Clinical Article
J Korean Neurosurg Soc 66 (2) : 144-154, 2023
https://doi.org/10.3340/jkns.2022.0120
pISSN 2005-3711 eISSN 1598-7876

Recanalization Rate and Clinical Outcomes of Intravenous Tissue Plasminogen Activator Administration for Large Vessel Occlusion Stroke Patients

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Objective : Stroke caused from large vessel occlusion (LVO) has emerged as the most common stroke subtype worldwide. Intravenous tissue plasminogen activator administration (IV-tPA) and additional intraarterial thrombectomy (IA-Tx) is regarded as standard treatment. In this study, the authors try to find the early recanalization rate of IV-tPA in LVO stroke patients.

Methods : Total 300 patients undertook IA-Tx with confirmed anterior circulation LVO, were analyzed retrospectively. Brain computed tomography angiography (CTA) was the initial imaging study and acute stroke magnetic resonance angiography (MRA) followed after finished IV-tPA. Early recanalization rate was evaluated by acute stroke MRA within 2 hours after the IV-tPA. In 167 patients undertook IV-tPA only and 133 non-recanalized patients by IV-tPA, additional IA-Tx tried (IV-tPA + IA-Tx group). And 131 patients, non-recanalized by IV-tPA (IV-tPA group) additional IA-Tx recommend and tried according to the patient condition and compliance.

Results : Early recanalization rate of LVO after IV-tPA was 12.0% (36/300). In recanalized patients, favorable outcome (modified Rankin Scale, 0–2) was 69.4% (25/36) while it was 32.1% (42/131, $p<0.001$) in non-recanalized patients. Among 133 patients, non-recanalized after intravenous recombinant tissue plasminogen activator and undertook additional IA-Tx, the clinical outcome was better than not undertaken additional IA-Tx (favorable outcome was 42.9% vs. 32.1%, $p=0.046$). Analysis according to the perfusion/diffusion (P/D)-mismatching or not, in patient with IV-tPA with IA-Tx (133 patients), favorable outcome was higher in P/D-mismatching patient (52/104; 50.0%) than P/D-matching patients (5/29; 17.2%; $p=0.001$). Which treatment tired, P/D-mismatching was favored in clinical outcome (iv-tPA only, $p=0.008$ and IV-tPA with IA-Tx, $p=0.001$).

Conclusion : The P/D-mismatching influences on the recanalization and clinical outcomes of IV-tPA and IA-Tx. The authors would like to propose that we had better prepare IA-Tx when LVO is diagnosed on initial diagnostic imaging. Furthermore, if the patient shows P/D-mismatching on MRA after IV-tPA, additional IA-Tx improves treatment results and lessen the futile recanalization.

Key Words : Intraarterial thrombectomy · Larger vessel occlusion · Perfusion/diffusion mismatching · Recanalization rate · Tissue plasminogen activator.

• Received : May 10, 2022 • Revised : July 19, 2022 • Accepted : September 17, 2022
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INTRODUCTION

Stroke from large vessel occlusion (LVO) has emerged as the most common stroke subtype worldwide, especially in patients of Asian, Hispanic, and African origins[7,11,12,18,40]. A review of previous papers suggests that medium-sized intracranial arteries and their major branches, anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), posterior inferior cerebella artery (PICA), anterior inferior cerebella artery (AICA), superior cerebella artery (SCA), and the distal basilar artery are most often affected[12]. Some papers report LVO accounts for more than one-third of cases of acute anterior circulation stroke, and about one-third of such major artery occlusion patients were recanalized after intravenous tissue plasminogen activator administration (IV-tPA)[5,18,39].

LVO causes large hemispheric infarct (up to 10% of all ischemic strokes) and is associated with high mortality (case fatality rate of approximately 80%) and morbidity[6,18,21,22,30].

The principal treatment for ischemic stroke is reperfusion of the ischemic penumbra tissue in order to salvage the threatened, but potentially viable brain tissues[4,15,17,28,29,35,44]. IV-tPA within 4.5 hours after the onset of stroke is currently a standard treatment modality for acute ischemic stroke patients[20], and additional intra-arterial thrombolysis with a stent retrieval device is an accepted treatment modality after the results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial[5,10,17,19,25,41].

Early recanalization of the occluded artery is considered a prognostic factor for good outcome[3,34,39,40,45]. Reperfusion up to 6 hours after the onset of stroke symptoms is beneficial in most patients, and studies performed with multimodal magnetic resonance or computed tomography imaging indicate that some patients will still harbor a substantial residual penumbra beyond 6 hours and would benefit from reperfusion[2,3,34,39,40]. But, when considering additional intraarterial thrombectomy (IA-Tx) in the case of failed recanalization after IV-tPA, we should check the recanalization within 3 hours after IV-tPA for the next treatment step[20,35].

Bridging therapy, combined intravenous and intra-arterial therapy can safely produce an 80–90% recanalization rate[5,10,14,17,19,25-27,41]. Many papers reported about the low recanalization rate after IV-tPA in large artery occlusion patients[5,20,35], but the rate is inconsistent according to the study designs and diagnostic imaging methods[11-13,18]. We attempted this analysis to clarify the early recanalization rate of IV-tPA and IA-Tx in LVO patients. In our treatment protocol, all patients undertook magnetic resonance angiography (MRA) that included perfusion, diffusion and angiography imaging. The authors retrospectively analyzed the significance of P/D-mismatching on treatment results of intravenous recombinant tissue plasminogen activator (IV-rtPA) and IA-Tx.

MATERIALS AND METHODS

The treatment protocol was approved by the Institutional Review Board of Eunpyeong St. Mary's Hospital (UC11RISI0187 and PC17RES10028) (Fig. 1). All patients or their representatives provided informed written consent and were made aware that they were going to receive an additional treatment after IV-tPA therapy.

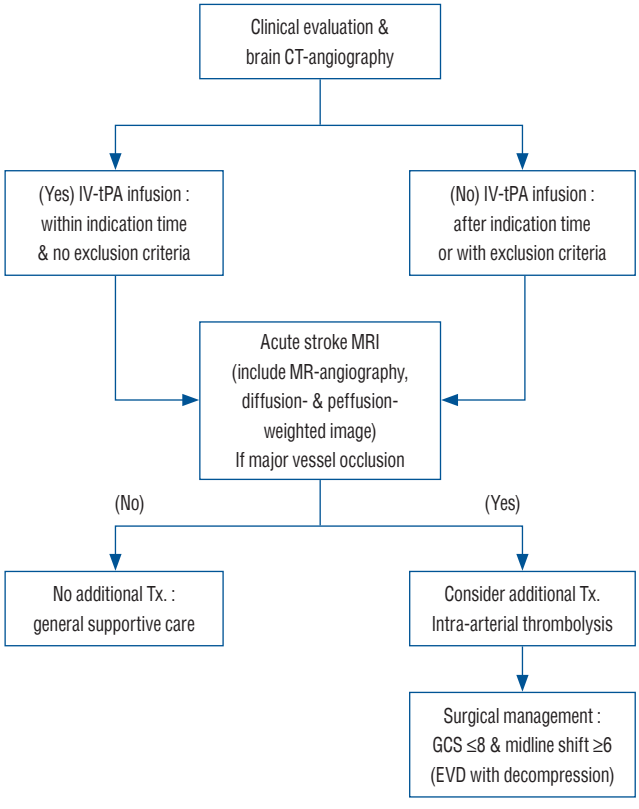

Fig. 1. Flow diagram of treatment protocol. CTA : computed tomography angiography, IV-tPA : intravenous tissue plasminogen activator administration, MRI : magnetic resonance imaging, Tx. : treatment, GCS : Glasgow coma scale, EVD : extraventriular drainage.

Table 1. Demography and clinical outcomes of the 300 patients with anterior circulation LVO, according to the treatments

	IV-tPA only	IV-tPA & IA-Tx	Total statistic value	*p*-value
Patients No.	167	133	300	
Age (years)	67.4±11.5	64.0±15.0	65.9±13.3	0.046
Median	69 (39–89)	65 (19–98)	68 (19–98)	
Male sex	101 (60.5)	88 (66.2)	189 (63.0)	0.186
NIHSS score	13.9±5.9	14.7±6.4	14.2±6.1	0.284
Median	13 (4–32)	14 (4–36)	14 (4–36)	
Heart disease	38 (29.9)	16 (12.0)	54 (18.1)	0.011
Atrial fibrillation	72 (43.1)	42 (31.6)	114 (38.0)	0.027
Hypertension	99 (59.3)	74 (55.6)	173 (57.7)	0.303
Dyslipidemia	49 (32.9)	31 (23.8)	80 (28.7)	0.062
Diabetic mellitus	50 (30.1)	43 (32.3)	93 (31.1)	0.387
Smoking	42 (25.3)	31 (23.7)	73 (24.6)	0.426
Occlusion vessel site				
ACA	5 (3.0)		5 (1.7)	
MCA Lt.	45 (26.9)	36 (27.1)	81 (27.0)	
MCA Rt.	66 (39.5)	49 (36.8)	115 (38.3)	
ICA Lt.	27 (16.2)	23 (17.3)	50 (16.7)	
ICA Rt.	24 (14.4)	25 (18.8)	49 (16.3)	
Time to tPA (minutes)	128.4±51.5	123.6±55.8	126.3±53.4	0.214
Median	119 (45–270)	110 (45–270)	120 (45–270)	
Time to femoral artery puncture (hours)		5.4±1.7 (5.0)		
Median		5 (1–11)		
Recanalized after IV-tPA	36 (12.0)			
Recanalized after IA-Tx		113 (87.3)		
Neurologic outcomes				
mRS				
0	23 (13.8)	19 (14.3)	42 (14.0)	
1	22 (13.2)	19 (14.3)	41 (13.7)	
2	22 (13.2)	21 (15.8)	43 (14.3)	
Favorable	67 (40.1)	59 (44.4)	126 (41.3)	0.068
3	35 (21.0)	27 (20.3)	62 (20.7)	
4	14 (8.4)	21 (15.8)	35 (11.7)	
5	16 (9.6)	16 (12.0)	32 (10.7)	
Unfavorable	65 (38.9)	64 (49.6)	129 (43.7)	
6	35 (21.0)	10 (7.5)	45 (15.0)	0.001
Sx-Hx	13 (7.8)	22 (16.5)	35 (11.7)	0.010
Reperfusion injury	17 (13.0)	63 (47.4)	86 (28.7)	<0.001
Decompressive surgery	18 (10.8)	16 (12.0)	34 (11.3)	0.436
P/D-mismatching	108 (64.7)	104 (78.2)	212 (70.7)	0.008

Values are presented as mean±standard deviation, number (range), or number (%). LVO : large vessel occlusion, IV-tPA : intravenous tissue plasminogen activator administration, IA-Tx : intra-arterial thrombolytic therapy, NIHSS : National Institutes of Health Stroke Scale, ACA : anterior cerebral artery, MCA : middle cerebral artery, Lt. : left, Rt. : right, ICA : internal cerebral artery, mRS : modified Rankin Scale, Sx-Hx : symptomatic hemorrhage, P/D : perfusion/diffusion

 https://doi.org/10.3340/jkns.2022.0120

Patient and neurologic examination

Between January 2010 and June 2021, 535 patients arrived within the standard treatment time from the stroke onset and were treated with IV-tPA. We excluded 235 patients because of

Table 2. Clinical characteristic and outcomes of the IV-rtPA treated, 167 anterior circulation large vessel occlusion patients

	Recanal after IV-tPA	Not recanal after IV-tPA	Total statistic value	*p*-value
Patients No.	36 (12.0)	131 (78.4)	167	
Age (years)	64.9±11.6	68.1±11.4	67.4±11.5	0.766
Median	68 (42–82)	70 (39–89)	69 (39–89)	
Male sex	24 (66.7)	77 (58.8)	101 (60.5)	0.255
NIHSS score	12.6±6.4	14.2±5.7	13.9±5.9	0.761
Median	11 (4–32)	14 (4–32)	13 (4–32)	
Heart disease	4 (11.1)	34 (26.2)	38 (22.9)	0.041
Atrial fibrillation	13 (36.1)	59 (45.0)	72 (43.1)	0.222
Hypertension	15 (41.7)	84 (64.1)	99 (59.3)	0.013
Dyslipidemia	11 (35.5)	38 (32.2)	49 (32.9)	0.442
Diabetic mellitus	11 (30.6)	39 (30.0)	50 (30.1)	0.550
Smoking	8 (22.2)	34 (26.2)	42 (25.3)	0.404
Alcohol	11 (30.6)	39 (30.7)	50 (30.7)	0.580
Occlusion vessel site				
ACA	0 (0.0)	5 (3.8)	5 (3.0)	
MCA Lt.	11 (30.6)	34 (26.0)	45 (26.9)	
MCA Rt.	23 (63.9)	43 (32.8)	66 (39.5)	
ICA Lt.	0 (0.0)	27 (20.6)	27 (16.2)	
ICA Rt.	2 (5.6)	22 (16.8)	24 (14.4)	
Time to tPA (minutes)	121.7±57.0	130.0±50.0	128.4±51.5	0.619
Median	120 (45–270)	120 (45–270)	119 (45–270)	
Neurologic outcomes				
mRS				
0	12 (33.3)	11 (8.4)	23 (13.8)	
1	8 (22.2)	14 (10.7)	22 (13.2)	
2	5 (13.9)	17 (13.0)	22 (13.2)	
Favorable	25 (69.4)	42 (32.1)	67 (40.1)	<0.001
3	6 (16.7)	29 (22.1)	35 (21.0)	
4	1 (2.8)	13 (9.9)	14 (8.4)	
5		16 (12.2)	16 (9.6)	
Unfavorable	7 (19.5)	58 (44.3)	65 (38.9)	
6	4 (11.1)	31 (23.7)	35 (21.0)	0.075
Sx-Hx	3 (8.3)	10 (7.6)	13 (7.8)	0.561
Decompressive surgery	2 (5.6)	16 (12.2)	18 (10.8)	0.206
P/D-mismatching	29 (80.6)	79 (60.3)	108 (64.7)	0.018

Values are presented as mean±standard deviation, number (range), or number (%). IV-rtPA : intravenous recombinant tissue plasminogen activator, IV-tPA : intravenous tissue plasminogen activator administration, IA-Tx : intra-arterial thrombolytic therapy, NIHSS : National Institutes of Health Stroke Scale, ACA : anterior cerebral artery, MCA : middle cerebral artery, Lt. : left, Rt. : right, ICA : internal cerebral artery, mRS : modified Rankin Scale, Sx-Hx : symptomatic hemorrhage, P/D : perfusion/diffusion

early transfer to another hospital (16 patients), Moyamoya disease (three patients; one of these patients was transferred to another hospital), Todd's paralysis after seizure attack (one patient), posterior circulation strokes (42 patients), tried wrong injection (one patient with subarachnoid hemorrhage) small vessel disease (126 patients). Finally, the data on anterior circulation major vessel occlusion were analyzed for 300 patients (Table 1).

All patients underwent clinical assessment (including determination of the National Institutes of Health Stroke Scale [NIHSS] score) at baseline, after 24 hours, and at 5 to 7 days, or at discharge, if earlier. A single experienced trial investigating physician, who was unaware of the treatment assignments, conducted the follow-up neurologic evaluation using the modified Rankin Scale (mRS) scale at 90±5 days when the patients visited our out-patient clinic department (Tables 1 and 2).

Neuroradiological evaluations

The neuro-radiological results were analyzed retrospectively by neuro-radiologists who had not participated in acute patient management. All patients underwent brain computed tomography angiography (CTA) (Somatom Definition AS; Siemens Medical Systems, Munich, Germany) as the initial diagnostic imaging study. If there was no flow or severe stenosis at the clinically suspected affected artery, the patient was diagnosed with LVO. Three hundred had anterior circulation LVO; their demographics are listed in Table 1. Stroke protocol magnetic resonance imaging (MRI) was performed immediately following the completion of IV-tPA administration. Obtained images included T1-weighted sagittal scans, T2-weighted turbo-gradient, spin echo/echo-planar DWI, and PWI. On the acute stroke MRI, the absence of flow signal after the suspected offending lesion as determined by the initial CTA, was correlated with non-recanalization after IV-tPA treatment. Recanalization was defined as flow that could be traced on an MRA image. Early recanalization was defined within 3 hours after IV-rtPA administration because this time window increases the chance of additional IA-Tx and is associated with

Table 3. Patient characteristics and clinical outcomes according to the treatment methods and P/D-mismatching or not

	IV-tPA (n=167)			IV-tPA & IA-Tx (n=133)		
	Mismatched	Matched	*p*-value	Mismatched	Matched	*p*-value
Patients No.	108	59		104	29	
Age (years)	67.4±11.8	67.7±11.0	0.827	64.6±15.4	61.8±13.4	0.538
Median	69 (39–89)	69 (46–86)		65 (19–98)	62 (24–82)	
Male sex	62 (57.4)	39 (66.1)	0.176	66 (63.5)	22 (75.9)	0.152
NIHSS score	12.9±5.1	15.8±6.8	0.006	13.8±6.0	18.0±6.7	0.685
Median	13 (4–28)	15 (4–32)		13 (4–36)	17 (5–32)	
Time to tPA (minutes)	126.5±50.0	131.9±55.1	0.557	123.5±54.6	130.2±53.7	0.738
Median	120 (45–270)	120 (48–270)		110 (45–270)	116 (65–270)	
Femoral artery puncture time (hours)				5.0±2.1	5.2±1.6	0.312
Median				50 (1.5–15)	50 (2.5–11)	
Recanalized by IV-rtPA or IA-Tx	29 (26.9)	7 (11.9)	0.018	96 (92.3)	20 (69.0)	0.002
Neurologic outcomes						
Favorable	51 (47.2)	16 (27.1)	0.008	52 (50.0)	5 (17.2)	0.001
Unfavorable	43 (39.8)	22 (37.3)		19 (45.2)	19 (65.6)	
Dead	14 (13.0)	21 (35.6)	0.001	5 (4.8)	5 (17.2)	0.040
Sx-Hx	8 (7.4)	8 (13.6)	0.042	16 (15.4)	7 (24.1)	0.202
Reperfusion injury	13 (12.0)	10 (16.9)	0.256	43 (41.3)	20 (69.0)	0.007
Decompressive surgery	9 (8.3)	9 (15.3)	0.133	7 (6.7)	9 (31.0)	0.001

Values are presented as mean±standard deviation, number (range), or number (%). P/D : perfusion/diffusion, IV-tPA : intravenous tissue plasminogen activator administration, IA-Tx : intra-arterial thrombolytic therapy, NIHSS : National Institutes of Health Stroke Scale, Sx-Hx : symptomatic hemorrhage

 https://doi.org/10.3340/jkns.2022.0120

better clinical outcomes[42,43].

P/D-mismatching was also evaluated on the acute stroke MRI for further analysis[9,33,47,48]. IA-Tx was recommended for non-recanalized patients with P/D-mismatching after IV-tPA treatment unless they had a malignant profile on the follow-up MRI[2]. The P/D-mismatching profile was defined as a PWI lesion that was over 100 mL and 120% or more of the diffusion lesion[27,33]. Final classification of P/D-mismatching was decided by a radiologist who was not involved in acute stroke management (Table 3). In several cases, not undertook stroke MR instead CTP and analyzed Syngovia program, not included on Table 3.

Table 4. Two hundred sixty-four patient clinical results after IA-Tx, who were not recanalized by IV-rtPA

	IV-rtPA without IA-Tx	IV-tPA with add IA-Tx	Total statistic value	*p*-value
Patients No.	131	133	264	
Age (years)	68.1±11.4	64.0±15.0	66.0±13.5	0.056
Median	70 (39–89)	65 (19–98)	68 (19–98)	
Male sex	77 (58.8)	88 (66.2)	165 (62.5)	0.133
NIHSS score	14.2±5.8	14.7±6.4	14.5±6.1	0.199
Median	14 (4–32)	14 (4–36)	14 (4–36)	
Occlusion vessel site				
ACA	5 (3.8)		5 (1.9)	
MCA Lt.	34 (26.0)	36 (27.1)	70 (26.5)	
MCA Rt.	43 (32.8)	49 (36.8)	92 (34.8)	
ICA Lt.	27 (20.6)	23 (17.3)	50 (18.9)	
ICA Rt.	22 (16.8)	27 (18.8)	47 (17.8)	
Time to tPA (minutes)	121.7±57.0	123.6±55.8	127.6±52.5	0.191
Median	120 (51–270)	100 (45–270)	120 (45–270)	
Time to femoral artery puncture (hours)		5.0±1.8	5.0±1.8	
Median		5.0 (1.5–11.0)	5.0 (1.5–11.0)	
Recanalization after IA-Tx		116 (87.3)		
Neurologic outcomes				
mRS				
0	11 (8.4)	19 (14.3)	30 (11.4)	
1	14 (10.7)	19 (14.3)	33 (12.5)	
2	17 (13.0)	21 (15.8)	38 (14.4)	
Favorable	42 (32.1)	57 (42.9)	99 (37.5)	0.046
3	29 (22.1)	27 (20.3)	56 (21.2)	
4	13 (9.9)	21 (15.3)	34 (12.9)	
5	16 (12.2)	16 (12.0)	32 (12.1)	
Unfavorable	58 (44.3)	66 (49.6)	124 (47.0)	
6	31 (23.7)	10 (7.5)	41 (15.5)	<0.001
Sx-Hx	10 (7.6)	22 (16.5)	33 (12.5)	0.014
Decompressive surgery	16 (12.2)	16 (12.0)	32 (12.1)	0.557
P/D-mismatching	79 (60.3)	104 (78.2)	183 (69.3)	0.001

Values are presented as mean±standard deviation, number (range), or number (%). IA-Tx : intra-arterial thrombolytic therapy, IV-rtPA : intravenous recombinant tissue plasminogen activator, IV-tPA : intravenous tissue plasminogen activator administration, NIHSS : National Institutes of Health Stroke Scale, ACA : anterior cerebral artery, MCA : middle cerebral artery, Lt. : left, Rt. : right, ICA : internal cerebral artery, mRS : modified Rankin Scale, Sx-Hx : symptomatic hemorrhage, P/D : perfusion/diffusion

Patients who underwent IA-Tx therapy, also underwent a follow-up CT study immediately and then again within 24 hours after IA-Tx. Increased density on an immediate CT image was defined as extravasation of the contrast medium, and increased density on both follow-up CT scans was defined as a hemorrhagic complication[9,36,48]. Significant symptomatic intracranial hemorrhage was defined as neurological worsening of more than 4 points in the NIHSS score that was attributable to the presence of the clot[5,14,25].

Intra-arterial thrombectomy

Additional IA-Tx was attempted in 133 out of the 264 patients, who were not recanalized after IV-tPA treatment (Table 4). Angiograms (Axium Aristos plus; Siemens Medical Systems) were obtained using standard techniques. Once an occlusion was noted on angiography, the diagnostic catheter was exchanged for a 7-French guiding catheter (Guider Softip XF; Boston Scientific, Marlborough, MA, USA) or a balloon embolic protection device (Cello; Covidien, Irvine, CA, USA), which was placed into the internal cerebral artery. The IA-Tx was performed using stent retriever, and either Solitaire AB (EV3, Plymouth, MN, USA) or Trevo XP (Neurovascular; Stryker, Fremont, CA, USA) was selected according to the neurointerventionist's preference.

Surgical indications for decompressive craniectomy

Additional surgical decompression was performed in 34 patients. The indications for decompressive craniectomy included the appearance of massive brain swelling on CT with clinical deterioration, worsening of the Glasgow coma scale (GCS) score below 8 and/or a midline shift of more than 6 mm and/or obliteration of the perimesencephalic cistern on CT scans[46]. If the ventricular pressure exceeded 20 mmHg after decompression surgery, conventional medical management with hyperosmotic agents, hyperventilation, and extraventricular drainage was initiated.

Statistical analyses

All data are presented as the mean±standard deviation and/or as the median. A Wilcoxon signed-rank sum test was used to analyze NIHSS scores and mRS scores. Comparisons among groups were performed using the unpaired T-test and Fisher exact test. Statistical analyses for each outcome were analyzed with SPSS software, version 20 (IBM, Armonk, NY, USA). For all statistical analyses, significance was defined by a p-value ≤0.05.

RESULTS

Recanalization rate and treatment results after IV-tPA

The recanalization rate of LVO patients after IV-tPA was 12.0% (36/300) (Table 1). And the favorable outcome (mRS, 0–2) was 69.4% (25/36) in recanalized patients after IV-tPA treatment and 32.1% (42/131, p=0.000) in non-recanalized patients after IV-tPA treatment.

We compared the outcomes for recanalized patients (36 patients) and non-recanalized patients (131 patients) after IV-tPA without additional IA-Tx. The initial neurologic status was not different between the recanalized and non-recanalized after IV-tPA administration. The NIHSS was 12.6±6.4 (median, 11) in recanalized patients and 14.2±5.7 (median, 14) in non-recanalized patients (p=0.761) (Table 2).

Recanalization rate and treatment results after Additional IA-Tx

We attempted additional IA-Tx in 133 patients who were not recanalized by IV-tPA administration (Table 3). Additional IA-Tx was indicated in P/D-mismatching patients, based on the patients' general condition and agreed on further additional invasive therapy. And if the patient recanalized after IA-Tx, clinical outcome was significant better (linear regression test; p=0.026).

Recanalization rate after IA-Tx was 81.1% (116/133) (Table 3). The initial neurologic status in recanalized patients was similar with non-recanalized patients (14.0±6.1 vs. 18.3±6.6, p=0.246, data not shown), but favorable outcomes were more frequent in recanalized patients than in non-recanalized patients (46.6% [54/116] vs. 22.2% [6/27], p=0.016, data not shown).

Complication rate according to P/D-mismatching

We analyzed clinical data of 167 patients treated with IV-rtPA only, and 133 treated with IA-Tx after IV-rtPA according to the P/D-mismatching or not (Table 3). In 167 patients treated IV-rtPA only, in P/D-mismatching patients (108 patients) showed more favorable clinical outcome (51/108 [47.2%] vs.

 https://doi.org/10.3340/jkns.2022.0120

16/59 [27.1%], p=0.008), less death rate (14/108 [13.0%] vs. 21/59 [35.6%], p=0.001), more recanalization rate by IV-rtPA (29/108 [26.9%] vs. 7/59 [11.9%], p=0.018) and less clinically significant hemorrhage (8/108 [7.4%] vs. 8/59 [13.6%], p=0.042) than P/D-matching patients (Tables 3 and 4).

In 133 patients treated IA-Tx after IV-rtPA, in P/D-mismatching patients (104 patients) showed more favorable clinical outcome (52/104 [50.0%] vs. 5/29 [17.2%], p=0.001), less death rate (5/104 [4.8%] vs. 5/29 [17.2%], p=0.040), and more recanalization rate by IA-Tx (96/104 [92.3%] vs. 20/29 [69.0%], p=0.002) than P/D-matching patients. Clinically significant hemorrhage happened similarly in both groups (16/104 [15.4%] vs. 7/29 [24.1%], p=0.202), but reperfusion injury in recanalized patients (43/104 [41.3%] vs. 20/29 [69.0%], p=0.007) was less in P/D-mismatching patients (Table 3).

DISCUSSION

Treatment for cerebral ischemic stroke is based on the ischemic penumbra[4]. According to the recanalization hypothesis, a reopening of occluded vessels before critical cell injury might improve clinical outcomes in acute ischemic stroke through regional reperfusion and salvage of threatened tissues[1,4,12,39].

As soon as intracranial bleeding is ruled out by non-contrast enhanced brain CT, application of intravenous thrombolysis for ischemic stroke is beneficial for infarction patients[20,35]. Many medical systems have been upgraded to improve clinical outcomes in infarction patients[23,38].

Recently, recanalization rate of IV-tPA LVO stroke patients has been reported[42,43]. Indeed, on these reports, the recanalization rate of LVO by OV-rtPA is very low, and has been criticized as being ineffective[7,8,10,14,16,17,19,25-27,37,41].

LVO poses a major problem and has emerged as the most common stroke subtype worldwide, especially in patients of Asian, Hispanic, and African origins[7,11,12,18,40]. The etiology and treatment of this disorder remain poorly defined. A review of previous papers suggests that medium-sized intracranial arteries and their major branches, ACA, MCA, PCA, PICA, AICA, SCA, and the distal basilar artery are most often affected[12].

The overall recanalization rate after IV-rtPA administration ranges from 10% to 47% as evaluated by transcranial sonography, CT or CTA, and other imaging techniques[3,5,7,8,10,16,17,19,23,27,32,37,39-41,45].

In our study, 535 patients were treated with IV-tPA and among them 300 patients were defined as infarction caused from LVO of anterior circulation. Considering the high incidence of LVO in our country, recanalization rate after IV-rtPA is considered for additional IA-Tx management[18]. In this study, recanalization was based on CTA and MRA, and the early recanalization rate (about 1–2 hour after IV-tPA administration) in LVO patients was 12.0% (36/300 patients).

Early recanalization is closely linked to good final clinical outcomes in acute ischemic stroke[26]. Until now, most studies performed with multimodal magnetic resonance or computed tomography imaging, the overall recanalization rate is variable about 20% up to 60%[19,37,39,41]. If selected patients still harbor substantial residual penumbra beyond 6 hours, they would benefit from reperfusion[2,34,39-41]. But in practice, early recanalization should be defined as recanalization within 1 hour after IV-tPA administration[3]. In this study, we defined early recanalization as recanalization of the occluded larger vessel within 3 hours after IV-rtPA administration, because this time window increases chances of additional IA-Tx and is associated with better clinical outcomes[42,43].

The American Food and Drug Administration, the American Stroke Association and Korean Stroke Society have recommended IV-rtPA treatment as a standard treatment of stroke patients but after the MR CLEAN trial in 2015, IA-Tx with a stent-retrieval device became an additional treatment option after IV-rtPA[5,10,14,17,19,23,25-27,41]. The success of these studies can likely be attributed to the use of improved devices with better and faster recanalization, right patient selection with appropriate vascular imaging, and improved medical systems enabling organized care for patients treated with IA-Tx[10,17,19,25,41].

To accomplish rapid treatment, bridging therapeutic strategy, initiation of IV-tPA then followed by IA-Tx is necessary[5,8,10,14,19,25,27,41]. IA-Tx enables accurate diagnosis and can facilitate mechanical clot destruction, and in some instances increases the concentration of the thrombolytic agent in the vicinity of the clot[17,47]. IA-Tx increases recanalization rate by 45.5–94% and can extend the therapeutic time window by 6–8 hours from the onset of acute ischemic stroke[10,17,19,25,41,47]. Thanks to the development of intervention devices and increased interventional experience the recanalization rate of IA-Tx is increased, and several interventionists have said that one could recanalize all the LVO cases. This aggressive ap-

proach also increased futile recanalization, significant hemorrhage rate and reperfusion injury[23,24,31,38].

Conventional non-contrast CT or MRI remains the mainstay of suspected acute stroke imaging. However, recent advanced imaging techniques, such as CTA and acute-stroke MRI, have become important tools to identify the condition of ischemic brain tissue[1,3,33]. In our study, CTA provided an initial diagnostic image, but this dynamic study did not delay IV-tPA administration. Brain radiologic evaluation, including vascular imaging, is strongly recommended in patients with severe stroke to assess large cerebral artery occlusions. In such patients, additional treatment can be prepared and save time, if IV-tPA fails to reopen the occlusion[23,27]. Neuroimaging methods for evaluating blood flow and tissue viability are increasingly required because they allow tailoring therapeutic interventions to each patient's physiological state.

According to the authors of this study, acute stroke MRI after IV-tPA administration, especially for identifying P/D-mismatching, may identify tissue that is at risk for cerebral infarction unless blood flow is restored, and determine the risk of additional IA-Tx therapy[1,4,33].

In our study, among 133 patients who underwent IA-Tx after IV-tPA, patients with P/D-mismatching showed higher recanalization rates (92.3% in mismatching vs. 69.0% in matching, p=0.002), and higher incidence of favorable outcomes (50.0% in mismatching vs. 17.25% in matching, p=0.001). And the significant hemorrhage rate was less in P/D-mismatching patients (15.4% vs. 24.1%, p=0.202), but it was not statistically significant.

We should consider the deleterious influence of IA-Tx on hemorrhagic conversion of the infarct[36,48]. Some studies on intracerebral hemorrhage after IV-tPA reported that patient's age, clinical stroke severity, high blood pressure, hyper-glycemia, early CT changes, and leukoaraiosis on MRI are statistically significant predictors[14,16,20,33,36,37]. Randomized studies of thrombolysis with IV-rtPA reported a significant hemorrhage rate of 1.7–8.8%[5,10,14,19,25,27,37,41]. In our study, the incidence of significant hemorrhagic complications rate after IV-rtPA was 7.8%, and it was also higher in mismatching patients (7.4% vs. 13.6%, p=0.042). But in patients that undertook both IV-rtPA and IA-Tx, the significant hemorrhage was statistically similar both in P/D-mismatching and P/D-matching patients (15.4% vs. 24.1%, p=0.202), possibly because of aggressive trials to reopen the occluded vessel. And P/D-mismatching was statistically significantly correlated with favorable neurologic outcomes in IV-tPA group, IV-tPA & IA-Tx group and IA-Tx group.

Limitations of this study are that the initial imaging study was CTA and the follow-up imaging study after IV-tPA was MRI. Secondly, in our study, P/D-mismatching taken by MR imaging was analyzed to find the correlation with treatment results, but recently developed dynamic CT image (CT-perfusion) was used instead of MRI. In addition, this study is a retrospective study, and even though it was targeted to consecutive patients, some of the baseline demography–age, heart disease and atrial fibrillation–of the IA-rtPA group and the IA-Tx group showed statistical differences. More randomized, prospective studies should follow to clarify the correlation of the P/D-mismatching on MRI and dynamic CT imaging. And, the incidence of LVO is high in our country, so early recanalization rates might be different according to the reports of others.

CONCLUSION

If recanalization had failed after IV-tPA, additional IA-Tx might be beneficial for the patient outcome. And in this situation, P/D-mismatching on acute MR study was a good indicator for the additional IA-Tx with safety and efficacy. The authors would like to propose that we had better prepare IA-Tx when LVO is diagnosed on initial brain image. Furthermore, if the patient shows P/D-mismatching on MRA after IV-rtPA, additional IA-Tx improves treatment results and lessen the futile recanalization.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

Informed consent was obtained from all individual participants included in this study.

 https://doi.org/10.3340/jkns.2022.0120

Author contributions

Conceptualization : DSY; Data curation : DSY, MHL; Formal analysis : DSY, MHL; Funding acquisition : DSY; Methodology : DSY, SHI; Project administration : DSY; Visualization : KWJ; Writing - original draft : DSY, KWJ; Writing - review & editing : DSY

Data sharing

None

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- Acknowledgements

Authors appreciate the help of Neurosurgical nurse specialist (Min-Hee Kim, RN. & Hae-Sun Jung, RN.) to collect the data and the grammatical review of our manuscript by Ann C Rice, PhD of the J. Sargeant Reynolds Community College, Richmond, VA, USA.

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 https://doi.org/10.3340/jkns.2022.0120