

ORIGINAL ARTICLE

Systemic thrombolysis in ischaemic stroke patients with COVID-19

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Abstract

Objective: Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator is the core medical therapy of acute ischaemic stroke (AIS). COVID-19 infection negatively modifies acute stroke procedures and, due to its pro-coagulative effect, may potentially impact on IVT outcome. Thus, short-term efficacy and safety of IVT were compared in patients with and without evidence of SARS-CoV-2.

Methods: An observational, retrospective study included 70 patients with AIS, including 22 subjects (31%) with evidence of acute COVID-19 infection, consecutively treated with IVT in 4 stroke centres between 15 September and 30 November 2020.

Results: Patients infected with COVID-19 were characterized by higher median of National Institute of Health Stroke Scale (NIHSS) score (11.0 vs. 6.5; $p < .01$) and D-dimers (870 vs. 570; $p = .03$) on admission, higher presence of pneumonia (47.8% vs. 12%; $p < .01$) and lower percentage of 'minor stroke symptoms' (NIHSS 1–5 pts.) (2% vs., 18%; $p < .01$). Hospitalizations were longer in patients with COVID-19 than in those without it (17 vs. 9 days, $p < .01$), but impact of COVID-19 infection on patients' in-hospital mortality or functional status on dismissal has been confirmed neither in uni- or multivariate analysis.

Conclusion: SARS-CoV-2 infection prolongs length of stay in hospital after IVT, but does not influence in-hospital outcome.

KEYWORDS

COVID-19, functional outcome, intravenous thrombolysis, ischaemic stroke

1 | INTRODUCTION

The COVID-19 pandemic is associated with a variety of neurological symptoms. In the course of COVID-19 infection, hypercoagulability occurs that is likely a 'sepsis-induced coagulopathy' and may predispose to stroke.¹ The clinical course of COVID-19 is most severe in elderly patients, in men, and in patients with comorbidities as diabetes mellitus, obesity, hypertension and most cardiovascular risk factors.² The data from the 'first wave' of SARS-CoV-2 pandemic show

that the rates of stroke in hospitalized patients with COVID-19 range from 1% to 3% and up to 6% of critically ill patients.^{2,3} Strokes course in patients with COVID-19 may be more severe and associated with higher in-hospital mortality and disability on discharge.⁴

Intravenous thrombolysis (IVT) with the use of recombinant tissue plasminogen activator is an effective and universally recommended method of treatment in the acute ischaemic stroke (AIS).^{5,6} Unfortunately, COVID-19 resulted in a global decline in the volume of stroke hospitalizations and IVT treatments.⁷⁻¹⁰ Moreover,

inflammatory processes predict poor outcomes in ischaemic stroke treated with IVT,¹¹ and pneumonia especially predicts increasing mortality in these patients.¹² However, only a few reports associated the impact of SARS-CoV-2 infection on the outcome of patients treated with IVT.^{9,10,13-16} Therefore, our objectives were to determine short time safety and efficacy of IVT in patients with AIS and COVID-19.

2 | METHODS

2.1 | Study design

We conducted a retrospective observational study based on hospital-based stroke registries from Department of Neurology and Stroke Unit of Holy Spirit Specialist Hospital in Sandomierz, Department of Neurology and Stroke Unit of Regional Hospital in Kielce, Department of Neurology and Stroke Unit of Saint Lukas Hospital in Końskie and Department of Neurology and Stroke Unit of Skłodowska-Curie Hospital in Skarżysko-Kamienna located in Świętokrzyski region in Poland. Those stroke centres are equipped with the proper monitoring and diagnostic facilities and provide a 24-h stroke service seven days a week. In the stroke units, diagnostic and treatment procedure protocols with respect to unified regular protocols of the management of AIS, according to the Polish national and international recommendations, are in force.^{5,17} The ethics committee approved all data of analysis (Ethics Committee of Jan Kochanowski University in Kielce, Number 17/2020).

2.2 | Study population

Study population consisted of 70 Caucasian adults (51.4% of males, mean age 72, 7 ± 12 years)—all of those patients who were treated only with IVT between 15 September 2020 and 30 November 2020 (14.8% of 473 subjects with AIS consecutively hospitalized in study stroke units in recruitment period).

The severity of stroke symptoms was assessed using the National Institute of Health Stroke Scale (NIHSS) by stroke physician at admission to Emergency Departments.¹⁸ Stroke onset was defined as the last occasion on which the patient was known to be without neurological deficit. Brain computed tomography (CT) and/or magnetic resonance were performed upon admission to hospitals in order to establish the indication for treatment and between 22 and 36 h after treatment. Examinations to evaluate the inflammatory processes and the coagulation status and also chest X-ray and/or chest CT in all patients were performed. To evaluate the aetiology of the stroke transcranial doppler, carotid duplex ultrasonography, Holter electrocardiography and transthoracic echocardiography were performed. The stroke outcomes were measured using the modified Rankin scale (mRS).¹⁹ A favourable outcome was defined as an mRS score ≤2 points, whilst an unfavourable outcome was defined as an mRS score of 3–6 points. Symptomatic intracerebral haemorrhage rates were

assessed according to the ECASS II (European Cooperative Acute Stroke Study II) and III criteria.²⁰ To determine the type of ischaemic strokes, the TOAST (trial of ORG 10172 in acute stroke treatment) classification was also taken from the discharge summary.²¹

2.3 | Definition of stroke patients with SARS-CoV-2

All patients were tested for COVID-19 with the reverse transcriptase-polymerase chain reaction tests. For SARS-CoV-2-infected group, we included patients with positive test performed within 3 days of admission.

2.4 | Statistical analysis

This study was based on a retrospective database analysis. Data gathering, characteristics and univariate analysis were performed using Microsoft Excel 2017; statistical analysis was performed with STATISTICA v. 9.1. All continuous variables were tested for a normal distribution and equality of variances. Because of the non-normality of the variables, non-parametric Mann-Whitney U tests were used to perform the univariate analysis of the continuous variables. Categorical data were compared using chi-square tests; *p* values <.05 were considered statistically significant. The multivariate analysis was performed using multiple logistic regression models. Three separate models, each excluding correlating variables, were done. Factors identified in the univariate analysis with a *p* value <.01 were then examined using a multivariate models. Each model was created taking into account the correlation between the individual continuous variables.

3 | RESULTS

Patients infected COVID-19 were characterized by higher median of baseline NIHSS, lower percentage of diagnosis 'minor stroke' (NIHSS 1–5 pts.) and higher presence of pneumonia. Patients with COVID-19 stayed in the hospital longer. There was no difference between pre- and in-hospital delays, risk factors profile, presence of fever at admission and complications rate between the two groups. Median of D-dimers was higher in COVID than in non-COVID patients; no other differences of biochemical parameters between patients with and without COVID infection existed. Proportion of patients functionally independent (mRS 0–2) on discharge tended to be lower in patients with COVID infection; in-hospital mortality did not differ between both groups (Table 1).

However, there were no differences regarding presence of COVID infection between patients with favourable (mRS 0–2 pts) and unfavourable hospital outcome (mRS 3–6 pts) (22.9% vs. 40%, *p* =.12). Stroke survivors functionally independent on discharge were characterized by younger age (69.2 + 11.4 vs. 77.4 + 10.1 years,

TABLE 1 The clinical characteristics of the of stroke patients with and without COVID infection treated with iv-thrombolysis

Variables	With COVID infection	Without COVID infection	p-value
n(%)	22(31)	48(69)	-
Age (mean; SD) (years)	74.5(±7.9)	72.9(±12.8)	.60
Gender (male) n(%)	15(65.5)	21(42.0)	.10
NIHSS on admission (median; range) [points]	11(3–20)	6.5(2–25)	<.01
'Minor' stroke symptoms (NIHSS 1–5 pts) n(%)	2(9.1)	18(37.5)	<.01
Onset to treatment time (mean, SD) (min)	177(±60)	191(±51)	.34
'Door to needle' time (median, range) (min)	52(15–123)	61(10–170)	.12
SBP on admission (median; range) (mmHg)	148(100–230)	151(112–250)	.22
DBP on admission (median; range) (mmHg)	84(70–120)	81(52–130)	.65
Heart rate on admission (median; range) (beats/min)	85(68–134)	80(55–120)	.41
Saturation (median; range) (%)	93(60–98)	95(60–99)	.06
Pneumonia n(%)	11(47.8)	6(12)	<.01
Fever on admission n(%)	2(22.2)	4(14.5)	.45
Hyperlipidemia n(%)	9(40.9)	25(52.8)	.38
Antibiotic prior admission	2(10.5)	1(2.0)	.38
Diabetes Mellitus n(%)	8(33.3)	8(16.0)	.10
Current smoking n(%)	2(10.5)	5(10)	.70
Arterial hypertension n(%)	8(33.3)	8(16)	.09
BMI ≥26 kg/m ²	12(54.6)	18(37.5)	.18
Previous myocardial infarction n(%)	2(10.5)	4(8.0)	.74
Carotid stenosis >50% or occlusion n(%)	3(13.6)	10(20.83)	.46
Atrial fibrillation n(%)	5(20.8)	7(14)	.46
Statin therapy before stroke n(%)	4(18.2)	14(29.2)	.32
Antiplatelet therapy before stroke n(%)	5(26.3)	17(34)	.53
NOAC therapy before stroke n(%)	0	1(2)	.61
VKA therapy before stroke n(%)	0	1(2)	.61
Lacunar aetiology of stroke n(%)	8(33.3)	7(14)	.06
Old ischaemic lesions in CT on admission n(%)	7(36.8)	21(42.9)	.65
CRP (median; range) (µg/ml)	25.9(0.39–234)	2.83(0.32–9.32)	.07
Fibrinogen (mean, SD) (mg/dl)	390(±159)	341(±188)	.60
D-dimers (median; range) (ng/ml)	870(386–34300)	570(250–2296)	.03
eGFR (mean, SD) (ml/min/m ²)	72(±24)	64(±19)	.19
WBC (median; range) (10 ³ /µl)	8.2(3.4–13.8)	8.6(4.9–29.3)	.29
PLT (median; range) (10 ³ /µl)	214(127–408)	231(108–565)	.48
HGB (median; range) (g/dl)	14.1(10.8–15.6)	13.6(4.39–15.9)	.10
Glucose (median; range) (mg%)	118(77–359)	127(83–349)	.60
sICH	1(4.55)	0	.68
mRS 0–2 pts. at discharge n(%)	8(33.3)	27(56.2)	.06
Length of stay in hospital (median; range) (days)	17(1–39)	9(1–16)	<.01
Death within hospitalization n(%)	5(20.8)	6(12)	.33

Abbreviations: BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HGB, haemoglobin; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NOAC, novel oral anticoagulants; PLT, platelets; pts, points; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; sICH, symptomatic intracerebral haemorrhage; VKA, vitamin K antagonists; WBC, white blood cells.

$p < .01$, lower baseline NIHSS score (6.0, 2–12 vs. 12.0, 3–25 pts, $p < .01$), or CRP level (3.4, 0.4–269 vs. 27.5, 0.7–264 µg/ml, $p = .02$) and less frequent history of carotid stenosis (5.7 vs. 31.4%, $p = .01$)

or atrial fibrillation (5.7% vs. 28.6%, $p = .01$) than those with functional dependency or death prior discharge. They were also characterized by higher proportion of patients with lacunar stroke (31.4%

vs. 11.4%, $p = .04$) or body mass index (BMI) ≥ 26 kg/m² (57.1% vs. 28.6%, $p = .01$) and a higher baseline percentage of saturation on admission than patients with mRS 3–6 pts (96, 81–99 vs. 93, 60%–98%, $p < .01$). Initial saturation was also higher amongst stroke survivors than those who died during hospitalization (96, 81–99 vs. 90, 60%–96%, $p < .01$). No other differences between patients with and without favourable clinical outcome were found; significant correlations between CRP and saturation or NIHSS score on admission and between saturation and door-to-needle time or NIHSS score on admission in studied group existed (Table 2).

Multivariate logistic regression models showed that only baseline NIHSS, higher age and presence of carotid stenosis had an impact on patients' outcome on discharge (Table 2).

4 | DISCUSSION

The results of our study indicate that routinely performed IVT had similar short-term efficacy and safety profile in patients with COVID-19 as in patients without COVID-19. Our findings are similar to the observation of the Chinese patients from Wuhan by Zhou et al.²² However, there is not much information available about IVT in Caucasian AIS patients infected with SARS-CoV-2 to date, and previously published reports analysed small groups of patients and did not include a control groups or they were case reports.^{12–15} To the best of our knowledge, in addition to our study there is only one more based on multicentre consecutive recruitment in regional hospitals.⁸

In our AIS patients treated with IVT infected with COVID-19 ischaemic strokes were more severe than in the controls and in the infected group, there were lower percentage of the diagnosis of 'minor strokes'. Similarly, AIS were more severe in the group of patients from the UK multicentre case-control study.⁴ Pooled analysis of all consecutive patients hospitalized with laboratory-confirmed COVID-19 and AIS in 28 sites from 16 countries (The Global COVID-19 Stroke Registry) published by Ntaios et al. founded that AIS patients infected with COVID-19 had significantly greater stroke severity according to NIHSS scale and had higher risk for severe disability and death compared with patients without COVID-19.²³ Higher baseline NIHSS and higher in-hospital mortality rate in patients with stroke and COVID-19 confirmed also meta-analysis by Nannoni et al.²⁴ Amongst patients with COVID-19 treated with IVT during the first wave of pandemic in Italy, the median NIHSS score was 12 and was similar to our patients,¹⁴ and in patients from 9 stroke centres in the United States, the median NIHSS score was higher (14.5 pts.).¹⁵ In both studies, there were no control groups or no consecutive data collection. The results of many studies and meta-analyses showed that initial stroke severity is known to be the strongest predictor of functional outcome and mortality for ischaemic stroke patients.²⁵ In the group of Italian patients mentioned above, baseline NIHSS score was higher in patients who died.¹⁴ In our group of thrombolytic patients, high NIHSS score was a predictor of unfavourable outcome on discharge and inpatient mortality.

We showed that SARS-CoV-2 infection prolongs length of stay in hospital after IVT. Similar results were presented by Wang et al.⁸

TABLE 2 Multivariate logistic regression models showing factors for unfavourable hospital outcome (mRS 3–6 pts)

	Model 1		Model 2		Model 3	
	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>
COVID-19 infection	0.47 (0.09–2.6)	.39	0.21 (0.04–1.03)	.05	0.26 (0.06–1.20)	.08
Lacunar aetiology of stroke	5.35 (0.44–65.4)	.18	3.4 (0.57–20.1)	.17	2.75 (0.48–15.8)	.26
Atrial fibrillation	0.17 (0.02–1.28)	.09	0.31 (0.05–1.89)	.21	0.36 (0.06–2.39)	.29
Carotid stenosis	0.12 (0.01–1.13)	.07	0.15 (0.02–1.29)	.08	0.08 (0.01–0.71)	.02
BMI ≥ 26 kg/m ²	2.44 (0.49–12.0)	.27	1.9 (0.46–7.8)	.36	2.38 (0.62–9.25)	.21
Age (years)	1.13 (1.03–1.24)	<.01	1.1 (1.0–1.2)	<.01	1.1 (1.01–1.16)	.02
NIHSS score on admission ^a (pts)	1.5 (1.15–1.95)	<.01	-	-	-	-
CRP ^a (μg/ml)	-	-	1.0 (0.99–1.1)	.25	-	-
Saturation ^a %	-	-	-	-	0.89 (0.79–1.00)	.06

Abbreviations: BMI, body mass index; CRP, C-reactive protein; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

^aCorrelations in studied group: CRP versus Saturation: $R = -0.26$ $p = .03$; CRP versus NIHSS score on admission: $R = 0.34$ $p < .01$; Saturation versus NIHSS score: $R = -0.5$ $p < .01$

Differences in the results of routine inflammatory markers or fever on admission between patients with and without COVID-19 were not found in our cohort. However, similarly to previous authors, we found higher levels of D-dimers in patients with COVID-19. Formerly, lower platelet counts and higher level of D-dimers in the group of infected patients with AIS from Wuhan were reported.²² Also majority of the patients treated with IVT from United States described in case series by Caineiro et al had high level of D-dimers, and only 2 patients had high level of fibrinogen.¹⁵

Stroke-associated pneumonia often negatively influences the prognosis of stroke patients.¹¹ Pneumonia occurred more frequently in our patients with COVID-19.²⁶ In patients with stroke and pneumonia, the saturation decreases more often than in patients without pneumonia. Almost 20% patients with COVID-19 have hypoxic respiratory failure.²⁷

We showed that stroke survivors functionally independent on discharge were characterized a higher baseline percentage of saturation on admission than patients with mRS 3–6 pts. However, similarly to the group from Wuhan, blood oxygen saturation was significantly lower in those patients who died.²⁸

The severity of the neurological condition and the accompanying lung infection prolonged the patients' stay in the hospital, which was pointed out in previous publications.^{29,30}

First of all, this was an observational study of only four regional stroke centres and, consequently, the group of analysed patients was not large. Thus, small size of the study may mask the results and lack of statistical significance. Although the data collection was conducted in a prospective manner and included all patients admitted within the observation period. Second, the treatment results were only limited to the in-hospital period, and long-term outcome has not been assessed. However, as it has been recently reported, independence on discharge may predict 90-Day Outcome after Thrombolysis.³¹

5 | CONCLUSION

Based on our results, we suggest that patients with AIS infected COVID-19 may be safely treated with IVT in routine practise. However, when treating patients with COVID, one should strive to achieve the improvement in blood saturation, whose decrease can adversely affect the in-hospital outcome. SARS-CoV-2 infection prolongs length of stay in hospital after IVT.

CONFLICT OF INTEREST

P. Sobolewski has had lectureship fees covered by Boehringer-Ingelheim, Ever Pharma, Allergan and travel expenses to scientific conferences covered by Boehringer-Ingelheim, Ipsen and Ever Pharma and Angels Initiative. W. Broła has received speaker fees and/or served on Advisory Boards by Bayer, Biogen, Sanofi Genzyme, Merck, Novartis and Roche. He also received support for congress participation, travel and accommodation grants from Biogen, Merck, Roche and Sanofi Genzyme. G. Kozera's research

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AUTHOR CONTRIBUTIONS

PS and GK conceived the study. PS and GK wrote and distributed the protocol, designed the case report form and registration log, received the case report forms and uploaded them into the database. PS, JA, WB and MF extracted data from clinical records and completed case report forms. GK and LB performed statistical analyses. PS and GK wrote the manuscript. JA, WB, MF and LB were the members of the Core Writing Group and critically reviewed the protocol, case report form and manuscript. All authors critically reviewed the manuscript and approved the final version.

ETHICAL APPROVAL

The ethics committee approved all data of analysis (Ethics Committee of Jan Kochanowski University in Kielce).

DATA AVAILABILITY STATEMENT

Data are available on reasonable request, subject to restrictions imposed by patient confidentiality.

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