

# Review of the Current Status of Intra-Arterial Thrombolysis for Treating Acute Cerebral Infarction: a Retrospective Analysis of the Data from Multiple Centers in Korea

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## Index terms :

Brain ischemia  
Brain infarction  
Thrombolytic therapy

## Korean J Radiol 2007; 8: 87-93

Received February 28, 2006; accepted after revision May 29, 2006.

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This study was supported by a grant from Guerbet Korea, Seoul, Korea.

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**Objective:** The purpose of the study was to review the current status of intra-arterial (IA) thrombolysis in Korea by conducting a retrospective analysis of the data from multiple domestic centers.

**Materials and Methods:** The radiologists at each participating institution were asked to fill out case report forms on all patients who had undergone IA recanalization due to acute anterior circulation ischemia. These forms included clinical, imaging and procedure-related information. A central reader analyzed the CT/MR and angiographic results. The rates of successful recanalization, hemorrhagic transformation and functional outcome were obtained. The univariate analyses were performed together with the multivariate analysis.

**Results:** We analyzed the data from 163 patients, and they had been treated at seven institutes. The initial imaging modalities were CT for 46 patients (28%), MR for 63 (39%), and both for 54 (33%). Various mechanical treatment methods were applied together in 50% of the patients. Radiologically significant hemorrhage was noted in 20/155 patients (13%). We found various factors that influenced the recanalization rate and the occurrence of significant hemorrhagic transformations. The favorable outcome rate, reported as modified Rankin Scale  $\leq 2$ , was 40%, and the mortality rate was 11%. The factors that predicted a poor functional outcome were old age ( $p = 0.01$ ), initially severe neurological symptoms ( $p < 0.0001$ ), MR findings of a wide distribution of lesions ( $p = 0.001$ ), involvement of the basal ganglia ( $p = 0.01$ ), performance of procedures after working hours ( $p = 0.01$ ), failure of recanalization ( $p = 0.003$ ), contrast extravasation after the procedure ( $p = 0.007$ ) and significant hemorrhagic transformation ( $p = 0.002$ ). The subsequent multivariate analysis failed to show any statistically significant variable.

**Conclusion:** There was a trend toward increased dependency on MR imaging during the initial evaluation and increased usage of combined pharmacologic/mechanical thrombolysis. The imaging and clinical outcome results of this study were comparable to those of the previous major thrombolytic trials.

**W**ith the first successful use of local intra-arterial (IA) thrombolysis for vertebrobasilar disease (1), many studies have shown that IA application of thrombolytics can successfully treat hyperacute ischemic strokes (2 – 8). However, in Korea, this procedure has yielded variable results (9 – 11). A combination of microcatheter techniques with their improved performance has increased the effectiveness and safety of IA thrombolysis. In addition to the local infusion of

thrombolytics, balloon angioplasty catheters, various metallic stents and other mechanical measures have also been used to increase the recanalization rate (12–14).

In the single successful randomized controlled trial of IA thrombolysis that has been conducted to date, the PROACT-II Trial (7), thrombolytic pro-urokinase was infused over two hours without manipulation of the clot. Yet the techniques used for IA thrombolysis differ from one center to another, according to the endovascular technique, and the outcomes of this procedure, as measured by the recanalization rate and the functional outcome, have not been consistent (15). This lack of standardization, along with the inconsistent outcomes, has prompted us to investigate the current IA thrombolysis techniques and their radiological and clinical results in Korea. Therefore, in conjunction with the Stroke Study Group of the Korean Society of Neuroradiology and Head & Neck Radiology (KSNHNR), we retrospectively analyzed the current status of IA thrombolytic therapy for the treatment of acute cerebral ischemic lesions. We determined what modalities are used for the radiological evaluation and the findings, the treatment patterns and the short-term clinical results, including the rate of hemorrhagic transformation, the mortality rate and the clinical outcome, and we determined some of factors that are prognostic for a poor outcome.

## MATERIALS AND METHODS

The study was designed as a multicenter, retrospective collection of cases with using a case reporting form. Only patients who underwent an IA recanalization procedure due to acute anterior circulation ischemia in the internal carotid artery (ICA) and the middle cerebral artery (MCA), and this was performed within the past five years, were included in this review.

The case reporting form was provided to each enrolled institute. This form included the basic clinical information, the initial imaging results, the angiography and procedure-related information, the follow-up imaging results and the clinical outcome of each patient together with the actual imaging data. We requested that the clinical and procedure-related parts of the form be filled out by the radiologist at each center.

The basic clinical information included age, gender, National Institute of Health Stroke Scale (NIHSS) score at the time of presentation and the presence of underlying diabetes, hypertension and/or heart disease. Selection of the initial imaging modality, the time from symptom onset to the time of imaging, the time from symptom onset to the initiation of angiography (the first angiographic run), and

the time of day of the procedure (i.e., during or after working hours) were analyzed.

The pre- and post-procedure CT/MR images and angiographic findings were evaluated by the board-certified radiologist who had more than five years of experience with IA thrombolysis. The CT results were analyzed for the presence of early CT signs, involvement of basal ganglia and the presence of hyperdense MCA signs. The MR findings were analyzed to determine the extent of the lesion on the diffusion-weighted images (DWI), involvement of the basal ganglia, the presence of perfusion/diffusion mismatch and presence of microbleeds. The angiographic results were analyzed for the anatomic location of the culprit steno-occlusive lesions and the initial and post-procedure Thrombolysis in Myocardial Infarction (TIMI) grades. We regarded a post-procedure TIMI grade of II or III as indicative of successful recanalization.

The immediate post-procedure CT was reviewed for the presence of hemorrhages and parenchymal hyperdensity that was observed due to the contrast media used during the thrombolytic procedure. The follow-up CT or MR findings were analyzed for occurrence of hemorrhagic transformation, which was evaluated by the European Cooperative Acute Stroke Study (ECASS) classification method. We calculated the rates of occurrence of any hemorrhage and any radiologically significant hemorrhage, with the latter regarded as hemorrhage with a mass effect, such as parenchymal hematoma type 2 or some cases of hemorrhagic infarction type 2. These rates were surrogate indicators of symptomatic hemorrhages (16, 17).

The clinical outcome analysis was performed using the modified Rankin Scale (mRS), which was recorded at various time points after the procedure (at 1–12 months, except for the patients who died in the interim). If the clinical outcome data were not available, the case was dropped from the clinical outcome analysis. We calculated

**Table 1. Demographic Characteristics at the Baseline**

	n/N* (percentage)
Total number of patients	163
Men	110/163 (68%)
Mean age (yrs)	63 ± 12
Mean initial NIHSS score	14 ± 5
Diabetes	24/147 (16%)
Hypertension	78/150 (52%)
Etiologic classification**	
Large artery stenosis	57/163 (35%)
Cardioembolism	54/163 (33%)
Other causes or unclassified	51/163 (32%)

Note.—n = number, \* N = the number of patients with available data.

\*\*According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST).

the percentage of patients with each mRS score, as well as the mortality rate, which was defined as the rate of procedure-related deaths within one month.

Univariate logistic regression methods were used to analyze the factors that had an influence on successful recanalization, significant hemorrhagic transformation and poor functional outcome results. The proportion of patients with a mRS of more than 3 was used for the latter. Variables with *p* values less than 0.05 on the univariate analyses were chosen as the variables for the multivariate logistic regression analysis. In both analyses, *p* values less than 0.05 were considered statistically significant.

**RESULTS**

**Patient Demographics**

The basic demographic characteristic of the 163 patients from seven domestic institutes are summarized in Table 1. The mean time interval from the symptom onset to the initial CT scanning was 139 ±145 minutes and the mean time interval from the symptom onset to the first angiography was 280 ±178 minutes (Table 2). Out of the 149 patients for whom we were able to obtain the time of day of their angiography, 92 (62%) had the procedures

**Table 2. Time from Symptom Onset to the Initial Imaging and Treatment (the First Angiography)**

Time to Imaging	Minutes
From symptom onset to CT (n = 71)	139 ±145
From symptom onset to MR (n = 61)	206 ±207
From CT to MR (n = 47)	60 ±52
<b>Time to Treatment</b>	
From symptom onset (n = 144)	280 ±178
From CT (n = 71)	128 ±68
From MR (n = 61)	107 ±53

**Table 3. Initial CT Findings in 69 Patients**

	N (percentage)
Early CT sign	
None	31 (45%)
Less than 1/3 of the MCA territory	31 (45%)
Over 1/3 of the MCA territory	7 (10%)
Low density involving the basal ganglia	
No	52 (75%)
Less than 1/2	8 (12%)
Over 1/2	9 (13%)
Positive hyperdense MCA sign	
No	49 (71%)
Yes	20 (29%)

Note.—N = number, MCA = middle cerebral artery.

performed during normal working hours (09:00–18:00).

**Initial Imaging Results**

The initial imaging modalities were CT in 46 patients (28%), MR in 63 (39%), and both CT and MR in 54 (33%). We were able to review the CT images of 69 of the 100 (69%) patients who initially underwent CT. The basic initial CT and MR findings are summarized in Tables 3 and 4, respectively.

**Angiography and Procedure**

The site of arterial stenosis (TIMI grade 1, n = 18) or occlusion (TIMI grade 0, n = 145) was the ICA, including the carotid ‘T’ occlusion, in 62 patients (38%), the MCA, including M2 occlusion, in 99 (61%) and the anterior cerebral artery in two patients (1.2%) (Table 5). Before the initiation of IA thrombolysis, 73 patients (45%) were administered intravenous tissue plasminogen activator (*t*-PA, 0.6 or 0.9 mg/kg). Urokinase at a median dosage of 400,000 IU (range 40,000–1,000,000 IU) was the IA fibrinolytic agent in 139 patients (85%), *t*-PA at a median dosage of 10 mg (range 5–20 mg) was used in 11 patients

**Table 4. Initial MR Findings in 98 Patients**

	N/Total (percentage)
Extent of the DWI lesion in the involved vascular territory	
Less than 1/3	54/98 (55%)
Less than 1/2	19/98 (19%)
Over 1/2	25/98 (26%)
Location of the DWI lesion	
Predominantly cortical	13/98 (13%)
Predominantly subcortical	30/98 (31%)
Both cortical and subcortical	55/98 (56%)
Lesion involvement of basal ganglia	
None	32/98 (32%)
Less than 1/2	29/98 (30%)
Over 1/2	37/98 (38%)
Diffusion/perfusion mismatch in 56 patients who underwent PWI	
No	7/56 (13%)
Yes	49/56 (87%)
GRE dark clot sign	
GRE (+)	35/98 (36%)
No	24/35 (69%)
Yes	11/35 (31%)
Microbleed on GRE	
GRE (+)	42/98 (43%)
None	29/42 (69%)
Less than 5	7/42 (17%)
More than 6	6/42 (14%)

Note.—N = number, DWI = diffusion-weighted image, PWI = perfusion-weighted image, GRE = gradient echo image.

(7%), and the procedure was performed without IA fibrinolytics in 13 patients (8%). In the latter case, mechanical methods were primarily applied, except for one patient, who received an IA infusion of abciximab. Various mechanical methods were applied, along with local infusion of fibrinolytics, in 82 patients (50%), including those patients who were treated with primary mechanical thrombolysis. The methods employed included mechanical disruption of the clot using a micro-guidewire (n = 49, 60%), stenting of the steno-occlusive lesion using various kinds of metallic stents (n = 17, 21%), balloon catheter angioplasty or clot disruption (n = 12, 14%) and aspiration of the clot using a large-bore guiding catheter (n = 4, 5%). A combination of these methods was used in patients for whom the primary mechanical method was ineffective in recanalization.

Postprocedure angiography was available for 152 patients. The final TIMI grades were zero in 21 patients (14%), one in 23 (15%), two in 31 (20%) and three in 77 (51%). The successful recanalization (TIMI grade 2 or 3) rate was 71%.

**Postprocedure Imaging Results**

Immediate postprocedure CT was available for 117 patients. Various patterns of parenchymal high densities were observed in 54 patients (47%), and 24 (21%) of them showed obvious hematoma formation and/or high density with a mass effect.

Hemorrhagic transformation of the lesion was evaluated in 155 patients whose follow-up CT and/or MR images were available for the review, and 55 (35%) of these patients showed variable amounts of hemorrhage. The hemorrhage pattern was hemorrhagic infarction (HI) type

1 in 15 patients (27%), HI type 2 in six (11%), parenchymal hematoma (PH) type 1 in 17 (31%) and PH type 2 in 17 (31%). Radiologically significant hemorrhage was noted in 20 of these 155 patients (13%).

**Clinical Outcome**

The clinical follow-up data were available for 158 patients. The follow-up period varied from one to 12 months, except for those patients who died in the interim. We noted mRS scores of zero in 17 patients (11%), one in 27 (17%), two in 19 (12%), three in 20 (13%), four in 33 (21%) and five in 24 (15%); these findings were comparable with those of other major thrombolysis trials (Fig. 1). Out of the 158 patients, 18 died, yielding a mortality rate of 11%.

**Results of the Univariate and Multivariate Analyses**

Among the various factors considered, an initial NIHSS score of less than 15 was the only factor that positively influenced successful recanalization (p = 0.001). Table 6 shows the univariate analysis of the factors that influenced significant hemorrhage after the procedure, and Table 7 shows the factors that influenced the poor functional outcome. Subsequent multivariate analyses failed to show any statistically significant variables both for significant hemorrhage and for a poor functional outcome.

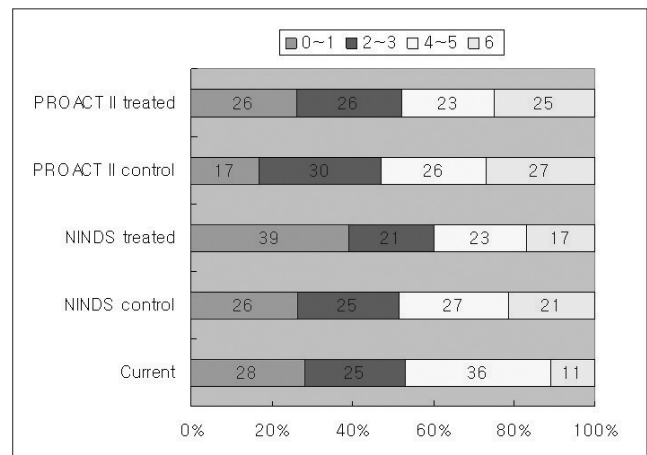
**DISCUSSION**

The results of our analysis provide an overview on the current practice status of IA thrombolysis in Korea. Although more than 30 centers in Korea actively perform neurointerventional procedures (see the 2005 member list of the Korean Society of Interventional Neuroradiology),

**Table 5. Anatomic Sites of Stenosis or Occlusion on the Initial Angiography**

Anatomic Site	N (percentage)
ICA	62 (38%)
Proximal ICA	13 (8%)
Proximal ICA and tandem MCA occlusion	7 (4%)
Distal ICA	6 (4%)
Carotid T lesion	36 (22%)
MCA	99 (61%)
Proximal MCA trunk	35 (22%)
Mid MCA trunk	16 (10%)
Distal MCA trunk	35 (22%)
M2	13 (8%)
ACA	2 (1%)

Note.—N = number, ICA = internal carotid artery, MCA = middle cerebral artery, ACA = anterior cerebral artery.



**Fig. 1.** Functional outcome represented as modified Rankin Scale and comparison of the current results with those of the control and treated groups of the major thrombolysis trials.

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**Table 6. Univariate Relationships of the Significant Hemorrhage after Thrombolysis**

Variable	Odds Ratio	P value
Demographic		
Age (> 65 yrs)	0.70	0.46
Sex (male)	0.32	0.08
Diabetes	0.96	0.95
Hypertension	3.03	0.044
Cardioembolism	1.38	0.51
Initial NIHSS score $\geq$ 15	3.75	0.046
CT findings		
Positive early CT sign	1.80	0.38
Violation of one-third rule	4.42	0.08
Basal ganglia involvement	4.08	0.03
Hyperdense MCA sign (+)	1.21	0.73
MR findings		
DWI lesion over 1/3 of MCA territory	0.86	0.81
DWI lesion over 1/2 of MCA territory	1.55	0.51
Basal ganglia involvement	3.93	0.042
Presence of diffusion-perfusion mismatch	0.84	0.88
Visible dark clot on T2*-weighted images	8.63	0.08
Procedure and post-procedure imaging findings		
After working hours	2.82	0.038
Within 3 hours after symptom onset	1.64	0.46
Within 6 hours after symptom onset	0.39	0.22
Combined IV thrombolysis	0.79	0.62
Combined mechanical thrombolysis	0.93	0.88
Failed recanalization	0.86	0.77
Any contrast staining on post-CT	15.8	< 0.0001
Contrast extravasation on post-CT	14.9	< 0.0001

Note.—DWI = diffusion-weighted image, MCA = middle cerebral artery.

**Table 7. Univariate Relationships with a Poor Functional Outcome (mRS > 3)**

Variable	Odds Ratio	P value
Demographic		
Age (> 65 yrs)	2.27	0.01
Sex (male)	0.87	0.68
Diabetes	1.52	0.35
Hypertension	1.12	0.73
Cardioembolism	0.88	0.70
Initial NIHSS score $\geq$ 15	4.88	< 0.0001
CT findings		
Positive early CT sign	1.57	0.37
Violation of the one-third rule	5.8	0.12
Basal ganglia involvement	1.26	0.68
Hyperdense MCA sign (+)	1.21	0.73
MR findings		
DWI lesion over 1/3 of MCA territory	2.35	0.04
DWI lesion over 1/2 of MCA territory	6.14	0.001
Basal ganglia involvement	3.22	0.01
Presence of diffusion-perfusion mismatch	—	0.003
Visible dark clot on T2*-weighted images	2.10	0.33
Procedure and post-procedure imaging findings		
After working hours	2.41	0.01
Within 3 hours after symptom onset	0.98	0.97
Within 6 hours after symptom onset	0.93	0.87
Combined IV thrombolysis	1.08	0.80
Combined mechanical thrombolysis	0.96	0.89
Failed recanalization	0.31	0.003
Any contrast staining on post-CT	2.33	0.03
Contrast extravasation on post-CT	4.00	0.007
Significant hemorrhage	26.7	0.002

Note.—DWI = diffusion-weighted image, MCA = middle cerebral artery.

only seven of these centers participated in this study. It is likely that many of the other centers have been reluctant to perform IA thrombolysis, primarily due to a shortage of trained personnel. In Western countries also, IA thrombolysis is performed less frequently than the IV method due to a shortage of interventional specialists (15).

We found that from the symptom onset, the mean time before the imaging was 2.3 hours, and the mean time before the treatment was 4.7 hours; these results are comparable with those reported in the PROACT II Trial (7). The mean delay between the CT and MR imaging was about 60 min, which was one of the in-hospital delay factors for IA thrombolysis (18).

About 40% of these procedures were performed before or after normal working hours, and the functional outcome results of these patients were generally poorer than those of the patients who were treated during normal working hours. One of the primary reasons for the poorer outcome in the former group of patients may be the in-hospital

delay. A well-organized stroke team and an on-call system may improve the results for these patients.

One notable finding of our survey was the preference for MR as the initial imaging modality. MR was the sole initial imaging modality in 39% of patients, and it was combined with the CT imaging in 33%. Although MR has the potential disadvantage of time delay, it has shown an advantage for the initial evaluation of acute ischemic stroke (19–22). However, a delay in the initiation of the optimal treatment due to logistic limitations of MR imaging cannot be justified. Many centers use multi-detector CT imaging to overcome the inevitable logistic limitation of MR imaging (21, 23).

It was notable that about 10% of the cases in the study were in violation of the ‘one-third rule’, which is one of the most important exclusion criteria of the European thrombolysis trial (24) and the PROACT II trial (7). Out of all the patients evaluated by the MR imaging, 26% showed

DWI lesions covering more than half of the involved vascular territory. This was probably due to a lack of certain inclusion or exclusion criteria for MR imaging in respect to the patient selection for IA thrombolysis.

Although we limited our study to patients with anterior circulation infarction and so increasing the homogeneity of the study group, we found a wide variation in the occlusion site, from the proximal ICA to the proximal portion of the MCA.

Our observed recanalization rate, 71%, was slightly higher than that reported in the PROACT II trial (7), which may have been due, at least in part, to the liberal use of mechanical methods (14). We were disappointed to find that only one factor, the lower initial NIHSS score, had a significant effect on the successful recanalization rate. In contrast to reports on the combined or sequential thrombolytic treatments (25–27), we found that the use of IV thrombolytics prior to the IA procedure did not affect the recanalization rate. However, in many of these patients, however, the initial IV administration of thrombolytics was ineffective. About half of the patients received a combination of IA and mechanical thrombolysis, although the use of mechanical methods failed to improve the recanalization rate ( $p = 0.083$ ).

One of the major concerns after the IA thrombolytic treatment is hemorrhagic transformation of the affected lesion (28, 29). We found that the rate of any amount hemorrhagic transformation was 35%, and the rate of the significant hemorrhagic transformation was 13%. The univariate analysis showed that several factors that had influence on significant hemorrhagic transformation, including the presence of hypertension, severe initial neurological symptoms, involvement of the basal ganglia on CT/MR and the performance of procedures after normal working hours. In addition, the risk of significant hemorrhage was increased by the presence of any contrast density on the CT obtained immediately after the thrombolysis procedure. Violation of the one-third rule on the initial CT tended to increase the occurrence of significant hemorrhage ( $p = 0.08$ ), whereas extensive involvement of the affected vascular territory on the DWI ( $p = 0.51$ ) and the combined use of IV thrombolytics and mechanical methods had no effect.

Although direct comparison is not possible because of the differences in the patient groups, the functional outcome in our series of patients was similar to that of other major thrombolysis trials (7, 30). Among the factors that were found to influence the poor functional outcome were the old age, severe initial neurological symptoms, more extensive initial DWI lesions and involvement of basal ganglia on MR, failed recanalization, any contrast

staining on CT immediately after the procedure and the presence of significant hemorrhagic transformation. Other studies have found that these same factors were predictive of poor prognosis (8, 31, 32).

The primary limitations of this analysis were its retrospective design and the collection of data from several centers, all of which had different clinical and imaging indications for the procedure and different clinical settings. In addition, the data we collected were not representative of practice throughout Korea because only a few active centers contributed to the study. Due to our inability to collect some data from the participating centers, we were unable to perform appropriate multivariate analyses. This could be one of the possible reasons for our failure to determine any significant variables that affected the results of significant hemorrhagic transformation and poor functional outcomes. Furthermore, our analysis of the imaging data was limited due to the between-center differences in the imaging protocols, including the use of contrast enhancement, MR pulse sequences and the angiographic filming techniques. Nevertheless, the results presented here may be representative of the nation-wide data on current IA thrombolytic treatment, and they could serve as a basis for clinical practice guidelines, as well as for designing a prospective study on the basis of this protocol.

In conclusion, our multicenter, retrospective analysis of IA thrombolysis showed an increased dependency on MR imaging during the initial patient evaluation and increased application of combined pharmacologic/mechanical thrombolysis in Korea. Both our imaging and clinical outcome results were comparable with those of the other major thrombolytic trials. Our results could be used as the basis for clinical practice and for future prospective studies.

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