Intravenous Thrombolysis After Idarucizumab Application in Acute Stroke Patients—A Potentially Increased Sensitivity of Thrombi to Lysis?

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Background: Rapid inactivation of dabigatran by its specific inhibitor idarucizamab allows intravenous thrombolysis (IVT) in patients suffering ischemic stroke while being treated with dabigatran. Only limited data of this approach is available and numerous questions regarding efficacy/safety remain to be answered. Herein, we present the findings from the Slovenian national cohort study. *Methods:* Retrospective analysis of all stroke patients treated with idarucizumab and IVT (n = 11) in the period from July 2016 to February 2018 from Slovenian region were analyzed. *Results:* The indication for dabigatran treatment in all 11 cases was nonvalvular atrial fibrillation. Importantly, 6 out of 11 cases were classified as severe ischemic strokes (National Institutes of Health Stroke Scale; NIHSS ≥ 10) with a median NIHSS 13. At admission, prolonged activated partial thromboplastin time was present in 9 patients indicating therapeutic anticoagulation activity. The average door-to-needle time was 156 minutes. After 3 months, 9 patients had a modified Rankin Score of less than or equal to 2 and 7 patients had mRS less than 1 whereas, 2 patients died due to symptomatic intracranial hemorrhage (sICH); 1 due to spontaneous sICH, and the other due to a large ischemic stroke with hemorrhagic transformation. No thrombotic complications were observed. *Conclusions:* Our data show that IVT after idarucizumab administration is a safe and effective method of treatment in ischemic stroke patients on dabigatran. We recorded a higher proportion of patients with favorable outcome as well as with sICH compared to the randomized controlled studies which could suggest a higher sensitivity of thrombi to IVT in dabigatran treated patients.

Key Words: Dabigatran—acute ischemic stroke—idarucizumab—intravenous thrombolysis

Introduction

Although nonvitamin K oral anticoagulants have been proven to be effective and safe for stroke prevention,[1,2,3,4] the lack of their antidotes remains one of the major concerns for their use. The recent introduction of idarucizumab into clinical practice made dabigatran the first nonvitamin K oral anticoagulant with a safe and effective antidote.[5,6] Idarucizumab, a humanized monoclonal antibody fragment, reverses the anticoagulant effect of dabigatran within minutes of administration, has no known interaction with other drugs, and seems not to have procoagulant effect.[5,6] It is thus recommended for first-line treatment in patients with serious bleeding who require an urgent surgical procedure.[5]

According to the American Stroke Association Guidelines, intravenous thrombolysis (IVT) with a recombinant tissue plasminogen activator (rt-PA) is the recommended therapy for acute ischemic stroke even in patients taking

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Received June 25, 2018; revision received November 8, 2018; accepted November 14, 2018.

Financial Disclosure: The authors received no financial support for the research, authorship, and/or publication of this article.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.11.019

anticoagulant therapy, provided that there is no anticoagulant effect at the time of rt-PA application.[7] Theoretically, dabigatran patients who receive idarucizumab would not have any disturbance of coagulation, either probleeding or prothrombotic,[5] and are therefore eligible candidates for IVT. However, solid clinical data definitively proving these assumptions is still missing. The use of idarucizumab followed by rt-PA is covered by the labels of both drugs; furthermore, it is recommended by most experts.[8,9]

There is only limited data on idarucizumab usage in the patients treated with dabigatran who suffer from acute ischemic stroke and are candidates for IVT. To the best of our knowledge, there are only a few case series[10-12] and several single case reports of dabigatran-treated acute stroke patients who received idarucizumab before IVT.[13-26] Most authors described a good outcome after IVT.[11-18,20-26] Overall, there is not enough clinical data about the safety and effectiveness of IVT in dabigatran-treated patients pretreated with idarucizumab. While large clinical studies are expected, real-time clinical experience such as case reports and case series are highly needed to provide the clinicians inside information and unmask possible complications.

The lysibility of thrombi is an important predictor of IVT efficacy. Numerous factors, including structural, mechanical, functional, and biochemical properties could influence thrombus sensitivity to lysis.[27] The widely known is the facilitating effect of ultrasound waves on the susceptibility of thrombi to lysis.[28] In addition, anticoagulants could influence the lysability of thrombi arising in patients with atrial fibrillation while being anticoagulated.[29] Importantly, it has been suggested in vitro that dabigatran at clinically relevant concentrations, enhances the susceptibility of plasma clots to t-PA-induced lysis by reducing thrombin-activatable fibrinolysis inhibitor (TAFI) activation and by altering the clot structure.[30] There is no data in regard to possible effect of idarucizumab on thrombi sensitivity to lysis. Overall, it seems possible that intracranial thrombi (pathological and haemostatic) arising/presenting during treatment with dabigatran and/or idarucizumab could be more prone to thrombolysis. If so, this should be considered in clinical practice. We aimed to investigate this relevant issue that has not been addressed yet in our cohort of patients.

Aims

The aim of this cohort study was to report on the safety and outcome of IVT in all the consecutive dabigatran-treated acute stroke patients who received idarucizumab. In addition, we aimed to explore whether there is any signal suggesting higher than expected efficacy of IVT.

Methods

Study Population

Department of Vascular Neurology, University Medical Centre Ljubljana provides stroke care and hospitalization to approximately 1 million persons who live in the central Slovenia. In addition, it provides neurological consultations using telemedicine to all secondary hospitals in Slovenia. Therefore, it provides tertiary neurovascular diagnostics and therapy to all Slovenian population which is about 2 million.

According to the Health Insurance Institute of Slovenia there are currently roughly 9000 patients treated with dabigatran in Slovenia. Most patients on dabigatran treatment who suffer intracerebral hemorrhage as well as ischemic stroke are therefore either treated in the Department of Vascular Neurology, University Medical Centre Ljubljana, or using its consultations via telemedicine. Since the introduction of idarucizumab in 2017 acute stroke patients on dabigatran treatment became potential candidates for IVT and local hospitals interconnected by telemedicine use our consultations or share information regarding the treatment decisions in these patients. Although the Department of Vascular Neurology, University Medical Centre Ljubljana does not have an official registry, it probably disposes with the complete data on dabigatran-treated acute stroke patients who received idarucizumab before IVT in Slovenia.

This cohort study was restricted to all the consecutive dabigatran-treated acute stroke patients who received idarucizumab before IVT from July 2016 to February 2018. Eight of the patients were treated in the Department of Vascular Neurology, University Medical Centre Ljubljana and 3 patients were treated in the regional hospitals Celje, Jesenice, and Murska Sobota.

Study Protocol

All patients received the standard dose of 5 g of idarucizumab, followed by IVT using a (rt-PA) in the recommended dosage of .9 mg/kg of body weight.

The anonymized patient data included baseline characteristics, laboratory and coagulation parameters clinical data such as prestroke modified Rankin Score (mRS), the National Institutes of Health Stroke Scale (NIHSS) upon admission, the NIHSS and mRS at discharge, mRS after 3 months, computed tomography (CT) of the head and CT angiography upon admittance, CT of the head after 24 hours, time to IVT, and time to anticoagulation restart. In all cases the NIHSS and mRS evaluation were performed by a vascular neurologist who was not necessarily the same person upon admission and at discharge. All data were retrospectively collected, anonymized, and transferred for analysis.

Results

Eleven patients (6 males, 5 females, aged 73.7 ± 12.5 years) receiving dabigatran treatment presented with acute ischemic stroke symptoms within the 4.5-hour time window and were eligible candidates for systemic IVT set apart from anticoagulation history (Table 1). Prestroke mRS in all patients was 0. Median NIHSS at admission

Table 1. *Patients' data prior to intravenous thrombolysis*

Case no.	Sex	Age	D dose	Indication for OAC	CrCl (ml/min)	aPTT (s)	TT (s)	Hemoclot	CHADS-VASc	Arterial hypertension	Diabetes
1	F	83	110	NVAF	40	26.4	19.9	<8	4	Yes	No
2	F	41	150	NVAF, stroke	>90	40.5	95	28	3	No	No
3	M	70	150	NVAF	>90	40.2	>150	112	2	Yes	No
4	M	78	110	NVAF	81	51.1	138	90	3	Yes	No
5	F	80	110	NVAF	82	39.9	49.5	10	4	Yes	No
6	M	63	150	NVAF	>90	n.a.	n.a.	5	2	No	No
7	M	73	150	NVAF	n.a.	82.6	36.1	26	3	Yes—not well controlled	No
8	F	78	110	NVAF	78	42.1	>150	95	4	Yes	No
9	M	82	110	NVAF	71	44.9	>150	/	3	No	No
10	F	79	150	NVAF TIA	49	65	/	/	6	Yes	No
11	M	84	110	NVAF, stroke	67	56	>150	131	5	No	No

Abbreviations: Ad, admission; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; D, dabigatran; Dis, discharge, mRS, modified Rankin Scale; n.a., not applied; NIHSS, National Institutes of Health Stroke Scale; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulation; TT, thrombin time.

was 10 points. Six out of 11 patients had a severe ischemic stroke (NIHSS ≥ 10). Median NIHSS of the 6 severely affected patients was 13. There were no signs of bleeding or early infarct on CT scans of the head at admission.

Five patients received 150 mg and 6 patients received 110 mg of dabigatran twice daily. In 3 patients, dabigatran was initiated as secondary stroke prevention and in others as the primary prevention of stroke due to nonvalvular atrial fibrillation. The median CHADS2-VASc score was 3 (Table 1).

Upon arrival at the hospital, the activated partial thromboplastin time aPTT was normal in 1 patient, elevated in 9 patients, and not measured in 1 patient. Thrombin time was normal in 1 patient, prolonged in 8 patients, and not measured in 2 patients. The thrombin time specific for dabigatran (Haemoclot assay) was normal in 2 patients, prolonged in 7 patients, and not measured in 2 patients. The creatinine clearance was above 50 mL/min in 7 patients, below 50 mL/min in 2 patients, and not measured in 1 patient (Table 1).

Although mechanical thrombectomy was available for most of our patients none of them needed it since they improved clinically after IVT and/or did not have occlusions of the large intracranial arteries.

The idarucizumab infusion was well-tolerated in all patients. The time between the application of idarucizumab and the application of rt-PA was 10-20 minutes. The mean time from the start of neurological symptoms to the application of IVT was 156 minutes (Table 2).

In-hospital Course

Two of the 11 patients included in our case series died. The first was a 78-year-old female patient (number 8) who was prescribed dabigatran 2 days before admittance due to transient aphasia and newly discovered atrial fibrillation. Before the dabigatran introduction, the head CT scan showed no pathological changes, and the CT angiography of the aortocervical and intracranial arteries showed no hemodynamically important stenosis. Two days later, the patient presented with signs of acute ischemic stroke in the posterior cerebral artery region (PCA) and a NIHSS of 12. Upon admittance the CT of the head was insignificant; CT perfusion revealed penumbra in the territory of the left PCA, and CT angiography showed an occlusion of the left P1 segment. Haemoclot assay as well as aPTT were prolonged and within therapeutic limits (Table 1). The patient was treated with idarucizumab followed by rt-PA 120 minutes after symptom onset. Four hours after the IVT introduction, her neurological status worsened with sopor, aphasia, and right-sided hemiplegia. The control head CT scan showed intracerebral hemorrhage in the left frontoparietal region, with haematocephalus and no pathological changes in the PCA region. Later on, aspiration pneumonia developed and she was duly treated with antibiotics; nonetheless, the patient died 8 days after admittance due to cardiorespiratory failure.

Table 2. *Outcome after intravenous thrombolysis*

Case No.	Sex	Age	Time to IVT (min)	NIHSS Ad	NIHSS dis	mRS Ad	mRS Dis	mRS 3 Mo	CT after 24 h	Anticoagulation restart
1	F	83	165	14	7	5	2	1	Hemorrhagic transformation of ischemic stroke	14 d warfarin
2	F	41	90	6	1	4	0	0	No pathological changes	2 d D 150 mg bid
3	M	70	240	3	0	1	0	0	No pathological changes	7 d warfarin
4	M	78	140	10	4	4	2	0	Ischemic stroke	10 d D 110 mg bid and ASA 100 mg
5	F	80	206	7	2	5	2	1	Ischemic stroke	7 d D 110 mg
6	M	63	150	6	0	3	0	0	No pathological changes	3 d D 150 mg bid
7	M	73	160	16	0	4	0	0	No pathological changes	11 d D 150 mg bid
8	F	78	120	12	n.a.	3	6	6	Hemorrhage with hematocephalus	n.a.
9	M	82	75	21	n.a.	5	6	6	Ischemic stroke with hemorrhagic transformation (ACM dex)	n.a.
10	F	79	150	11	1	5	1	0	No pathological changes	3 d D 150 mg bid
11	M	84	220	4	0	3	0	0	No pathological changes	10 d D 110 mg bid

3 Mo, after 3 months; Ad, admission; bid, twice a day; D, dabigatran; Dis, discharge; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

The second patient with a fatal outcome was an 82-year-old male (number 9) who presented with clinical signs of a large ischemic stroke in the right middle cerebral artery and a NIHSS of 21. Although Haemoclot was not performed, aPTT was prolonged and within therapeutic limits (Table 1). The patient was treated with idarucizumab followed by rt-PA 75 minutes after symptom onset. However, the patient did not clinically improve, and the control CT scan of the head after 24 hours showed a large ischemic infarction in almost the entire territory of the middle cerebral artery with hemorrhagic transformation. Later on, he developed aspiration pneumonia, which was treated with antibiotics, but the patient died due to cardiocirculatory decompensation 22 days after the acute stroke onset.

Additionally, in one of the patients (No. 1), the control CT scan of the head 24 hours after the IVT showed a small hemorrhagic transformation of the ischemic stroke without any clinical worsening; in 2 patients (No. 4 and No. 5), a small ischemic stroke developed; in 6 patients, no ischemic infarction was seen.

Follow-up

At discharge, 7 patients benefited with an improvement of 5 points in the NIHSS score. At discharge, the median NIHSS of the patients who survived was 1 and the median mRS was 1. Nine out of 11 patients benefited significantly from IVT. Nine patients had mRS of less than or equal to 2 after 3 months, 7 patients had mRS less than or equal to 1 (Table 2).

Re-initiation of Treatment

In all 9 patients who survived, anticoagulation therapy was restarted. Anticoagulation therapy was reintroduced between 2 and 14 days postischemia, depending on the infarct size and the accompanying comorbidities. In 7 patients, we restarted dabigatran treatment and in 2 patients, we introduced warfarin (renal insufficiency, transient thrombocytosis). The reinitiation of anticoagulation was delayed in 3 patients (in 1 due to hemorrhagic transformation, in 1 due to transient thrombocytosis, and in 1 due to carotid thrombendarterectomy).

Discussion

Although the use of idarucizumab followed by rt-PA in acute stroke patients is covered by the labels of both drugs and is even recommended by expert opinion,[8,9] clinical experience regarding this treatment is limited, and the number of described cases is less than 50.[10-26] Since the introduction of idarucizumab into clinical practice in 2016, most authors described its use in order to perform IVT as single cases.[13-26] So far, there have been only 3 case series of 19,[10] 5,[12] and 3 cases.[11] In most cases the outcome of treatment was excellent; namely in 67% of cases in the German study mRS less than

or equal to 2 has been described.[10] Furthermore, a systematic analysis of all additional published case reports has shown an excellent outcome in 72% of described cases.[12] In addition, low mortality rate has been described; overall there are only 3 published cases of fatal outcomes[10,19] and 1 of significant deterioration.[10] More specifically, 2 patients died due to a repeated ischemic event (since anticoagulation was temporarily stopped)[10,19] and 1 due to a hemorrhagic transformation of a large ischemic infarction.[19] Additional deterioration was reported in a patient with a large ischemic infarction in whom IVT was not successful.[10]

It is well known that the outcome of IVT depends very much on the stroke severity.[31] It needs to be emphasized that so far, 90% of the described stroke patients on dabigatran who were thrombolyzed had a mild stroke severity with NIHSS less than or equal to 10.[12] Randomized trials that are commonly used to compare the outcome of IVT have included significantly more severely affected patients. Namely, a metanalysis of the randomized trials has shown that only 47% of the observed patients had a NIHSS less than or equal to 10.[31] Mild stroke severity of the patients on dabigatran could therefore be the cause of the excellent outcome after IVT.

In our national cohort study we report the outcome of 11 consecutive patients in which idarucizumab was used for the rapid reversal of the anticoagulant effect of dabigatran in order to perform IVT. Eight patients (73%) had a mRS less than or equal to 2 at discharge from the hospital. Two of the patients died—1 due to the consequences of intracranial hemorrhage, and the other due to a large ischemic stroke with hemorrhagic transformation. Both patients who died received lower dosage of dabigatran. In 1 patient lower dosage was prescribed due to age whereas in the other the reason is not clear. Lower dosage probably predisposed them to the formation of thrombi nevertheless it clearly did not protect them from the hemorrhagic transformation or even spontaneous hemorrhage.

The mortality rate of 18% in our small study is certainly higher than previously reported. However as opposed to the previously reported cases, our cohort study consisted of significantly more severely affected stroke patients, namely 7 out of 11 patients (64%) had a moderate-to−severe clinical involvement with NIHSS greater than or equal to 10. Metanalysis of the IVT studies with similar share of the severely affected stroke patients (63%) has shown that only 31% of patients had a mRS less than or equal to 2 and 16% of patients died within 90 days after stroke.[31]

Recently, Tse et al reported a similar cohort study based on the New Zeeland national registry of thrombolyzed stroke patients.[32] They reported the outcome of 7 consecutive patients who received idarucizumab prior to IVT and endovascular clot retrieval.[32] Similar to our study the described patients had a more severe neurological deficit at presentation. Namely, the median NIHSS score in these patients was 21 (2 patients had a NIHSS $\leq$ 10 and 5 had a NIHSS $\geq$ 15). One of the patients died due to complications of ischaemic cerebral oedema and 1 significantly deteriorated due to symptomatic intracranial hemorrhage. Only 2 of the patients had a mRS less than or equal to 2. The authors concluded that according to their real life experience the IVT in dabigatran treated patients is safe. Nevertheless, the severity of stroke as well as door-to-needle time of 211 minutes makes the general outcome hard to compare to the previous case reports or to our study.

According to our results as well as to the literature, the outcome of IVT in dabigatran treated patients seems to differ from IVT in the regular stroke patients. Our hypothesis is that the patients on dabigatran treatment have thrombi that are more susceptible to lysis that has been already convincingly shown in in vitro conditions.[28] Whether these in vitro findings could be translated in in vivo conditions remains unanswered so far, but merit to be addressed. Increased sensitivity of thrombi to lysis could be due to the consequences of altered fibrin structure in probably fresh thrombi arising and embolizing during dabigatran treatment and/or reduced activity of thrombin-activatable fibrinolysis inhibitor in these thrombi.[28] This might have only minor clinical relevance or could importantly influence the outcome of thrombolysis. Our results revealed the second assumption, since favorable outcome of IVT was obtained in a higher proportion of patients compared to the randomized controlled studies.[31] On the other hand, bleeding complications might be also influenced by the same changes making also thrombostatic clots (particularly fresh) more susceptible to thrombolysis. The fact that a large proportion of the described case report patients had a mild stroke could be a coincidence but could also be an indirect proof of the effectiveness of dabigatran. Nevertheless, large cohort studies based on national stroke registries that would include all the consecutive patients that received such treatment are needed to further support these hypothetical conclusions about increased sensitivity of thrombi, arising during treatment with dabigatran, to lysis. If assumption would be confirmed, it would be clinically relevant.

In conclusion we can state that according to the current information, IVT after idarucizumab administration is a safe and effective method of treatment in ischemic stroke patients on dabigatran. Review of the literature reveals a remarkable effectiveness of this therapy which is at least partially due to the relatively mild stroke severity in the majority of the previously described cases, as well as to the fast application of IVT. Likewise, in our study we recorded a higher proportion of patients with favorable outcome as well as with symptomatic intracranial hemorrhage compared to the randomized controlled studies which could suggest a higher sensitivity of thrombi to IVT in dabigatran treated patients.

Acknowledgments

We thank Iwona Eva Kosi, MD, from General Hospital Celje; Janja Borič, MD, from General Hospital Jesenice; and all the colleagues at the Department of Vascular Neurology, UMC Ljubljana who were involved in treating these patients.

Authors' Contributions

J.P.O. took part in the study design, data analysis, data interpretation, and writing. M.S. took part in the study design, data interpretation, and writing. S.F. took part in the study design, data collection, and writing.

Conflict of Interests

In the last 2 years J.P.O., M.S., and S.F. received honoraria for oral presentations from: Bayer, Boehringer Ingelheim, and Pfizer.

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