Letter

Intravenous thrombolysis for acute ischaemic stroke during COVID-19 pandemic in Wuhan, China: a multicentre, retrospective cohort study

INTRODUCTION

COVID-19 has become a global pandemic. The rapid outbreak has overwhelmed healthcare system and exhausted medical resources. There is a concern that many patients with other diseases cannot be promptly treated.

Stroke is the leading cause of death and disability worldwide. In the context of COVID-19 epidemic, stroke remains to be a medical emergency. Ultraearly intravenous thrombolysis for patients with acute ischaemic stroke (AIS) is highly time-sensitive.[1] How to balance the benefit of timely and efficacious care of the stroke patients to the risk of SARS-CoV-2 infection of healthcare professionals is the most challenging issue. Recently, there have been reports on the decreasing the Reporting of Observational Studies in Epide of cases of patients with stroke presented to the hospitals during the pandemic.[2] On the other hand, stroke is not uncommon among patients with COVID-19.[3] Here, we report intravenous thrombolytic therapy for patients with AIS at four stroke centres in the epicentre of Wuhan, Hubei during the epidemic, and compare the treatment provided during the same period in 2019.

METHODS

Study design

This is a retrospective analysis of two groups of patients with AIS received intravenous tissue plasminogen activator (tPA) during 1 January to 30 March[h] of 2019 and 2020 in four hospitals (Wuhan Union Hospital,Wuhan Puren Hospitol, Wuhan People's Hospital of Dongxihu District, People's Hospital of Three Gorges University in Yichang adjacent to Wuhan). All four hospitals continuously received emergency cases during COVID-19 epidemic. The deadline for follow-up was 30 April 2020.

Participants

All patients with AIS enrolled must meet the following criteria: (1) treated with intravenous tPA (0.9 mg/kg), (2) received either a CT or MRI of brain before/after intravenous tPA. All patients with AIS treated with intravenous tPA had real-time reverse-transcription PCR analysis (RT-PCR) from the throat swab specimens and a chest CT scan during hospitalisation and follow-up period. A confirmed case of COVID-19 was defined as a positive result on RT-PCR according to the WHO interim guideline.[4] We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Data collected and analyzed

The demographic information of all patients collected include age (<80 or ≥80 years), sex, smoke and alcohol history, medical history.

Stroke subtypes were classified into large artery atherosclerosis (LAA), cardioembolic (CE), small-artery occlusion (SAO), stroke of other determined aetiology and undetermined aetiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. Onset-to-needle time (ONT), door-to-needle time (DNT), National Institute of Health Stroke Scale (NIHSS) was recorded. Modified ranking scale (mRS) score was assessed centrally by telephone or in person visit at 1 month. Any haemorrhagic event and all-cause mortality were recorded.

Statistical analysis

Continuous variables were compared by using the t-test. Proportions for categorical variables were compared using the χ^2 test. Intracranial haemorrhage (ICH) and 1-month mRS were compared by linear regression adjusted on ONT. All statistical analyses were done with the R software V.3.3.0. The significance threshold was set at a $p<0.05$.

RESULTS

From 1 January 2020 to 30 March 2020, there were 683 patients admitted for stroke during epidemic and 1614 patients in the same period in 2019. Among them, 67 patients with AIS were treated with intravenous rtPA, and 131 patients were treated during the same period in 2019. The percentage of intravenous tPA eligible patients was 9.81% in 2020 and 8.12% in 2019. Patient's mean age was 66.55±13.01 in 2020 and 66.76±13.04 in 2019, respectively. Other demographic data were listed in table 1.

For the stroke subtype, compared with the group in 2019, more patients had CE, LAA or undetermined types of strokes in 2020(16.4% vs 10.7%, 43.3% vs 32.1%, 10.4% vs 1.5%, respectively, p=0.008).

Mean DNT was 74.24±41.71 (range 13–180) min, which was longer than that of last year (46.36±21.59 min, p<0.001). The ONT was also increased (199.34±68.95 min vs 155.12±62.46 min, p<0.001).

Before intravenous tPA, blood pressure and blood glucose level of the two groups were basically the same. The mean baselineNIHSS was 7.19±5.75 in 2020 and 5.73±4.95 in 2019 (p=0.079). There was no differences in the changes of NIHSS score after thrombolysis immediately and at 1 day, 7 days after thrombolysis. For functional outcome, mRS score at 1 month was higher in 2020 (1.75±2.06 vs .1.04±1.68, p=0.010 adjusted on ONT). The dichotomised change in mRS score also showed worseneing of functional prognosis in 2020 (p=0.020 adjusted on ONT). mRS score distribution at 1 month was shown in figure 1. There was no difference in 1-month mortality between the two cohorts (10.5% vs 4.6%, p=0.115). Of 67 patients treated in 2020, seven had an ICH; two were symptomatic. Rate of ICH was increased in 2020 (10.5% vs 1.5%, p=0.012 adjusted on ONT).

Among all 67 patients with AIS treated with intravenous tPA in 2020, 8 of 67 patients developed fever, 2 were RT-PCR+/chest CT+, and 5 of 67 were RT-PCR-/chest CT+.

DISCUSSION

In our study, there was a clear drop in the number of AIS patients treated with intravenous tPA during the epidemic. Regardless of the time from onset, there were 683 patients admitted for stroke during epidemic and 1614 patients in the same period in 2019. The percentage of intravenous tPA eligible patients between two periods are similar as 9.81% in 2020 and 8.12% in 2019. The reduction of total tPA treated patients was likely related to the lock down of the city, which made it difficult to access medical and nonmedical transportation for stroke patients from the surrounding community hospitals to the tertiary hospitals, especially if the initial stroke symptoms were mild. In addition, modifications of the environement, such as the decrease in air pollution, work stress and decreased alcohol binge drinking might have an impact on the incidence of stroke. Further studies are required to explore this hypothesis. Furthermore, the time to the administration of intravenous tPA was longer. The DNT was nearly doubled duing the epidemic. Such

Table 1 Characteristics and outcomes of AIS patients treated with intravenous TPA

	AIS patients treated with intravenous tPA		
Characteristics and outcomes	**2020 (n=67)**	**2019 (n=131)**	**P value***
Age(y), mean±SD	66.55±13.01	66.76±13.04	0.914
Age, n (%)			0.957
80	54 (80.6)	106 (80.9)	
≥80	13 (19.4)	25 (19.1)	
Sex, n (%)			0.457
Male	47 (70.1)	85 (64.9)	
Female	20 (29.9)	46 (35.1)	
Smoke history, n (%)			0.083
Yes	20 (29.9)	24 (18.3)	
No	47 (70.1)	103 (78.6)	
unknown	0 (0.0)	4 (3.1)	
Alcohol history, n (%)			0.924
Yes	14 (20.9)	26 (19.9)	
No	53 (79.1)	102 (77.9)	
Uunknown	0 (0.0)	3 (2.3)	
Comorbidities, n (%)			
Any	49 (73.1)	103 (78.6)	0.286
Cerebrovascular or cardiac disease	21 (31.3)	42 (32.1)	0.835
Hypertension	41 (61.2)	99 (75.6)	0.022
Diabetes mellitus	17 (25.4)	22 (16.8)	0.175
Classification, No. (%)			0.008
CE, n (%)	11 (16.4)	14 (10.7)	
LAA, n (%)	29 (43.3)	42 (32.1)	
SAO, n (%)	20 (29.9)	58 (44.3)	
SUE, n (%)	7 (10.4)	2 (1.5)	
Other/unknown	0 (0.0)	15 (11.5)	
Systolic-BP (mm Hg), mean±SD	150.75±22.64	147.14±19	0.266
Diastolic-BP (mm Hg), mean±SD	85.19±12.39	82.96±12.43	0.233
Blood glucose (mmol/L), mean±SD	7.4±2.56	7.34±3.65	0.888
Laboratory Findings			
Cholesterol, mmol/L	4.58±1.04	4.44±1.15	0.459
Triglycerides, mmol/L	1.51±0.65	1.83±1.52	0.065
HDL-C, mmol/L	1.17±0.36	1.21±0.5	0.557
LDL-C, mmol/L	2.91±0.94	2.68±0.87	0.134
D-dimer, mg/L	0.93±1.17	0.91±1.16	0.894
INR	1.04±0.08	1.04±0.1	0.845
APTT, s	30.99±7.9	32.72±7.67	0.155
FIB, g/L	3.15±0.75	3.41±0.99	0.047
White cell count,×10^9/L	7.61±2.16	7.32±2.56	0.416
Platelet count,×10^9/L	197.2±54.17	201.57±60.63	0.613
Percentage of thrombolysis	9.81%	8.12%	NA
DNT(min), mean±SD	74.24±41.71	46.36±21.59	<0.001
ONT(min), mean±SD	199.34±68.95	155.12±62.46	<0.001
NIHSS score			
Baseline NIHSS, mean±SD	7.19±5.75	5.73±4.95	0.079
Post-tPA NIHSS, mean±SD	4.96±5.3	3.47±4.85	0.058
1-day NIHSS, mean±SD	4.52±5.18	3.49±4.93	0.188
7-day NIHSS, mean±SD	3.44±4.77	2.45±4.31	0.166
1-month mRS, mean±SD†	1.75±2.06	1.04±1.68	0.010
1-month mRS, n (%)†			0.020
0–1	38 (56.7)	97 (74.0)	
2–6	26 (38.8)	33 (25.2)	
Unknown	3 (4.5)	1 (0.8)	
Intracranial haemorrhage, n (%)†	7 (10.5)	2 (1.5)	0.012
1-month mortality, n (%)	7 (10.5)	6 (4.6)	0.115

Data are presented as means±SD and No (%).
P values indicate differences between patients in epidemic period (2020) and non-epidemic period (2019).
p<0.05 was considered statistically significant.
*χ^2 test (categorical variable) or t-test (continuous variable) calculation.
†Compared by linear regression adjusted on ONT.
AIS, acute ischaemic stroke; APTT, activated partial thromboplastin time; BP, blood pressure; CE, cardioembolic; DNT, door-to-needle time; FIB, fibrinogen; HDL-C, High-density lipoprotein cholesterol; INR, international normalised ratio; LAA, large artery atherosclerosis; LDL-C, Low density lipoprotein cholesterol; mRS, modified ranking scale; ; NIHSS, National Institute of Health Stroke Scale; ONT, onset-to-needle time; SAO, small-artery occlusion; SUE, stroke of undetermined aetiology; tPA, tissue plasminogen activator.

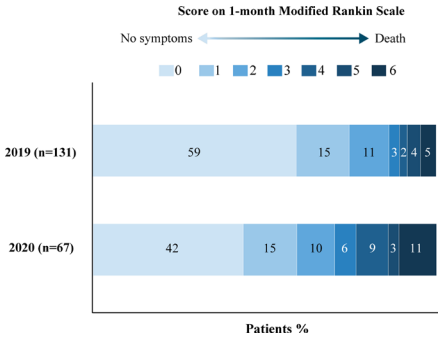

Figure 1 The distribution of 1 month modified Rankin scale score. Shown are the results of the ordinal analysis of the modified Rankin scale scores at 1 month among AIS patients treated with intravenous tissue plasminogen activator (tPA) in epidemic period (2020) and non-epidemic period (2019). Scores range from 0 to 6, with 0 indicating no neurological deficit, 1 no clinically significant disability, 2 slight disability (able to handle own affairs without assistance but unable to carry out all previous activities), 3 moderate disability requiring some help (eg, with shopping, cleaning and finances but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requiring constant nursing care and attention) and 6 death. AIS, acute ischaemic stroke.

delay could be due to: shortage of stroke team members, slow down of evaluations, practising precautionary procedures and obeying the mandatory traffic restriction.

There was no difference in 1-day NIHSS and 7-day NIHSS scores in patients treated in 2020 than in 2019. Baseline and post-tPA NIHSS scores in 2020 had a higher trend (p>0.05). Their 1-month mRS score, and rate of ICH (adjusted on the time from onset) were higher than those treated in 2019. Although there is no statistical difference, mortality doubled in 2020. The absence of significant difference may due to a limited statistical power in present study. We speculated that increased care delays, change of stroke subtypes and increased severity of disease might play a role in the unfavourable outcome.

As for the stroke subtype, patients with AIS who received intravenous tPA presented in 2020 had higher percentage of CE and LAA subtypes. It has been reported that patients with CE type of strokes had worse outcome comparing to others after intravenous tPA.[5] In our study, there were more CE and less SAO subtypes of stroke in 2020, which might partially explain the worse outcome in this cohort. We also observed an increase

in undetermined subtypes of strokes. The possibility that some of them were undetermined because of the limitation to complete the stroke work-up during their hospitalisation in the COVID-19 period.

It is worth noting that COVID-19 may cause strokes, especially in young people, and presented a challenge to workup and treat patients with AIS when cities are shut down and people are quarantined at home. During the pandemic, a survey of Asia, Africa, Europe and other countries showed that physical activity was significantly decreased during COVID-19 because of the home confinement. Furthermore, unhealthy dietary behaviours and stress on mental health,[6] improvement on air pollution,[7] and decreased alcohol binge drinking[6] might have an impact on stroke subtypes during epidemic. The present study helps to remind healthcare providers that the prevention and treatment strategy of AIS during COVID-19 may need to be tailored accordingly.

Our study indicated that the total amount of ischaemic stroke cases and thrombolysis cases during the COVID-19 epidemic has significantly decreased comparing to the same period in 2019. COVID-19 epidemic might inevitably lead to prolonged DNT. Intravenous rtPA remains to be effective even with a delay in DNT but for the short-term.

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Contributors BH was responsible for the concept and design of the study. YZ did the literature search. YZ, SC and CH acquired and interpreted data. JC analyzed the data. YZ, CH and SC wrote the manuscript. DW revised the the manuscript. HJ, YL, YX, LM, YW and LZ did the administrative, technical, or material support. CP, JH and MH did the material support.

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Competing interests None declared.

Patient consent for publication Not required.

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