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Intraarterial urokinase for thrombus migration after mechanical thrombectomy for large vessel ischemic stroke

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Author information:
Hiroaki Neki, Ph.D.
Takehiro Katano, M.D.
Takuma Maeda, M.D.
Aoto Shibata, Ph.D.
Hiroyuki Komine, Ph.D.
Yuichiro Kikkawa, Ph.D.

Department of Neurosurgery, Saitama Cardiovascular and Respiratory Center, Kumagaya, Saitama, Japan
Address: 1696 Itai, Kumagaya, Saitama, Japan, Zip 360-0197

Corresponding author: Hiroaki Neki, MD, PhD
1696 Itai, Kumagaya, Saitama, Japan, Zip 360-0197
Tel: +81485369900, Fax: +81485369920
Mail: nekihiro1004@gmail.com

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Abstract
[Background] Achieving rapid and complete reperfusion is the ultimate purpose for ischemic stroke with large vessel occlusion (LVO). Although mechanical thrombectomy (MT) had been a proverbially important procedure, medium vessel occlusion (MeVO) with thrombus migration can sporadically occur after MT.

Moreover, the safe and effective approach for such had been unknown. We reported thrombolysis with intraarterial urokinase for MeVO with thrombus migration after MT.
[Methods] We included 122 patients who were treated by MT with LVO stroke at our institution between April 2019 and March 2021. Of 26 patients (21.3%) who developed MeVO with thrombus migration after MT, 11 (9.0%) underwent additional MT (MT group) and 15 (12.3%) received intraarterial urokinase (UK group). The procedure time; angiographically modified Treatment in Cerebral Ischemia Scale (mTICI); functional independence, which was defined as modified Rankin Scale 0–2, on day 30 or upon discharge; and symptomatic and asymptomatic intracerebral hemorrhage (ICH) were compared between the UK and MT groups.
[Results] The procedure time, mTICI, and asymptomatic ICH did not significantly differ between the groups. In the UK group, 8 of 15 (53.3%) patients obtained functional independence, and the functional independence rate was significantly higher in the UK group than in the MT group ($p < 0.05$). Symptomatic ICH did not occur in the UK group, and its incidence was significantly smaller than that in the MT group ($p < 0.05$).
[Conclusion] The results of this study suggest that intraarterial urokinase for MeVO with thrombus migration after MT may safely improve angiographic reperfusion.
248 words

Key words: ischemic stroke, Urokinase-Type Plasminogen Activator, thrombosis, thrombectomy

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Abbreviations: large vessel occlusion, LVO. mechanical thrombectomy, MT. medium vessel occlusion, MeVO. modified Treatment in Cerebral Ischemia Scale, mTICI. intracerebral hemorrhage, ICH. Diffusion-Weighted Imaging - Alberta Stroke Program Early CT Score, DWI-ASPECTS. National Institutes of Health Stroke Scale, NIHSS. modified Rankin Scale, mRS. internal carotid artery, ICA. middle cerebral artery, MCA. basilar artery, BA. Diffusion-Weighted Imaging, DWI.

[Introduction]

Thrombectomy, along with intravenous alteplase, is the standard medical care for acute ischemic stroke(1). Achievement of rapid and complete reperfusion is the ultimate purpose for ischemic stroke with large vessel occlusion (LVO). Mechanical thrombectomy (MT), along with intravenous alteplase, had been the standard medical care for acute ischemic stroke with LVO(2). Although thrombus migration to the distal medium vessels after intravenous alteplase can reduce the rate of complete reperfusion, it can lead to better functional outcome; this had been suggested as the thrombus migration paradox(3). Thrombus migration after MT can occasionally occur and sustained endovascular treatment on medium vessels had been performed in several instances. MT for acute ischemic stroke with medium vessel occlusion (MeVO) was reported to be angiographically effective and safe(4-6). The patient status and vessel condition in MeVO with thrombus migration are different from those in direct MeVO. Moreover, the role of MT for MeVO after LVO remains unclear. Recently, adjuvant thrombolysis with MT have been reported to **improve recanalization rate for** failed, unsuccessful, or incomplete MT **as compared with MT alone**(7-10).

In this study, we focused on MeVO with thrombus migration and aimed to determine the outcome of thrombolysis with intraarterial urokinase (UK) for MeVO with thrombus migration after MT.

[Methods]

(Patient/ Procedure)

All consecutive patients who underwent MT for LVO at our institution between April 2019 and March 2021 were included in the analysis. Patients who presented within 6 h from symptom onset or from the time they were last noted to be well were selected for MT if they had a Diffusion-Weighted Imaging - Alberta Stroke Program Early CT Score (DWI-ASPECTS) (range, 0–11) ≥3, confirmed LVO on MRA, and National Institutes of Health Stroke Scale (NIHSS) of ≥5. Age, comorbidity status, baseline functional status, and vascular valiations were not considered exclusion criteria for MT. Patients with unclear time of onset or time of onset of > 6 h were selected for MT if a favorable DWI MRI (DWI-ASPECTS ≥7) with LVO(11, 12) was favorable. Patients with large infarct burden with DWI-ASPECTS<7 on presentation or rapidly resolving symptoms with or without intravenous rtPA did not undergo MT and were managed conservatively. All treatments were administered with the patients under local anesthesia. After introducing the sheath, intravenous infusion of heparin (4000 IU) was administered, except patients who have received intravenous rtPA. The guiding catheter was essentially balloon guide catheter. The choice of techniques and devices for endovascular treatment of LVO was made by the operator (e.g. stent retriever alone, direct aspiration, stent retriever with aspiration) was made by the operator. The **basic** choice between intraarterial UK (UK group) or additional MT (MT group) was made by the **initial procedure from the perspective of treatment costs**. Additional MT was performed after the initial procedure using with small size stent retriever including stent retriever alone and stent retriever with aspiration. **Intraarterial UK was performed after the initial procedure using with large size stent retriever relative to the diameter of the vessel including stent retriever alone and stent retriever with aspiration, and direct aspiration.** The procedure for MeVO was either UK or additional MT without UK. The indication for additional treatment at MeVO site was the only A2, M2, and P2 segment of the major branches such as anterior cerebral artery, middle cerebral artery (MCA), and posterior cerebral artery (PCA).

For intraarterial UK administration, a microcatheter with a single end hole (I.D. 0.027 inch) was placed near the proximal side of the thrombus before intraarterial infusion of 60,000 IU of UK for > 2 min: this was repeated until the total dose reached 600,000 IU in one vessel or when good recanalization, which was defined as a modified Treatment in Cerebral Ischemia Scale (mTICI) of 2b or 3, was achieved. **The dose of UK was determined based on previous study of The MELT**

Japan(13). Control angiography was performed for each infusion of 60,000 IU to evaluate recanalization. For additional MT, ASAP technique was performed with a large bore catheter(14).

Informed consent was obtained before treatment. This study was a single-center retrospective analysis of the treatment outcomes of patients, who were categorized into two groups (UK and MT). The protocol for endovascular treatment was approved by our institution.

(Clinical and radiological assessments)

Trained neurosurgeons or neurologists performed the clinical assessment at baseline and upon hospital discharge or 30 days after the stroke onset. Although clinical assessment had been usually performed at 90 days after stroke onset, we changed the period to 30 days because of difficulties in providing uniform and steady rehabilitation in the COVID-19 pandemic. The baseline neurological severity was evaluated using the NIHSS. Functional outcome was assessed using the modified Rankin Scale (mRS), and functional independence was defined as mRS of 0–2. We diagnosed thrombus migration when a new distal occlusion in addition to the primary occlusion was identified on angiography after the initial procedure (Fig. 1). Final angiographic evaluation was assessed using mTICI(15). Angiographically good recanalization was defined an mTICI scale of 2b or 3 based on the original LVO location. Symptomatic intracerebral hemorrhage (ICH) was defined based on evidence, with an increase of ≥ 4 points on the total NIHSS or a 1-point increase in the level of consciousness on the NIHSS, according to the PROACT-II criteria(16).

(Statistical analysis)

We performed statistical analysis using JMP 12 (SAS Institute Inc., Cary, NC, USA). Univariate comparisons between the UK and MT groups were performed using the Wilcoxon's rank sum test or two-sided Fisher exact test. P values of <0.05 were considered to indicate a statistical significance.

[Results]

Of the 122 patients who had LVO stroke during the study period, 26 (21.3%) developed MeVO with thrombus migration after MT and were analyzed in this study. There were 14 men and 12 women,

with a median age of 77 years (IQR, 68.5–84.5 years). The median **initial** NIHSS **on admission** was 18.5 (IQR, 15–21.5). All patients, except one who had VA occlusion, were assessed by DWI MRI, and the median DWI-ASPECTS was 7 (IQR, 5–8). In the 22 patients who were assessed by CT, the median CT-ASPECTS (range, 0–10) was 8 (IQR, 7.75–9). The LVO site was the ICA in15 patients, the ICA to MCA in 1 patient, the horizontal segment of the MCA in 9 patients, and the basilar artery in 1 patient. The cause of stroke was cardioembolic in 19 patients, large artery atherosclerosis in 2 patients, Trousseau syndrome in 2 patients, and noncardiac embolism in 2 patients. Intravenous rtPA was administered on four patients. As shown in Table 1, the median interval was 92.5 (IQR, 561–82) min for symptom onset or the time last seen well to admission; 52.5 (IQR, 44.75–61) min for admission to puncture; 39 (IQR, 30.25–62.25) min for groin puncture to thrombus migration; 198.5 (IQR, 159.25–290.5) min for symptom onset or the time last seen well to thrombus migration; and 65 (IQR, 45.25–103.25) min for groin puncture to final recanalization.

Of the 26 patients who developed MeVO with thrombus migration after MT, 11 (42.3%) were in the MT group and 15 (57.7%) were in the UK group (Fig. 2). The MeVO site was the M2 segment of the MCA in 25 patients and the P2 segment of the PCA in 1 patient. No patient had multiple sites of thrombus migration. The median volume of injected UK was 240,000 (IQR, 120,000–360,000) IU. We found no significant differences between the two groups in terms of age, sex, admission NIHSS, CT-ASPECTS, and DWI-ASPECTS. The median interval from symptom onset or the time last seen well to admission was significantly shorter in the UK group than in the MT group [65 (IQR, 45–120) min vs. 175 (IQR, 71–325) min, $p = 0.020$]. Conversely, compared with the MT group, the UK group tended to have shorter median intervals from symptom onset or the time last seen well to thrombus migration [174 (IQR, 119–250) min vs. 249 (IQR, 167–446) min, $p = 0.069$] and to final recanalization [207 (IQR, 170–289) min vs. 261 (IQR, 184–493) min, p = 0.092]. The median intervals from admission to groin puncture ($p = 0.959$), groin puncture to thrombus migration ($p = 0.659$), and thrombus migration to final recanalization ($p = 0.323$) were not significantly different between the two groups.

Angiographically good recanalization was frequently achieved in both groups, without significant differences. Significant difference in the incidence of symptomatic ICH was found ($p = 0.022$), but the incidence of asymptomatic ICH was not significantly different between the groups. The rate of

functional independence upon hospital discharge or at 30 days after stroke onset was significantly higher in the UK group than in the MT group (p = 0.036) (Table 2).

[Discussion]

MT, along with intravenous alteplase is the standard medical care for acute ischemic stroke with LVO(2). Achievement of rapid and complete reperfusion is the ultimate purpose that has been shown to have excellent outcomes for LVO stroke. Intraarterial thrombolysis with MT had been used in some large randomized clinical trials, but no subgroup analysis was conducted(1, 17, 18). Notably, adjunctive intraarterial rtPA with MT for LVO stroke was reported to achieve safe and relatively high reperfusion rates(7, 8). Kaesmacher et al reported that intraarterial UK was safe and improved angiographic reperfusion after failed, unsuccessful, or incomplete MT(9). Although intraarterial thrombolysis is assumed to be an effective tool during MT, its use in the studies was not standardized or controlled for during analysis. MeVO with thrombus migration to distal medium vessels is one of the frequent situations with failed, unsuccessful, or incomplete MT.

At present, the safety and effectiveness of intraarterial thrombolysis, including intraarterial UK, as an adjunctive treatment option for MeVO with thrombus migration after MT is unclear. Although the situations in which MeVO occurs vary, early recanalization for MeVO stroke had been strongly associated with functional independence. Ospel et al described that excellent functional outcomes after MeVO stroke were strongly associated with early recanalization, but the rate of recanalization with intravenous alteplase was only 47%(19). MT was suggested to provide similar safe access with high recanalization rates and functional independence between MeVO, which is mainly M2 occlusion, and LVO of M1(4-6, 20). Conversely, the tendency for an increased risk of symptomatic hemorrhage had been controversial(21, 22). Based on these circumstances, we focused on MeVO with thrombus migration after MT and reported the outcomes of intraarterial UK.

Our results revealed that both intraarterial UK and additional MT obtained rapid and angiographically good recanalization. Both procedures showed good efficacy, based on the rate of angiographically good reperfusion and the additional procedure time after thrombus migration. Compared with additional MT, intraarterial UK led to a decreased incidence of symptomatic ICH and an increased rate of functional independence. The result of symptomatic ICH and functional

independence of additional MT might be indicated by the significant difference in the median interval from symptom onset or the time last seen well to admission. Most importantly, there was no case of symptomatic ICH in the UK group. Therefore, intraarterial UK for MeVO with thrombus migration after MT was suggested to be effective and safe, with low risk of symptomatic ICH.

The major limitations of our case series were the retrospective design and the small number, given the difficult set of criteria for patient inclusion. The performance of endovascular procedures, including the initial MT and the inclusion criteria for additional treatment for MeVO with thrombus migration, was not uniform. Furthermore, functional outcome was evaluated only upon hospital discharge or at 30 days after stroke onset. A longer evaluation at 90 days after stroke onset may be acquired.

[Conclusion]

In conclusion, intraarterial UK for MeVO with thrombus migration after MT might safely improve angiographic reperfusion.

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[Conflict of Interest]

The authors declare that they have no conflict of interest.

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Figure 1. We present a typical case of thrombus migration. A 91-year-old woman, NIHSS on admission: 19, left ICA occlusion

A: Initial angiography of left ICA showed artery occlusion on ophthalmic segment of ICA.

B: Partial recanalization appeared on angiography of ICA after a combined technique with aspiration catheter and stent retriever. The angiography showed MeVO with thrombus migration on distal segment of left MCA (23).

C: Complete recanalization appeared on angiography of ICA after intraarterial UK administration of 180,000 IU.

Figure 2. Procedure diagram

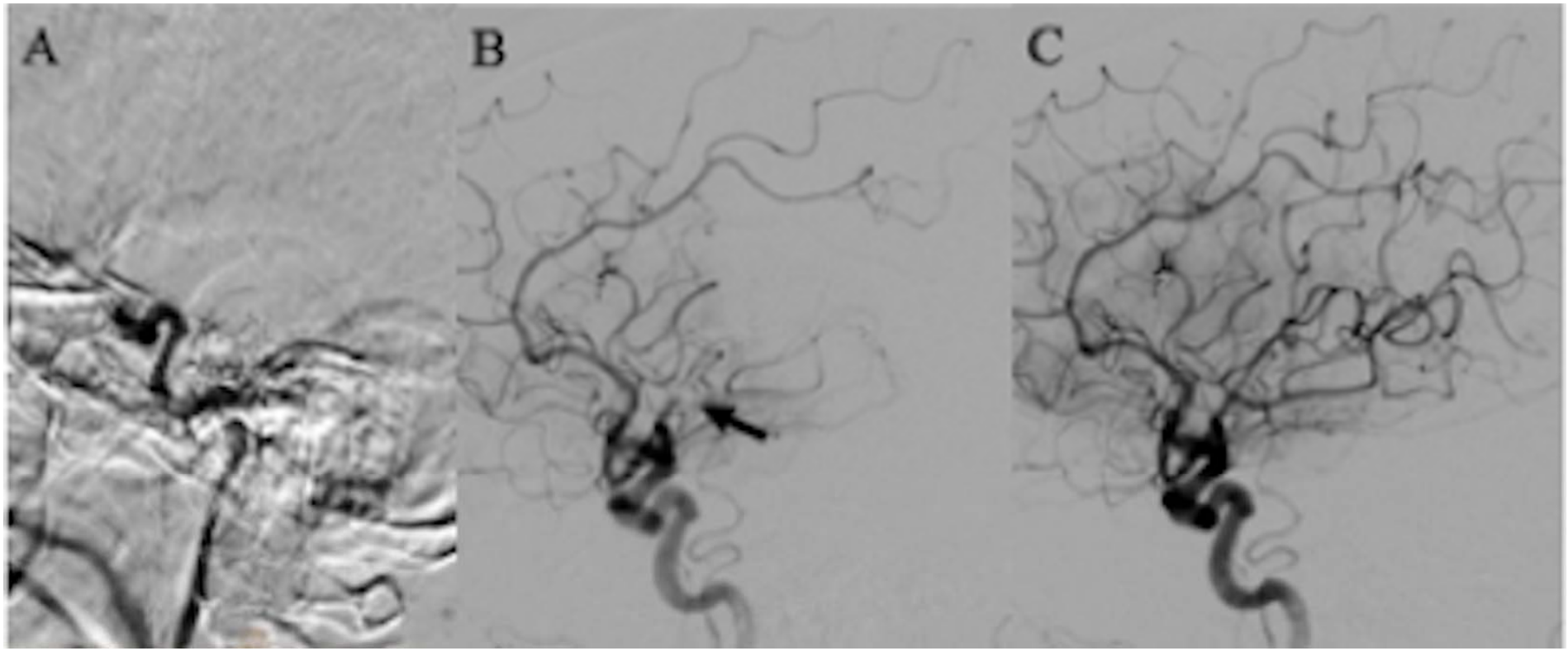

Figure 1

140x57mm（300 x 300 DPI）

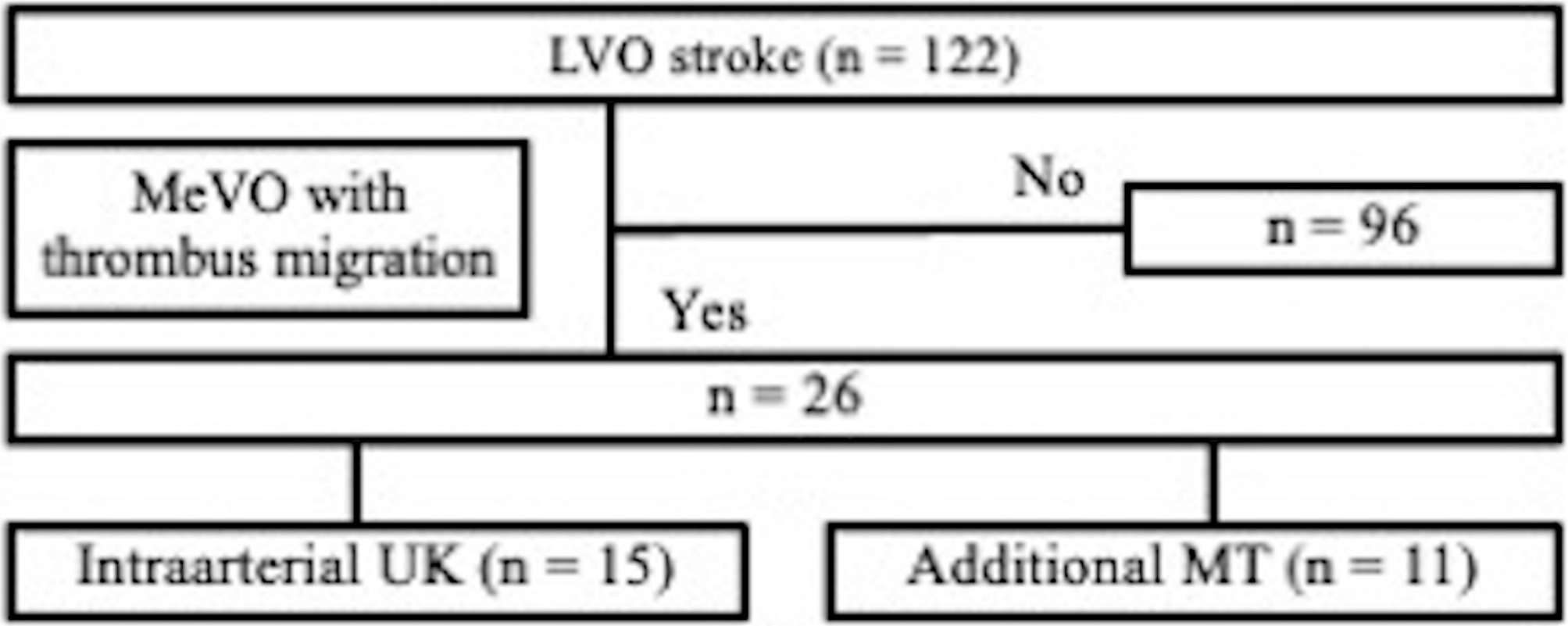

Fig 2

105x44mm（300 x 300 DPI）

Table 1. Characteristics of the patients and time couse before additional treatment

	All (N=26)	MT group (N=11)	UK group (N=15)	*p* value
Patient characteristics				
Sex, male/female	14/12	5/6	9/6	0.692
Age, median (IQR), years	77 (68.5-84.5)	79 (69-86)	76 (67-84)	0.938
Present status on admission				
NIHSS, median (IQR)	18.5 (15-21.5)	18 (17-21)	19 (13-24)	0.735
Vessel site of LVO				
ICA	15	6	9	0.895
ICA - MCA	1	0	1	
MCA(horizontal segment)	9	5	4	
BA	1	0	1	
DWI-ASPECTS, median (IQR)	7 (5-8)	7 (6-9)	6.5 (5-7.25)	0.209
CT-ASPECTS, median (IQR)	8 (7.75-9)	8 (7.5-8.5)	8 (7.5-9)	0.667
Time course				
Time from symptom onset or from time last seen well to admission, median (IQR), min	92.5 (56-182)	175 (71-325)	65 (45-120)	0.020*
Time from admission to puncture, median (IQR), min	52.5 (44.75-61)	53 (46-61)	52 (44-66)	0.959
Time from groin puncture to thrombus migration, median (IQR), min	39 (30.25-62.25)	37 (22-63)	41 (34-56)	0.659
Time from symptom onset or from time last seen well to thrombus migration, median (IQR), min	198.5 (159.25-290.5)	249 (167-446)	174 (119-250)	0.069

NIHSS: National Institutes of Health Stroke Scale, LVO: large vessel occlusion, ICA: internal carotid artery, MCA: middle cerebral artery, BA: basilar artery, DWI: Diffusion-Weighted Imaging, ASPECTS: Alberta Stroke Program Early CT Score

Table 2. Result of treatment for MeVO with thrombus migration

	All (N=26)	MT group (N=11)	UK group (N=15)	*p* value
mTICI scale 2b or 3	23 (88.5%)	10 (90.9%)	13 (86.7%)	1.000
mRS 0-2 at hospital discharge or 30 days after stroke onset	9 (34.6%)	1 (9.1%)	8 (53.3%)	0.036*
asymptomatic ICH	8 (30.8%)	3 (27.3%)	5 (33.3%)	1.000
symptomatic ICH	4 (15.4%)	4 (36.4%)	0	0.022*
Time course				
Time from thrombus migration to final recanalization, median (IQR), min	19.5 (15.75-36.75)	17 (21-36)	22 (18-39)	0.323
Time from symptom onset or from time last seen well to final recanalization, median (IQR), min	217.5 (178-311)	261 (184-493)	207 (170-289)	0.092

MeVO: Medium vessel occlusion, mTICI: modified Treatment in Cerebral Ischemia Scale, mRS: modified Rankin Scale, ICH: intracerebral hemohhage