2×150 mg of dabigatran at the time of stroke onset, and AF was the most frequent reason for anticoagulation therapy (84.6%).

Baseline laboratory parameters, including coagulation collected before the treatment with the antidote and IVT, are shown in Table 2 and Figure 1. The mean time of antidote administration after last intake of dabigatran was 427 ± 235 minutes. All patients were treated with a dose of 5 g of idarucizumab followed by a full dose of recombinant tissue plasminogen activator. Mechanical thrombectomy after IVT was performed in 1 patient (8.3%).

ICH after IVT was detected in 2 patients (15.4%), and 1 of these patients (7.6%) suffered from SICH (Table 3). In this patient, the admission creatinine clearance was 57 mL/s, the activated partial thromboplastin time (aPTT) was 56.1 seconds, the thrombin time (TT) was 60 seconds, and the diluted TT (Hemoclot test; Hyphen BioMed, Neuville-sur-Oise, France) was 60 ng/mL. IVT was initiated 23 minute after antidote administration and 14 hours after the last intake of dabigatran (dose of 150 mg). No other bleeding complications were recorded in the remaining patients.

Two (15.4%) patients suffered from recurrent ischemic stroke (RIS) after the first event, and both had known AF. In the first patient, RIS occurred 21 hours after the end of IVT, and the patient presented with sudden coma and generalized tonic-clonic seizures after respiratory failure. Immediate control CT showed occlusion in the intracranial parts of the basilar artery and both vertebral arteries.