MRI-guided Thrombolysis for Lenticulostriate Artery Stroke within 12 Hours after the Onset of Symptoms

jianying zhang
Fudan University Huashan Hospital Department of Nephrology https://orcid.org/0000-0001-5951-3925
Qingke Bai
The Affiliated Pudong People's Hospital of Shanghai University of Medicine and Health Sciences
Zhenguo Zhao
The Affiliated Pudong People's Hospital of Shanghai University of Medicine and Health Sciences
Yiting Mao
Huashan Hospital Fudan University Department of Neurology
Qiang Dong
Huashan Hospital Fudan University Department of Neurology
Wenjie Cao (wenjiecao@fudan.edu.cn)

Research article

Keywords: magnetic resonance imaging, lenticulostriate artery stroke, thrombolysis, time window, DWI/T2WI mismatch

Posted Date: December 5th, 2019

DOI: https://doi.org/10.21203/rs.2.18226/v1

Abstract

Background and purpose: We sought to analyze the efficacy of magnetic resonance imaging (MRI)-guided thrombolysis in patients with lenticulostriate artery stroke (LSAS) within 12 hours after onset of symptoms.

Methods: LSAS patients identified on diffusion-weighted imaging (DWI) within 12h after onset of symptoms were assigned to receive intravenous alteplase (iv-tPA). DWI/ T2-weighte imaging (T2WI) mismatch -/+ was defined as an acute ischemic lesion on DWI with/without a corresponding lesion on T2WI in the territory of lenticulostriate artery. Favorable clinical outcome was defined as modified Rankin Scale (mRS) score <2 at 90 days. Baseline demographic data and medical history were compared between outcomes.

Results: There were 160 LSAS patients received iv-tPA (104 within 4.5h) in 2008-2018 who had MRI data before treatment. DWI/T2WI-mismatch was detected in 73.1% (117/160) of patients. Lower admission systolic blood pressure (SBP) was significantly associated with 90d mRS<2 [adjusted odds ratio (OR) 0.93, 95%CI 0.88-0.99, p=0.026]. In overall patients, whether they received iv-tPA within 4.5h or not and whether they had DWI/T2WI-mismatch or not did not significantly impact the outcome. In DWI/T2WI-mismatch (+) group, hypertension negatively associated with favorable outcome (adjusted OR 0.15, 95% CI 0.04-0.59, p=0.007). In DWI/T2WI-mismatch (-) group, iv-tPA within 4.5h was an independent predictor of 90d mRS<2 (adjusted OR 7.38, 95% CI 1.25-43.48, p=0.027).

Conclusion: MRI-guided iv-tPA within 12h is safe and effective for LSAS patients. Hypertension and higher admission SBP are associated with poor outcome. In patients who have no DWI/T2WI-mismatch, iv-tPA within 4.5h independently predicts favorable outcome.

Introduction

Lenticulostriate arteries (LSA) infarctions are defined as cerebral ischemia involving the territory supplied by the deep perforating branches of the middle cerebral artery (MCA), including the regions of basal ganglia and periventricular. They represent approximately 11–13% of cerebral infarctions related to anterior circulation.[1-3] For patients with acute ischemic stroke (AIS), intravenous tissue-type plasminogen activator (iv-tPA) remains the only effective medical treatment shown to improve outcomes.[4-6] However, the efficacy of iv-tPA and the predictive factors associated with the clinical outcome in patients with lenticulostriate arteries stroke (LSAS) have not been well addressed.

Magnetic resonance imaging (MRI) based selection trials showed AIS patients who had diffusion-weighted imaging (DWI)/ fluid-attenuated inversion recovery (FLAIR) mismatch with unknown onset time were benefited from iv-tPA, most of whom were with large vessel occlusion.[7, 8] It is unclear whether DWI/ T2-weighte imaging (T2WI) mismatch, represent a salvageable tissue window, is also useful for the selection of LSAS patients for iv-tPA beyond 4.5h time window.

The aim of this study was to analyze the efficacy of MRI-guided thrombolysis in patients with LSAS within 12 hours after onset of symptoms and to analyze the predictive factors associated with the clinical outcome of iv-tPA in acute LSAS patients who were with or without DWI/T2WI mismatch in 12h after onset of symptom.

Methods

We performed a retrospective observational cohort study in patients with LSAS based on a single stroke center hospital database, analyzing data from July 2008 to April 2018. This study was approved by the hospital ethical committee. Written informed consent was obtained from all patients or their legal representatives.

Detection of neuroimaging evidence of LSA infarction within 12h of acute stroke symptom onset was mandatory for inclusion in this study. This evidence comprised a hyperintensity on diffusion-weighted sequences on MRI, with LSA region of basal ganglia, paraventricular and corresponding with the clinical deficit (Figure 1). We excluded patients with imaging evidence of extracranial or intracranial carotid stenosis, proximal vessel occlusion, clot retrieval, or with contraindications to iv-tPA.

Noncontrast CT and MRI, including DWI, T2WI and MRA, were performed before thrombolysis. The fast MRI scan required 5-10 minutes to complete, and an additional 10 minutes were used to transfer/position the patient and to process the MRI. Necessary lab tests, informed consent, and drug preparation for thrombolytic therapy were completed in conjunction with the fast MRI examination to shorten the time duration before administration of thrombolytic therapy.

MRI were retrospectively reviewed by using standard PACS software, allowing reviewers to freely window and view the images. DWI/T2WI-mismatch -/+ was defined as an acute ischemic lesion on DWI with/without a corresponding acute ischemic lesion on T2WI in the territory of LSA. DWI/T2WI mismatch was first independently assessed by a consultant neurologist and a senior stroke neurologist, blinded to clinical outcomes, and then reached consensus. As shown in Figure 1, MR images of LSAS patients with mismatch or no mismatch of DWI-T2WI within 12h after onset of symptom are provided.

Patients' characteristics, baseline National Institutes of Health Stroke Scale (NIHSS) score and clinical outcomes were obtained from data base. Favorable clinical outcome was defined as modified Rankin Scale (mRS) score <2 at 90 days.

Statistical analyses were performed by using the Statistical Package for the Social Sciences, Version 24 (IBM, Armonk, New York). P value<0.05 was considered statistically significant. Patients were dichotomized by using the 90-day mRS score into favorable (mRS score, <2) versus poor (mRS score, 2–6) outcome, in total and then in each DWI/T2WI mismatch subgroup. Differences in patient characteristics between outcomes were tested by the Chi-square test for categoric and the Mann-Whitney U test for continuous values. Multivariate binary logistic regression (including variables with P values<0.1) was used to assess the independent association of significances with 90-day outcome.

Data Availability Statement

Anonymized data will be shared by request from any quailified investigator.

Results

In 2008-2018, 160 LSAS patients within 12h of symptom onset who received MRI before iv-tPA were included, median age was 59 years (range from 26 to 80), 31.3% (50/160) were women, and median baseline NIHSS score was 7 (interquartile range [IQR], 5–10.75). Sixty-five percent (104/160) of patients were treated within 4.5h. DWI/T2WI mismatch was detected in 73.1% (117/160) of patients. Favorable outcome (90d-mRS 0-1) occurred in 73.1% (117/160) of patients. Symptomatic bleeding complications were not observed in any patient.

Clinical characteristics in total and stratified by 90-day clinical outcome are listed in Table 1. Lower present of hypertension (62.4%, p=0.023), lower baseline NIHSS score (median 6, p<0.001) and lower admission systolic blood pressure (SBP) (median154mmHg, p=0.014) were significantly seen in favorable outcome (mRS 0-1) than in poor outcome (mRS 2-6) (81.4%, 10, 160mmHg, respectively). No significant difference was seen in percent of DWI/T2WI mismatch (p=0.823), percent of treatment within 4.5h (p=0.722) and onset to treatment time (OTT) (p=0.463).

In patients with DWI/T2WI mismatch, percent of hypertension (58.5%, p=0.003) and NIHSS score (median 6, p<0.001) remained lower in group of mRS 0-1 than in group of mRS 2-6 (87.5% and 7, respectively). In patients who had no DWI/T2WI mismatch, median OTT was 200 mins (mRS 0-1) versus 270 mins (mRS 2-6) (p=0.028) and percent of iv-tPA within 4.5h was 75% (mRS 0-1) versus 36.4% (mRS 2-6) (p=0.031), which were the only two significant differences between outcomes (Table 2).

In multivariate analysis, admission SBP independently associated with favorable outcome in overall patients with an adjusted odds ratio (OR) of 0.93 (95%CI 0.88-0.99, p=0.026). In DWI/T2WI-mismatch (+) group, hypertension negatively associated with favorable outcome with an adjusted OR of 0.15 (95%CI 0.04-0.59, p=0.007). In DWI/T2WI-mismatch (-) group, iv-tPA within 4.5h independently predicted favorable outcome with an adjusted OR of 7.38 (95%CI 1.25-43.48, p=0.027). (Table 3)

Clinical characteristics and outcome stratified by 4.5h time window of iv-tPA and DWI/T2WI mismatch were listed in Table 4. No difference was found between patients received iv-tPA <4.5h and 4.5h-12h, or patients had DWI/T2WI mismatch and no DWI/T2WI mismatch.

Discussion

Our study suggests that fast MRI-guided intravenous thrombolysis is safe and effective in LSAS patients within 12 hours of symptom onset. No history of hypertension and lower admission SBP are two protective factors for patients to reach the good functional outcome. There was no significant difference in the outcome between treatment within 4.5h and 4.5h-12h, or DWI/T2WI mismatch and no DWI/T2WI mismatch patients. However, in patients who had no DWI/T2WI mismatch, iv-tPA within 4.5h time window was an important factor which brings more benefits.

LSAS, which occurs in a phylogenetically ancient part of the brain, the “vascular centrencephalon”, where short straight arteries with few branches transmit high blood pressure straight through to end-arterioles. Hypertension can accelerate neurological deficits in LSAS for the impaired auto-regulation of cerebral blood flow (CBF) and blood pressure (BP) gradients in lenticulostriate arteries. During acute ischemia, early activation of sympathetic adrenomedullary pathway and altered cerebral autoregulation within ischemic penumbra,[9] systemically elevated BP levels and increased BP variability (BPV are associated with compromised cerebral perfusion,[10,11] increased baseline thrombus burden and impaired endogenous capacity for fibrinolysis,[12] that likely predispose to poor functional outcomes in acute ischemic stroke (AIS) patients treated with IVT.

Our findings are in line with European Cooperative Acute Stroke Study (ECASS)and[13] ECASSII[14] documenting poor outcomes in AIS patients with elevated baseline SBP levels. No history of hypertension and lower SBP on admission may protect against brain ischemia through increased arterial compliance, normalization of

cerebrovascular auto-regulation, reduced CBF decrease during ischemia at the periphery of the lesion, and enhancement of collateral circulation during hypoperfusion.

Previous studies rarely focused on the validity of iv-tPA in LSAS because of the unpopular usage of MR in emergency, which make it difficult to detect the acute LSAS at admission. WAKE-UP trial provide evidence of benefit from iv-tPA among patients with acute stroke and an unknown time of symptom onset who had mismatch between MRI findings on DWI and FLAIR.[8] The results of secondary post hoc analysis suggest iv-tPA is safe and improves functional outcome in patients with lacunar infarct with a similar outcome as in patients with other stroke subtypes. [15] In the present study, we also identified LSAS patients by using emergency MR and found those within 4.5h-12h after onset of symptoms who have DWI/T2WI-mismatch may equally benefit from iv-tPA, compared with those within 4.5h.In patients with no DWI/T2WI-mismatch, iv-tPA within 4.5h was an independent predict factor associated with favorable outcome. That phenomenon suggests “DWI/T2WI-mismatch positive” is a radiological mark of LSAS patients who are appropriate for iv-tPA within 12h time window, however, patients with no DWI/T2WI-mismatch should not be excluded for iv-tPA within 4.5h time window.

In this study, we used T2WI instead of FLAIR because performing T2W images (50s) were about 100s faster than performing FLAIR.[16] Although cytotoxic edema on T2WI is less clearly indicated due to the increasing artefact and partial volume effect from cerebral spinal fluid (CSF) than FLAIR,[17] LSA infarctions are away from CSF and could be weakly influenced by those limitations. Meanwhile, the faster image formation of T2WI can save the time of OTT and reduce the impact of motion in less cooperative patients during the process of MR examination.

Results of this study are limited by the retrospective nature of analysis and small number of patients from a single center. Whether iv-tPA between 4.5-12h is superior than other therapy was not analyzed in our study due to the absence of randomization for different treatments.

Conclusions

MRI-guided iv-tPA within 12h is safe and effective for LSAS patients. Hypertension and higher admission SBP are associated with poor outcome. In patients who have no DWI/T2WI-mismatch, iv-tPA within 4.5h independently predicts favorable outcome.

Declarations

Disclosures

None.

Acknowledgement

This study was funded by Key Discipline Group Construction Project of Pudong Health Bureau of Shanghai (No. PWZxq2017-02), the Featured Clinical Discipline Project of Shanghai Pudong (No. PWYst2018-01) and the National Nature Science Foundation of China (No. 81801290).

References

1. Bladin PF, Berkovic SF. Striatocapsular infarction: Large infarcts in the lenticulostriate arterial territory. *Neurology*. 1984;34:1423-1430
2. Moulin T, Tatu L, Vuillier F, Berger E, Chavot D, Rumbach L. Role of a stroke data bank in evaluating cerebral infarction subtypes: Patterns and outcome of 1,776 consecutive patients from the besancon stroke registry. *Cerebrovasc Dis*. 2000;10:261-271
3. Ghika J, Bogousslavsky J, Regli F. Infarcts in the territory of the deep perforators from the carotid system. *Neurology*. 1989;39:507-512
4. National Institute of Neurological D, Stroke rt PASSG. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581-1587
5. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317-1329
6. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2018;49:e46-e110
7. Schwamm LH, Wu O, Song SS, Latour LL, Ford AL, Hsia AW, et al. Intravenous thrombolysis in unwitnessed stroke onset: Mr witness trial results. *Ann Neurol*. 2018;83:980-993
8. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, et al. Mri-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med*. 2018;379:611-622
9. Chamorro A, Amaro S, Vargas M, Obach V, Cervera A, Gomez-Choco M, et al. Catecholamines, infection, and death in acute ischemic stroke. *Journal of the neurological sciences*. 2007;252:29-35
10. Rusanen H, Saarinen JT, Sillanpää N. The association of blood pressure and collateral circulation in hyperacute ischemic stroke patients treated with intravenous thrombolysis. *Cerebrovasc Dis*. 2015;39:130-137
11. Kellert L, Hametner C, Ahmed N, Rauch G, MacLeod MJ, Perini F, et al. Reciprocal Interaction of 24-Hour Blood Pressure Variability and Systolic Blood Pressure on Outcome in Stroke Thrombolysis. *Stroke.* 2017;48:1827-1834
12. Tsivgoulis G, Saqqur M, Sharma VK, Lao AY, Hill MD, Alexandrov AV, et al. Association of pretreatment blood pressure with tissue plasminogen activator-induced arterial recanalization in acute ischemic stroke. *Stroke*. 2007;38:961-966
13. Yong M, Diener HC, Kaste M, Mau J. Characteristics of blood pressure profiles as predictors of long-term outcome after acute ischemic stroke. *Stroke*. 2005;36:2619-2625
14. Yong M, Kaste M. Association of characteristics of blood pressure profiles and stroke outcomes in the ecass-ii trial. *Stroke*. 2008;39:366-372
15. Barow E, Boutitie F, Cheng B, Cho TH, Ebinger M, Endres M, et al. Functional Outcome of Intravenous Thrombolysis in Patients With Lacunar Infarcts in the WAKE-UP Trial. *JAMA Neurol.* 2019.
16. Bai QK, Zhao ZG, Lu LJ, Shen J, Zhang JY, Sui HJ, et al. Treating ischaemic stroke with intravenous tpa beyond 4.5 hours under the guidance of a mri dwi/t2wi mismatch was safe and effective. *Stroke Vasc Neurol*. 2019;4:8-13
17. Noguchi K, Ogawa T, Inugami A, Fujita H, Hatazawa J, Shimosegawa E, et al. Mri of acute cerebral infarction: A comparison of flair and t2-weighted fast spin-echo imaging. *Neuroradiology*. 1997;39:406-410

Tables

1.Comparisons of Baseline and Clinical Characteristics of Patients Between Outcomes

ıcteristics	Total (n=160)	mRS 0-1 (n=117) n=117	mRS 2-6 (n=43)	*P* Value
(range)	59 (26-80	59 (26-80)	61 (36-78)	0.63
)	50 (31.3)	36 (30.8)	14 (32.6)	0.829
%)	69 (43.1)	50 (42.7)	19 (44.2)	0.87
ı, n (%)	108 (67.5)	73 (62.4)	35 (81.4)	0.023
%)	21 (13.1)	5 (12.8)	6 (13.9)	0.851
ion, n (%)	5 (3.1)	5 (4.3)	0	0.325
ke, n (%)	4 (2.5)	4 (3.4)	0	0.575
edian (IQR)	212.5 (152.5, 303.75)	210 (152, 300)	230 (167.5, 307.5)	0.463
, median (IQR)	7 (5, 10.75)	6 (5, 8)	10 (7, 14)	<0.001
ıcose, mmol/L, median (IQR)	6.65 (5.78, 8.19)	5 (4.6, 6)	5.4 (5, 6.45)	0.762
median (IQR)	157 (140, 169	154 (140, 168)	160 (148, 179)	0.014
median (IQR)	90.5 (82, 100	90 (80, 99.5)	93 (85, 100)	0.283
4.5h, n (%)	104 (65)	77 (65.8)	27 (62.8)	0.722
ismatch, n (%)	117 (73.1)	85 (72.6)	32 (74.4)	0.823

ied Rankin Scale; IQR, indicates interquartile range; OTT, onset to treatment time; NIHSS, National Institutes of Health St

systolic blood pressure; DBP, diastolic blood pressure; DWI, diffusion-weighted imaging; T2WI, T2-weighte imaging

Table 2.Baseline and Clinical Characteristics of Patients With or Without DWI/T2WI-mismatch Subdivided With Outcomes

	DWI/T2WI-mismatch (+)			DWI/T2WI-mismatch (-)		
characteristics	mRS 0-1 (n=85)	mRS 2-6 (n=32)	*P* Value	mRS 0-1 (n=32)	mRS 2-6 (n=11)	*P* Value
dian (range)	59 (26-80)	59 (36-77)	0.949	60 (42-78)	64 (56-69)	0.403
n (%)	22 (25.9)	10 (31.3)	0.562	14 (43.8)	4 (36.4)	0.736
, n (%)	40 (47.1)	14 (43.8)	0.749	10 (31.3)	5 (45.4)	0.394
nsion, n (%)	50 (58.8)	28 (87.5)	0.004	23 (71.9)	7 (63.6)	0.709
, n (%)	10 (11.8)	3 (9.4)	1.000	5 (15.6)	3 (27.3)	0.401
rillation, n (%)	3 (3.5)	0	0.561	2 (6.3)	0	1.000
stroke, n (%)	2 (2.4)	0	1.000	2 (6.3)	0	1.000
utic time window, n (%)	53 (62.4)	23 (71.9)	0.336	24 (75)	4 (36.4)	0.031
n, median (IQR)	215 (148.5, 319)	210 (152.5, 297.5)	0.755	200 (162.5, 264.25)	270 (205, 360)	0.028
median (IQR)	6 (5, 8)	11 (7, 14.75)	<0.001	7 (6, 9)	9 (7, 13)	0.097
n glucose, mmol/L, IQR)	6.62 (5.39, 8.52)	6.34 (5.76, 7.35)	0.978	7.48 (5.85, 9.91)	6.34 (6.2, 7.11)	0.721
nHg, median (IQR)	153 (139, 167)	160 (146.25, 177)	0.057	158.5 (143, 169.75)	163 (160, 182)	0.082
nHg, median (IQR)	90 (80, 99)	93.5 (84.25, 100)	0.361	90 (80, 100)	92 (88, 100)	0.612

Table 3.Predictors of Favorable Outcome in Total Patients, Patients With DWI/T2WI-mismatch and Patients Without DWI/T2WI-mismatch

	Multivariate analysis	
	OR (95% CI)	*P* Value
In total patients (including history of hypertension, NIHSS, and SBP)		
Hypertension	0.43 (0.07-2.43)	0.34
NIHSS	0.8 (0.62-1.02)	0.074
SBP	0.93 (0.88-0.99)	0.026
In patients with DWI/T2WI-mismatch (including history of hypertension, NIHSS and SBP)		
Hypertension	0.15 (0.04-0.59)	0.007
NIHSS	0.72 (0.62-0.83)	<0.001
SBP	0.98 (0.95-1)	0.153
In patients with no DWI/T2WI-mismatch (including iv-tPA within 4.5h*, NIHSS and SBP)		
iv-tPA within 4.5h	7.38 (1.25-43.48)	0.027
NIHSS	0.75 (0.58-0.98)	0.036
SBP	0.93 (0.87-1)	0.054

*OTT was excluded because it represented the same characteristic of time as “iv-tPA within 4.5h”

Table 4.Comparisons of Clinical Characteristics and Outcomes of Patients between iv-tPA Within 4.5h and 4.5h-12h and DWI/T2WI-mismatch (+) and DWI/T2WI-mismatch (-)

cal characteristics	iv-tPA within 4.5h (n=104)	iv-tPA between 4.5h and 12h (n=56)	*P* Value	DWI/T2WI-mismatch (+) (n=117)	DWI/T2WI-mismatch (-) (n=43)	*P* Value
years, (range)	59.5 (26, 78)	59 (32, 80)	0.776	59 (26, 80)	61 (52, 66)	0.41
ıale, n (%)	32 (30.8)	18 (32.1)	0.858	32 (27.4)	18 (41.9)	0.079
ɔking, n (%)	49 (47.1)	20 (35.7)	0.165	54 (46.2)	15 (34.9)	0.202
ertension, n (%)	71 (68.3)	37 (66.1)	0.777	78 (66.7)	30 (69.8)	0.71
ɔetes, n (%)	13 (12.5)	8 (14.3)	0.75	13 (11.1)	8 (18.6)	0.213
ıl fibrillation, n (%)	4 (3.8)	1 (1.8)	0.658	3 (2.6)	2 (4.7)	0.611
ʏious stroke, n (%)	3 (2.9)	1 (1.8)	1.000	2 (1.7)	2 (4.7)	0.293
', min, median (IQR)				215 (150, 316.5	210 (175, 290)	0.817
SS, median (IQR)	7 (5, 11)	7 (5, 8.75)	0.467	7 (5, 11)	7 (6, 10)	0.524
ıission glucose, ɔl/L, median (IQR)	6.67 (5.5, 8.39)	6.43 (5.9, 7.9)	0.628	6.61 (5.59, 8.08)	6.8 (5.91, 9.42)	0.095
, mmHg, median (IQR)	160 (140.5, 170)	153 (140, 169)	0.334	156 (140, 169)	160 (147, 170)	0.123
', mmHg, median (IQR)	92 (80, 100)	90 (84, 97)	0.438	91 (81, 99.5)	90 (82, 100)	0.968
time window, n (%)				79 (65)	28 (65.1)	0.985
natch, n (%)	76 (73.1)	41 (73.2)	0.985			

;			0.102			0.857
0	59 (56.7)	25 (44.6)		62 (53)	22 (51.2)	
1	18 (17.3)	15 (26.8)		23 (19.7)	10 (23.3)	
2	14 (13.5)	12 (21.4)		18 (15.4)	8 (18.6)	
3	13 (12.5)	3 (5.4)		13 (11.1)	3 (7)	
4	0	1 (1.8)		1 (0.9)	0	
5	0	0		0	0	
6	0	0		0	0	