Local Intra-arterial Thrombolysis during Mechanical Thrombectomy for Refractory Large-Vessel Occlusion: Adjunctive Chemical Enhancer of Thrombectomy

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ABSTRACT

BACKGROUND AND PURPOSE: Data on adjunctive intra-arterial thrombolysis during mechanical thrombectomy for refractory thrombus are sparse. The aim of this study was to evaluate the efficacy and safety of local intra-arterial urokinase as an adjunct to mechanical thrombectomy for refractory large-vessel occlusion.

MATERIALS AND METHODS: We retrospectively evaluated patients with acute ischemic stroke who underwent mechanical thrombectomy for anterior circulation large-vessel occlusion between January 2016 and December 2019. Patients were divided into 2 groups based on the use of intra-arterial urokinase as an adjunctive therapy during mechanical thrombectomy for refractory thrombus: the urokinase and nonurokinase groups. Herein, refractory thrombus was defined as the target occlusion with minimal reperfusion (TICI 0 or 1) despite >3 attempts with conventional mechanical thrombectomy. The baseline characteristics, procedural outcomes, and clinical outcome were compared between the 2 groups.

RESULTS: One hundred fourteen cases of refractory thrombus were identified. A total of 45 and 69 patients were in the urokinase and the nonurokinase groups, respectively. The urokinase group compared with the nonurokinase group showed a higher rate of successful reperfusion (82.2% versus 63.8%, $P = .034$), with lower procedural times (54 versus 69 minutes, $P = .137$). The rates of good clinical outcome, distal embolism, and symptomatic intracranial hemorrhage were similar between the 2 groups. The use of intra-arterial urokinase (OR = 3.682; 95% CI, 1.156–11.730; $P = .027$) was an independent predictor of successful reperfusion.

CONCLUSIONS: The use of local intra-arterial urokinase as an adjunct to mechanical thrombectomy may be an effective and safe method that provides better recanalization than the conventional mechanical thrombectomy for refractory thrombus in patients with embolic large-vessel occlusion.

ABBREVIATIONS: CA = contact aspiration; IA = intra-arterial; ICH = intracerebral hemorrhage; IQR = interquartile range; LVO = large-vessel occlusion; MT = mechanical thrombectomy; mTICI = modified TICI; SR = stent retriever; sICH = symptomatic ICH; UK = urokinase

Successful reperfusion is one of the most powerful factors for determining good clinical outcome in patients undergoing mechanical thrombectomy (MT) to treat acute ischemic stroke due to large-vessel occlusion (LVO).[1,2] Therefore, many studies have focused on improving the efficacy of MT.[3]

Although satisfactory recanalization rates can be obtained via standard MT, about 10%–35% of patients fail to achieve sufficient recanalization.[4,5] In these refractory cases, various rescue treatments such as local intra-arterial fibrinolysis, suction aspiration, mechanical thrombus disruption, balloon angioplasty, and stent placement have been proposed.[6-8] However, the rates of effective recanalization following these rescue treatment methods remain low.

Intra-arterial (IA) thrombolysis has been studied mainly as a primary therapy in previous randomized clinical trials before the era of newer-generation MT devices. Recent observational studies on the concomitant use of IA tissue-type tPA or urokinase (UK) during MT have demonstrated promising results with improved reperfusion rates, shortened procedural times, and acceptable safety profiles.[9-14] However, to date, data are limited on the use of local IA thrombolysis as an adjunct to MT in response to multiple failed attempts of conventional thrombectomy as a treatment for refractory thrombus. The impact of local IA thrombolysis as an adjunctive therapy to MT for refractory thrombus in terms of recanalization and hemorrhagic complications remains largely unknown.

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We hypothesized that the use of local IA UK as an adjunct to MT may improve the recanalization rate in refractory thrombus. The aim of this study was to evaluate the efficacy and safety of using local IA UK as an adjunctive therapy to MT for treating refractory thrombus in patients with LVO with failed conventional MT.

MATERIALS AND METHODS

Patients

This study was approved by the local institutional review board of Seoul National University Bundang Hospital (No. B-2102–667–112); the requirement of written informed consent was waived due to the retrospective nature of this study.

A retrospective analysis was performed in all consecutive patients with acute ischemic stroke who underwent endovascular treatment between January 2016 and December 2019 at our center. The inclusion criteria for the study were as follows: 1) time from symptom onset to groin puncture ≤24 hours, 2) occlusion of the intracranial segment of the ICA or MCA (M1 or M2 segment) visible on CT or MR angiography, 3) baseline NIHSS score of ≥6 points, 4) stent retriever (SR) or contact aspiration (CA) thrombectomy as the primary treatment, and 5) refractory thrombus, defined as the target occlusion with minimal reperfusion (TICI 0 or 1) despite >3 attempts with conventional MT. The exclusion criteria of this study were as follows: 1) posterior circulation occlusion, 2) large-artery atherosclerosis as the cause of stroke, 3) other etiologies of stroke such as dissection or vasculitis, 4) tandem or multiple occlusions, and 5) IA UK as a rescue therapy (UK alone without additional MT) or treatment for distal embolism.

Generally, local IA UK is administered if standard thrombectomy yields no response (modified TICI [mTICI] scale 0 or 1) for ≥3 attempts. Hence, refractory thrombus is defined on the basis of the number of passes. In particular, for the purpose of our analysis, refractory thrombus did not include atherosclerosis-related occlusion lesions because these generally require multiple attempts of MT due to elastic recoil and thrombus buildup.

Endovascular Treatment

All included patients underwent MT ≥3 times and were treated with one of the following techniques: SR, CA alone, or CA combined with SR. Patients were divided into 2 groups based on the use of IA UK: 1) the UK group, which included patients who received adjunctive IA UK during MT of the primary occlusion, and 2) the non-UK SR group, which included those who did not receive IA UK. In the UK group, IA UK was adjunctively used only for refractory thrombus that did not respond to a conventional MT using CA or SR or combined techniques (mTICI 0 or 1), and additional MT was performed subsequently after injection of UK.

All procedures were performed by 3 experienced neurointerventionalists (C.J., S.H.B., and J.Y.K.) in a single tertiary care center. The endovascular procedure was typically performed via a femoral approach through an 8F or 9F sheath with the patient under local anesthesia or conscious sedation. An 8F or 9F balloon guide catheter was routinely used whenever possible. The specific thrombectomy devices used and intervention strategies were at the discretion of the operator. If successful reperfusion was not achieved with the initially selected first-line MT despite multiple attempts, rescue therapy was performed by switching to the other primary method.

IA UK has long been used as a stand-alone intra-arterial thrombolysis at our center. Local intra-arterial urokinase was performed through a microcatheter (0.021 or 0.027 inch). Initially, the microcatheter was navigated across the thrombus and placed just distal to the thrombus. After confirmation of antegrade contrast opacification beyond the occlusion site, UK injection was started. Next, the microcatheter was gradually withdrawn and positioned within the offending thrombus while injecting the UK. Then, the microcatheter was pulled back and placed proximal to the thrombus, and the small amount of UK remaining was injected gently. More proximal regional infusion was prohibited. After the completion of UK administration, additional mechanical thrombectomy followed after waiting 3–5 minutes. This method was used by all 3 operators. The details of the conventional MT technique were described previously.[15,16]

Data Collection and Outcome Measures

Clinical and radiologic data, including patient demographics, angiographic and radiologic findings, time intervals (ie, onset, puncture, reperfusion time), and clinical information, were prospectively collected. Two interventional neuroradiologists (C.J. and S.H.B.) independently evaluated all images. Discordance between the 2 readers was resolved by consensus. In patients with successful reperfusion, the procedure time was defined as the interval from puncture to final recanalization, whereas in patients with unsuccessful reperfusion, it was defined as the time interval from puncture to the last angiographic series. The reperfusion status was assessed on the final angiogram and was classified according to the mTICI scale. The primary outcome was the rate of successful reperfusion, which was defined with an mTICI score of 2b or 3. Complete reperfusion was defined as an mTICI grade of 3. Good clinical outcome was defined as a 3-month mRS score of 0–2. The angiographic findings such as time intervals, number of passes, and reperfusion status before and after the administration of IA UK were checked.

The safety outcomes included procedural complications (perforation and dissection) and hemorrhagic complications. An intracerebral hemorrhage (ICH) was classified on the basis of the second European-Australasian Acute Stroke Study classification, and symptomatic intracerebral hemorrhage (sICH) was defined as any hemorrhage associated with an increase in the NIHSS score by ≥4 within a 24-hour period.[17]

Statistical Analysis

The differences in the baseline characteristics and the procedural and clinical outcomes between the UK and non-UK groups were compared. The Pearson χ^2 test or Fisher exact test was used for categoric variables, and the Mann-Whitney *U* test, for continuous variables. Multivariable logistic regression was performed to evaluate the independent variables for successful reperfusion in patients with refractory thrombus. All statistical analyses were performed using SPSS for Windows (Version 20.0; IBM). A *P* value < .05 was considered statistically significant.

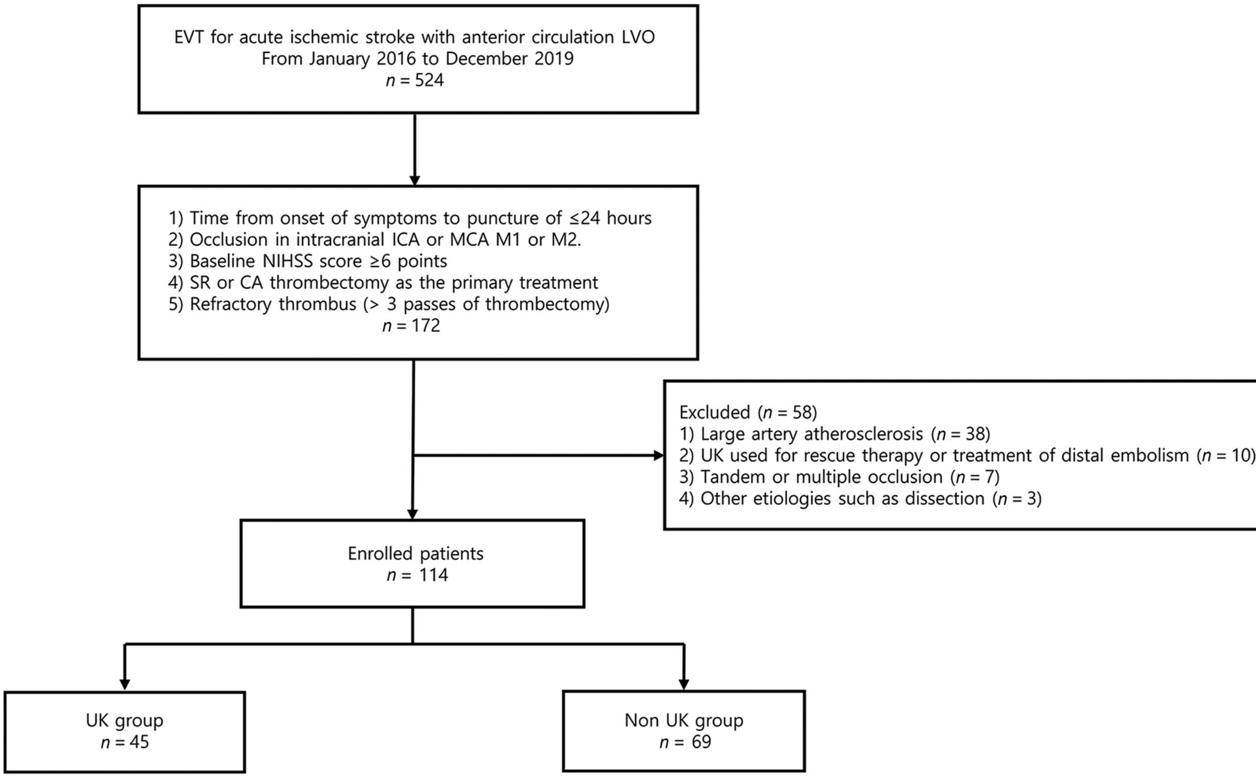

FIG 1. Flow chart of patient selection. EVT indicates endovascular treatment.

RESULTS

A flow chart depicting the patient recruitment process is shown in Fig 1. Between January 2016 and December 2019, a total of 524 patients with acute ischemic stroke with LVO in the anterior circulation underwent endovascular treatment within the first 24 hours after symptom onset. Of the 524 patients, 172 patients were identified as having refractory thrombus. Of these, 58 patients were excluded due to the following reasons: 1) large-artery atherosclerosis ($n = 38$); 2) use of UK for rescue therapy or treatment of distal embolism ($n = 10$); 3) tandem or multiple occlusions ($n = 7$); and 4) other etiologies of stroke, such as dissection ($n = 3$). Finally, 114 patients (median age, 75 years; interquartile range [IQR], 65–81 years; 56 men [49.1%]) with refractory thrombus qualified for the final analysis. Of the included 114 patients, 45 patients (39.5%) were included in the UK group and administered IA UK as an adjunct to MT, and the remaining 69 patients (60.5%) were included in the non-UK group and did not receive IA UK during MT.

The baseline characteristics of all patients and 2 subgroups are shown in Table 1. The median NIHSS score was 15 (IQR, 12–18). Seventy-seven (67.5%) patients were identified as having cardioembolism, and 17 (14.9%) patients had active cancer at the time of acute stroke. Forty-five patients (39.5%) had MCA M1 occlusions, and 29 patients (25.4%) received intravenous tPA before endovascular treatment. There were no significant differences in the baseline characteristics between the 2 groups.

The procedural and clinical outcomes are summarized in Tables 2 and 3. A total of 45 patients received adjunctive IA UK (median dose, 40,000; IQR, 20,000–60,000 IU) during MT to treat refractory thrombus despite conventional MT (before IA UK; median number of passes, 4; IQR, 3–5). IA UK was administered at a median of 244 minutes (IQR, 182–470 minutes) after symptom onset or after last seen well. The UK group showed a higher rate of successful reperfusion (82.2% versus 63.8%, $P = .034$) and complete reperfusion (35.6% versus 17.4%, $P = .044$) compared with the non-UK group. Additionally, the procedure time was shorter in the UK group (median, 54 versus 69 minutes; $P = .137$), with fewer rescue therapies, albeit without statistical significance (60.0% versus 73.9%, $P = .118$). After the injection of UK, final reperfusion was obtained after a mean of 15 minutes (range, 10–18 minutes), and 2 additional thrombectomies (range, 1–4) were performed on average. Furthermore, conversion to the other MT technique was performed in 10 (22.2%) patients. With respect to the number of passes, there were more patients who underwent MT with ≥8 passes in the non-UK group than in the UK group (13.3% versus 18.8%, $P = .441$). Among patients who had ≥8 MT passes, the non-UK group showed lower rates of successful reperfusion compared with the UK group (100.0% versus 30.8%, $P = .011$) (Fig 2).

Regarding procedural complications, the incidence of vessel perforation and dissection was comparable between the 2 groups (2.2% versus 1.4% and 2.2% versus 5.8%, respectively). Overall, vessel perforation occurred in 2 (1.8%) patients, and dissection occurred in 5 (4.4%) patients. sICH and SAH were not different between the 2 groups (11.1% versus 14.5%, $P = .602$, and 4.4% versus 7.2%, $P = .702$, respectively).

In a subgroup analysis, comparison of successful reperfusion rates according to the etiology of stroke is presented in the

Table 1: Baseline characteristics between the 2 groups[a]

	Total (*n* = 114)	UK Group (MT+UK+MT) (*n* = 45)	Non-UK Group (MT+MT) (*n* = 69)	*P* Value
Age[b]	75 (65–81)	74 (63–81)	75 (65–82)	.615
Male	56 (49.1)	21 (46.7)	35 (50.7)	.672
Risk factor				
Hypertension	59 (51.8)	23 (51.1)	36 (52.2)	.912
Diabetes	27 (23.7)	12 (26.7)	15 (21.7)	.545
Dyslipidemia	20 (17.5)	10 (22.2)	10 (14.5)	.289
Smoking	15 (13.2)	7 (15.6)	8 (11.6)	.541
Coronary artery disease	9 (7.9)	3 (6.7)	6 (8.7)	1.000
Atrial fibrillation	72 (63.2)	26 (57.8)	46 (66.7)	.336
TOAST				
LAA	0 (0.0)	0 (0.0)	0 (0.0)	
CA	77 (67.5)	29 (64.4)	48 (69.6)	.568
SUD	19 (16.7)	6 (13.3)	13 (18.8)	.441
Cancer-related stroke	17 (14.9)	9 (20.0)	8 (11.6)	.218
IV tPA	29 (25.4)	9 (20.0)	20 (29.0)	.282
Admission NIHSS[b]	15 (12–18)	15 (10–18)	15 (12–19)	.080
Baseline ASPECTS[b]	8 (7–9)	8 (7–9)	8 (7–9)	.328
Occlusion site				.182
ICA	42 (36.8)	12 (26.7)	30 (43.5)	
M1	45 (39.5)	20 (44.4)	25 (36.2)	
M2	27 (23.7)	13 (28.9)	14 (20.3)	

Note:—TOAST indicates Trial of Org 10172 in Acute Stroke Treatment[31]; LAA, large-artery atherosclerosis; CA, cardioembolism; SUD, stroke of undetermined etiology.
[a] Values in parentheses represent the number of patients (%).
[b] Data are median and numbers in parentheses are IQR.

Table 2: Procedural characteristics in the UK group

Characteristics	Quartile or No. (%)
Dose of IA UK (IU)	40,000 (20,000–60,000)
Dose of IA UK based on site	*P* value = .056[a]
ICA (IU)	60,000 (58,000–100,000)
M1 (IU)	40,000 (28,000–60,000)
M2 (IU)	40,000 (20,000–50,000)
UK to reperfusion time (min)	15 (10–18)
Rescue therapy after IA UK	10 (22.2)
No. of passes before IA UK	4 (3–5)
No. of passes after IA UK	2 (1–2)
Final reperfusion status	
0–1	2 (4.4)
2a	6 (13.3)
2b	21 (46.7)
3	16 (35.6)

[a] *P* value was calculated by the Kruskal-Wallis test.

Online Supplemental Data. Among patients who had cardioembolism or active cancer, the UK group showed a higher rate of successful reperfusion in the refractory thrombus group (86.2% versus 54.2%, $P = .004$; 77.8% versus 50.0%, $P = .335$, respectively); however, the latter did not reach statistical significance compared with the non-UK group.

Multivariate logistic regression analysis showed that the procedure time (OR = 0.98; 95% CI, 0.962–0.998; $P = .026$) and intra-arterial urokinase (OR = 3.682; 95% CI, 1.156–11.730; $P = .027$) were independent predictors of successful reperfusion in patients with multiple MT passes (≥3) when adjusted for age, intravenous tPA, baseline NIHSS, M2 occlusion, onset to puncture time, rescue therapy, distal embolism, and number of passes (Table 4).

DISCUSSION

The results of our study indicate that patients with embolic LVO with refractory thrombus who were treated with IA UK as an adjunct to MT showed a higher rate of successful reperfusion and a shorter procedure time compared with those who were not treated with IA UK. In addition, the adjunctive use of IA UK for refractory thrombus did not increase the risk of procedural and hemorrhagic complications. Moreover, the use of IA UK was shown to be an independent predictor of successful reperfusion in patients with embolic LVO with refractory thrombus after adjustment for multiple confounders.

Only a handful of retrospective studies to date have evaluated the safety and efficacy of IA thrombolysis before, after, or during MT for various purposes. Kaesmacher et al[12] recently reported that in selected patients, the use of IA UK during or after MT may not only be safe but may also improve angiographic reperfusion. However, this study included the use of IA UK not only as adjunctive therapy to MT (25%) but also as a rescue therapy (without additional MT) (15%), as a method to improve reperfusion (from TICI 2a or 2b) (53%) and treatment of emboli to new territory (7%). Zaidi et al[11] also recently reported that IA tPA could be used as a rescue treatment in patients who were refractory to SR therapy, showing a successful reperfusion in 61.2% of cases without increasing the incidence of sICH. Similarly, Heiferman et al[9] and Yi et al[10] showed that using adjuvant IA tPA injection combined with SR thrombectomy improved revascularization without increasing adverse effects. Our results are in line with these studies. However, our study included only refractory cases that did not respond to multiple attempts of conventional MT; herein, we demonstrated that the IA UK as an adjunct to MT increased the rate of successful and complete reperfusion and shortened the procedure time without increasing the rate of hemorrhagic complications compared with the non-IA UK group. To the best of our knowledge, this is the first report to explore the efficacy of IA UK as an adjunctive option to augment MT in the setting of embolic LVO with refractory thrombus.

The greatest concern of using IA UK is the risk of hemorrhage. The most severe complication of IA UK is sICH, which is known to occur in 10% of patients in the recombinant prourokinase group, as shown in the previous Prolyse in Acute Cerebral Thomboembolism (PROACT-II) trial,[18] and in 5.2% in those

Table 3: Procedural and clinical outcomes between the 2 groups[a]

	Total (*n* = 114)	UK Group (MT+UK+MT) (*n* = 45)	Non-UK Group (MT+MT) (*n* = 69)	*P* Value
Onset to puncture time (min)[b]	158 (110–413)	182 (122–412)	149 (102–420)	.561
Procedure time[b]	62 (42–93)	54 (39–88)	69 (49–113)	.137
Onset to reperfusion time[b]	253 (169–491)	254 (195–481)	231 (164–503)	.561
First-line technique				.533
SR	72 (63.2)	31 (68.9)	41 (59.4)	
CA	29 (25.4)	9 (20.0)	20 (29.0)	
Combined technique	13 (11.4)	5 (11.1)	8 (11.6)	
Rescue therapy	78 (68.4)	27 (60.0)	51 (73.9)	.118
Switch to SR	24 (21.1)	9 (20.0)	15 (21.7)	
Switch to CA	23 (20.2)	8 (17.8)	15 (21.7)	
Switch to SR+CA	34 (29.8)	10 (22.2)	24 (34.8)	
Total No. of passes[b]	5 (5–6)	6 (5–6)	6 (6–7)	.289
4–5 Passes	49 (43.0)	22 (48.9)	27 (39.1)	.304
6–7 Passes	46 (40.4)	17 (37.8)	29 (42.0)	.651
≥8 Passes	19 (16.7)	6 (13.3)	13 (18.8)	.441
Other adjuvant treatments	22 (19.3)	7 (15.6)	15 (21.7)	.414
Final reperfusion status				
2b–3	81 (71.1)	37 (82.2)	44 (63.8)	.034
3	28 (24.6)	16 (35.6)	12 (17.4)	.044
mRS at 90 days[b]	3 (2–5)	3 (1–4)	3 (2–5)	.352
mRS 0–2 at 90 days	41 (36.0)	17 (37.8)	24 (34.8)	.745
Mortality at 90 days	16 (14.0)	7 (15.6)	9 (13.0)	.706
Vessel perforation	2 (1.8)	1 (2.2)	1 (1.4)	1.000
Dissection	5 (4.4)	1 (2.2)	4 (5.8)	.647
ICH	15 (13.2)	5 (11.1)	10 (14.5)	.602
SAH	7 (6.1)	2 (4.4)	5 (7.2)	.702
HI1 or HI2	20 (17.5)	7 (15.6)	13 (18.8)	.652
PH1 or PH2	8 (7.0)	2 (4.4)	6 (8.7)	.476

Note:—HI indicates hemorrhagic infarction; PH, parenchymatous hematoma.
[a] Values in parentheses represent the number of patients (%).
[b] Data are medians and numbers in parentheses are IQR.

receiving IA UK as an adjunct treatment to MT, as shown in a recent report.[12] However, our study shows that the occurrence of sICH was 11.1% in those with IA UK. However, the patients in our study consisted of only those who had refractory occlusion due to embolic thrombi, which is usually related to large clot burden, a long procedure time, and an increased number of passes. Thus, our patients were, at baseline, probably at higher risk of poor outcome. Despite these circumstances, we found that the occurrence of sICH was comparable between the UK and non-UK groups. This finding may be explained by an improvement in the procedural efficacy and perfusion, which minimizes infarction expansion, ultimately reducing the overall ICH risk.[19,20]

Despite significant improvements in the various endovascular techniques, some situations are not amenable to conventional methods, especially in the case of large and/or stubbornly rooted thrombi.[8] Recently, several studies reported a novel rescue technique using double SRs, showing safe and effective outcomes and thereby demonstrating it as a potential option for refractory LVO.[8,21,22] Besides, Chang et al[23] reported that rescue stent placement for failed MT achieved successful reperfusion in 64.6% of cases. Nonetheless, double-stent thrombectomy is a relatively complex technique that demands extensive technical experience as well as specific anatomic features, like arterial bifurcation.[21,22] In addition, the increased cost of 2 SRs is another disadvantage. Moreover, rescue permanent stent placement is preferable for refractory occlusion caused by atherosclerotic stenosis or arterial dissection rather than for embolic occlusion. In addition, a drawback of permanent stent placement is that it requires antiplatelet medication during or immediately after the treatment in patients with acute stroke.

Our results showed that the efficacy of reperfusion is better with the use of IA UK than without it in patients with refractory thrombus. There are several possible advantages to using local IA UK as an adjunct to MT in refractory thrombus. First, the local IA thrombolysis enhances the efficacy of thrombectomy by fibrin degradation which softens and increases the surface area of the clots enabling easier detachment.[24,25] Second, UK thrombolysis also decreases the surface area interaction with the vessel wall, which reduces friction/adhesion.[3] These theoretic advantages of combining IA UK and MT could help explain the improvement in reperfusion in patients with LVO with refractory thrombus.

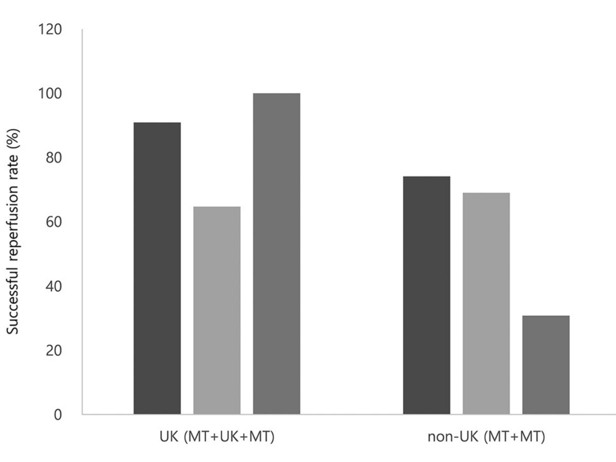

FIG 2. Comparison of successful reperfusion rates according to the total number of passes between the 2 groups.

Previous reports indicated that fibrin-rich thrombi are less responsive to SR thrombectomy and thrombolysis compared with red blood cell–rich thrombi.[26,27] Thrombi retrieved from active cancer usually show high fibrin/platelet and low erythrocyte fractions, whereas cardioembolic stroke is associated with red blood cell–rich thrombi.[28] In exploring the effect of IA UK on reperfusion of refractory LVO, according to stroke etiology, IA UK enhanced the reperfusion among patients with cardioembolism. Moreover, we found a trend toward higher successful reperfusion in patients with active cancer who received IA UK than in those who did not. This finding may be explained by the lysis effect of IA UK on dense fibrin fiber within the thrombi from active cancer, despite its resistance to lysibility compared with red blood cell–rich thrombi.[27] Our subgroup results implied that the use of local IA UK as an adjunct to MT could be a treatment option for refractory occlusion from cancer-related stroke as well as cardioembolism.

Table 4: Multivariable analysis of successful reperfusion in patients with multiple passes (≥4) of mechanical thrombectomy

	Successful Reperfusion (mTICI 2b/3)	
	Adjusted OR (95% CI)	*P* Value
Age	1.018 (0.971–1.066)	.463
IV tPA	0.773 (0.240–2.485)	.665
Baseline NIHSS	0.986 (0.881–1.104)	.806
ICA occlusion	1.287 (0.405–4.091)	.669
Onset to puncture time	0.999 (0.997–1.001)	.385
Procedure time	0.980 (0.962–0.998)	.026
Rescue therapy	0.816 (0.252–2.961)	.816
No. of passes	0.778 (0.538–1.125)	.182
Distal embolism	0.828 (0.248–2.765)	.759
Intra-arterial urokinase	3.682 (1.156–11.730)	.027

There were scarce and discrepant data for determining the optimal number of passes and the optimal timing of switching to the other rescue therapies during MT.[29] Some previous studies suggested ≥4 passes of thrombectomy as the maximum cutoff point before futile reperfusion,[25] while others found that patients who achieve successful reperfusion after ≥4 MT passes still had better outcomes compared with patients without reperfusion.[30] In our study, the UK group compared with the non-UK group showed not only fewer cases of an excessive number of passes (≥8 passes), but among those with an excessive number of passes, the rate of successful reperfusion was higher. Nevertheless, our findings should not be interpreted as suggestive of endless efforts to achieve favorable reperfusion. In our cohort, 33 cases still remained unsuccessful, even with the use of IA UK as an adjunct to MT. Furthermore, multiple attempts at MT could be associated with an increased procedure time and higher complication rates. Thus, we believe that the early use of adjunctive IA UK may be beneficial when thrombus is deemed not responsive to the standard MT.

To the best of our knowledge, there are limited data on the role of IA UK and its relation to a modern MT technique. Although several previous studies reported various techniques and doses of IA UK, it has mostly been used as a rescue therapy or for distal embolism.[12,14,18] Currently, there is no standardized protocol for dosing and administration of IA UK as an adjunct to MT for refractory thrombus. In our cohort, IA UK tends to be given in various doses, depending on the occlusion site; generally, if it is locally administrated, a lower dose (median, 40,000 IU) of IA UK seems to be sufficient to enhance the efficacy of thrombectomy, which is followed by a relatively short duration of action (median UK injection to reperfusion time, 15 minutes) (Fig 3). However, further research on the optimal protocol of IA UK is warranted.

There are several limitations to this study. First, due to the nonrandomized, retrospective design, there could be bias; the use of IA UK and the selection of the MT technique for refractory occlusion were at the discretion of the operator. Hence, the conclusion of improved reperfusion without an increase in the risk of hemorrhage should be interpreted cautiously. Second, the sample size may not have been large enough to show

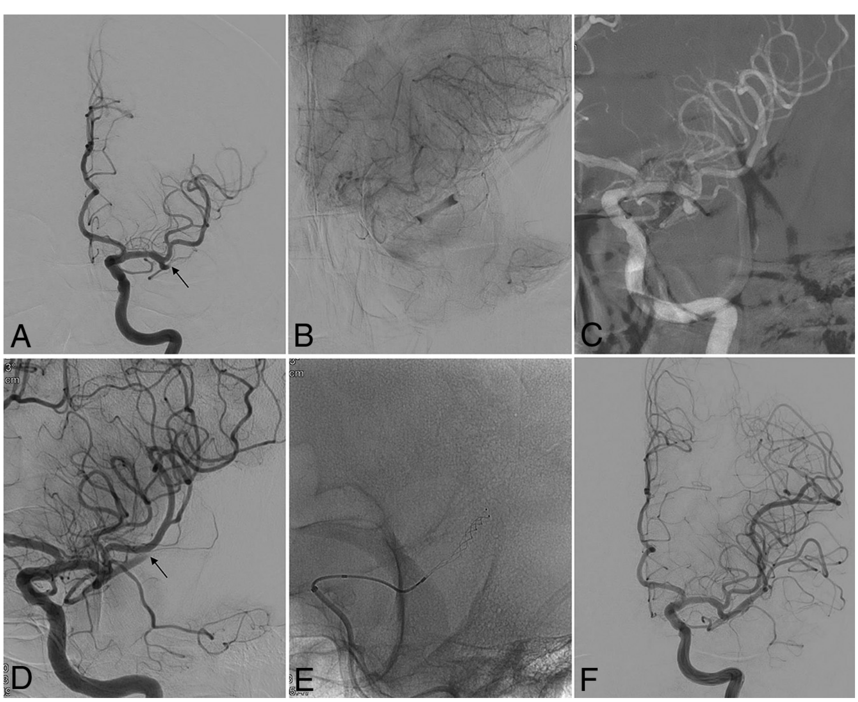

FIG 3. *A*, A-63-year-old male patient with acute stroke due to left MCA proximal M2 occlusion (*arrow*). *B*, Left ICA angiogram obtained after SR thrombectomy (twice) and CA thrombectomy (twice) (not shown) still shows complete occlusion at the left MCA M2 segment. *C*, Intra-arterial urokinase (40,000 IU) is injected through a 0.021-inch microcatheter from the distal-to-proximal portion of the thrombus. *D*, After completion of urokinase administration, additional SR thrombectomy followed (not shown). The angiographic morphology of the thrombus is changed, and minimal recanalization is achieved (*arrow*). *E* and *F*, After 1 more attempt of SR thrombectomy, complete recanalization is achieved.

statistical differences between the subgroups of this cohort. Another limitation could be the lack of histologic examination of the retrieved clots. The relationship between the thrombus composition and the efficacy of combining IA UK with MT could be a topic for future research.

CONCLUSIONS

The use of local IA UK as an adjunct to MT seems to be a safe and effective method for treating embolic LVO with refractory thrombus that is unresponsive to conventional MT. The use of adjunctive IA UK may provide enhanced reperfusion not only in patients with cardioembolism but also in those with cancer-related stroke. Further prospective studies are needed to verify this method.

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