A retrospective study on intracerebral haemorrhage reduction by MRI versus CT in intravenous thrombolysis for acute ischaemic stroke

於急性缺血性中風以靜脈注射溶解血栓，比較磁力共振及電腦掃描在減少大腦內出血方面的一個回顧性研究

YH Yun, JY Chung, MJ Kang, JT Huh, KW Park, JK Cha

Introduction: Multimodal MRI may be an effective tool for selecting suitable acute ischaemic stroke patients for thrombolysis, reducing the risk of haemorrhage. In this study, we demonstrated the usefulness of our central alerting system to reduce door-to-needle time for thrombolysis following MRI. This system allowed timely intervention and reduced the rate of symptomatic haemorrhage. ***Methods:*** We reviewed the records of 73 patients with hyperacute ischaemic stroke who received intravenous (IV) tissue plasminogen activator (t-PA) between January 2006 and December 2007 following the adoption of a central stroke alerting system in our hospital. ***Results:*** Of the 73 patients who received IV t-PA, 44 were based on CT and 29 on MRI findings. The door-to-needle time was 10 minutes longer for the MRI group (49.9±23.2 min) compared to the CT group (39.6±19.7 min) but it was still within the recommended 60 minutes time frame. On the other hand, the rate of symptomatic haemorrhage was lower, though insignificantly, in the MRI group (0%) compared to the CT group (13.6%) (p=0.08). ***Conclusions:*** In this study, we demonstrated that the combination of diagnostic MRI and a central alerting system might reduce the rate of symptomatic haemorrhage without compromising the door-to-needle time. (*Hong Kong j.emerg.med.* 2010;17:5-12)

導言：多方式磁力共振可以是選擇合適的急性缺血性中風病人作血栓溶解的有效工具，以減少出血的風險。這研究展示我們的中央警報系統的用處，以減少磁力共振後血栓溶解的「到診至施藥」時間。這系統容許及時介入，及減少有症狀的出血率。**方法：**在我們醫院採用了中央中風警報系統後，審查在 2006 年 1 月至 2007 年 12 月期間因超急性缺血性中風而接受靜脈注射組織纖維蛋白溶酶原激活劑的 73 名病人的記錄。**結果：**73 名病人中，44 名是基於電腦掃描結果及 29 名是基於磁力共振結果而接受靜脈注射組織纖維蛋白溶酶原激活劑。磁力共振組的「到診至施藥」時間（49.9±23.2 分鐘）比電腦掃描組（39.6±19.7 分鐘）多 10 分鐘，但仍然在建議的 60 分鐘時間框架內。相反地，磁力共振組的有病

Correspondence to:
Cha Jae Kwan, MD, PhD
Dong-A University Medical Center, Center of Stroke,
1, Dongdaesin-dong 3-ga, Seo-Gu, Busan, Korea
Email: dolsoi1323@hanmail.net

Kang Myong Jin, MD
Huh Jae Tahck, MD, PhD
Park Kyung Won, MD, PhD

Dong-A University College of Medicine, Department of Emergency Medicine, Busan, Korea
Yun Young Hyun, MD
Chung Jun Young, MD, PhD

狀出血率（0%）比電腦掃描組（13.6%）較低，雖然並不顯著（p=0.08）。**結論：**這研究顯示結合磁力共振診斷及中央警報系統可減少有症狀的出血率，而不會危及「到診至施藥」的時間。

Keywords: Cerebrovascular disorder, computed tomography, magnetic resonance imaging, tissue plasminogen activator

關鍵詞：腦血管病、電腦掃描、磁力共振造影、組織纖維蛋白溶酶原激活劑

Introduction

The only widely-accepted way to open up an obstructed vessel in acute ischaemic stroke patients is to inject intravenous (IV) tissue plasminogen activator (t-PA) within 3 hours of the onset of symptoms.[1,2] By reperfusing the ischaemic penumbra, this treatment reduces neurologic damage and produces better functional outcomes at three months post-stroke.[3] However, a major limitation is that t-PA has to be injected within 3 hours of the onset of symptoms. If it is not given within this time window, it may be ineffective or the risk of adverse events may outweigh the benefits.

This time restriction means that only 5% of ischaemic stroke patients in the United States[4-6] and 4% of patients in Korea[7] could receive t-PA. There are many reasons for the low utilisation rate of t-PA despite its known effectiveness. One of the major causes of delay is the time taken to exclude other differential diagnoses using computed tomography (CT) or magnetic resonance imaging (MRI).[8] As CT is considered less time-consuming than MRI, American ischaemic stroke guidelines recommend using CT.[8]

As about 30 minutes are required to get an image of MRI, it seems almost impossible to meet the 60 minute door-to-needle time as recommended by the National Stroke Association (door-to-needle time refers to the time interval between patient arrival at the emergency room [ER] and the administration of t-PA). Although MRI may require more processing time than CT, it provides very specific information about the extent of the damaged tissues and its use may reduce the frequency of intracerebral haemorrhage (ICH) which is a known complication of t-PA.[9]

In this study, we investigated whether it would be possible to keep the door-to-needle time to less than 60 minutes when using MRI by adopting a simple "central alerting system" to reduce the processing time of acute ischaemic stroke patients presenting to the ER.

Materials and methods

We retrospectively analysed acute ischaemic stroke patients who presented to the Dong-A University Hospital Emergency Center and received IV t-PA between 1st January 2006 and 31st December 2007, following the adoption of a basic form of central alerting system called "code RED" (Rescue Emergency stroke patients in Dong-A University Hospital).

We had two MRI machines in our hospital. When a patient presented to the Emergency Center within 3 hours of the onset of symptoms suggestive of acute ischaemic stroke, the patient would be assessed by a medical practitioner followed by an immediate broadcast to the entire hospital to notify the neurology stroke specialist and the three resident medical officers designated to the stroke service. The stroke team would immediately gather in the Emergency Center. The essential tasks of taking necessary blood tests, organising CT or MRI, getting consent from the patient or guardian, and injecting t-PA (Actylase®, Behringer Ingelheim) would be performed rapidly and, where possible, simultaneously. The patient would be asked for a simple history and examined neurologically by the neurology specialist, allowing a National

Institutes of Health Stroke Scale (NIHSS) score and modified Rankin Scale (mRS) to be calculated before transferral for CT or MRI examination, depending on which modality was available earlier.

The findings of CT or MRI were interpreted by the neuroradiologist. During MRI examination, if the area of ischaemic stroke was found to be less than half of the territory of the middle cerebral artery shown on diffusion weighted imaging (DWI) and there was no haemorrhage on the T2 image, we would inject one-tenth of the planned total dose of t-PA of 0.9 mg/kg IV, before completing the MR angiogram (MRA).

Intravenous thrombolysis would be performed ≤3 hours according to the National Institute of Neurological Disorders and Stroke criteria. Any patient with signs of ICH on MRI and those with large DWI lesion (more than 50% of the middle cerebral artery territory) would not be given IV t-PA. Treatment would be initiated either in the emergency room or in the stroke unit. The patient would receive t-PA at a dose of 0.9 mg/kg, 10% as a bolus and the rest by infusion over one hour. The management after the t-PA infusion would follow published guidelines.[3]

A brain CT would be performed immediately after t-PA treatment to evaluate whether there was ICH or not. Diffusion MRI and MRA would be used to determine the size of the ischaemic stroke and whether the obstructed vessel was reopened within 24 hours after using t-PA. If there was haemorrhage and the NIHSS score had increased by ≥4 points, the haemorrhage would be considered as significant.

We would measure the mRS again 90 days after the t-PA treatment and a mRS of ≤2 was defined as a favourable outcome. We defined "time to needle" as the time interval between the onset of stroke symptoms and the commencement of t-PA. We defined "door-to-needle" time as the time interval between the patient's arrival at the Emergency Center and the start of t-PA. Both measurements were recorded in minutes.

For statistical analysis, we performed t-test for continuous variables and Chi square or Fisher's exact test for categorical variables with $p<0.05$ considered as statistically significant.

Results

Between 1st January 2006 and 31st December 2007, a total of 806 patients presented to the Emergency Center with the diagnosis of acute ischaemic stroke, of which 73 patients received IV t-PA. The average age of these patients was 63.6±11.2 years and the average time of arrival after the start of symptoms was 85.2±42.4 min. Among the 73 patients, 44 (60.3%) patients received IV t-PA after CT and 29 (39.7%) after MRI. The average NIHSS score on arrival was 13.5±4.9 (Table 1).

Table 1. Comparisons of clinical findings between CT and MRI based thrombolysis in acute ischaemic stroke

	CT based N=44	MRI based N=29	P
Age (years)	63.7±11.1	63.3±11.6	0.89
Male	30 (68.2%)	18 (62.1%)	0.59
Door-to-needle time (min)	39.6±19.7	49.9±23.2	0.04
Door-to-needle time >60 min	6 (13.6%)	6 (20.7%)	0.43
NIHSS	14.2±5.1	12.4±4.4	0.14
Large artery atherosclerotic infarction	24 (54.5%)	14 (48.3%)	0.60
Recanalization	26 (59.1%)	21 (72.4%)	0.25
Favourable outcome (mRS≤2)	23 (53.3%)	18 (62.1%)	0.41
Symptomatic intracerebral haemorrhage	6 (13.6%)	0 (0%)	0.08
Serum glucose (mmol/dL)	9.3±5.9	7.9±2.4	0.24

mRS=modified Rankin Score; NIHSS=National Institutes of Health Stroke Scale

Thirty-eight patients had an ischaemic stroke secondary to atherosclerosis, 27 secondary to cardiac embolism, 5 patients had a lacunar infarct, and the reason for the stroke was unknown for 3 patients. The site of vessel obstruction was the M1 in 34 patients and M2 in 10 patients. Nine patients had a T-shape obstruction, 6 patients a tandem-type obstruction, 9 patients a basal artery obstruction, and 5 patients a lacunar infarct.

The average door-to-needle time between arrival at the Emergency Center and the use of IV t-PA was 43.7±21.6 min. The door-to-needle time was significantly shorter in the patient group receiving IV t-PA following CT (39.6±19.7 min) compared to the MRI group (49.9±23.2 min). There was no significant difference between the CT and MRI groups in terms of the number of patients whose door-to-needle time exceeded the time limit of 60 minutes as recommended by the National Stroke Association (6 in the CT group, 6 in the MRI group; p=0.43).

No patients in the MRI group had a symptomatic ICH while 6 patients in the CT group had haemorrhage (p=0.08). Additionally, at the 90 day assessment, the outcome was 8.8% better in the MRI group compared to the CT group, although this finding was not statistically significant.

The 6 (8.2%) patients who had ICH had a higher NIHSS score on arrival at the Emergency Center compared to the 67 patients who did not have haemorrhage (p=0.00) and all these 6 patients underwent CT before receiving t-PA (p=0.08) (Table 2).

After using IV t-PA, we would transfer the patient to the angio-room when a neuro-radiologist would be available. If the 4-vessel angiography showed a persistent occlusion (grade 0) or trickle flow (grade 1) in Thrombolysis in Cerebral Infarction (TICI) grading, we would perform intra-arterial (IA) thrombolysis.[10] Twenty-six such patients had received additional IA thrombolysis. There was no significant difference in the number of patients receiving IA t-PA between the CT and MRI groups.

The obstructed vessel was recanalized in 47 out of 73 (64.4%) patients. At 90 days after IV t-PA, 41 (56.2%) patients had a favourable outcome which was defined as a mRS≤2. We compared the patients having favourable outcome (mRS≤2) with those having poor outcome (mRS>2) at 90 days after t-PA and found that older age (p=0.02), higher serum glucose level (p=0.04), severe neurological deficit at baseline (p=0.00), and non-recanalized vessels in follow-up MRA (p=0.00) were factors significantly associated with poor outcome. The presence of symptomatic ICH was likely to associate with poor outcome but the association was not statistically significant (Table 3).

A flow-chart of the case distribution and management sequence is shown in Figure 1.

Table 2. Comparisons of clinical findings between patients with and without symptomatic brain haemorrhage

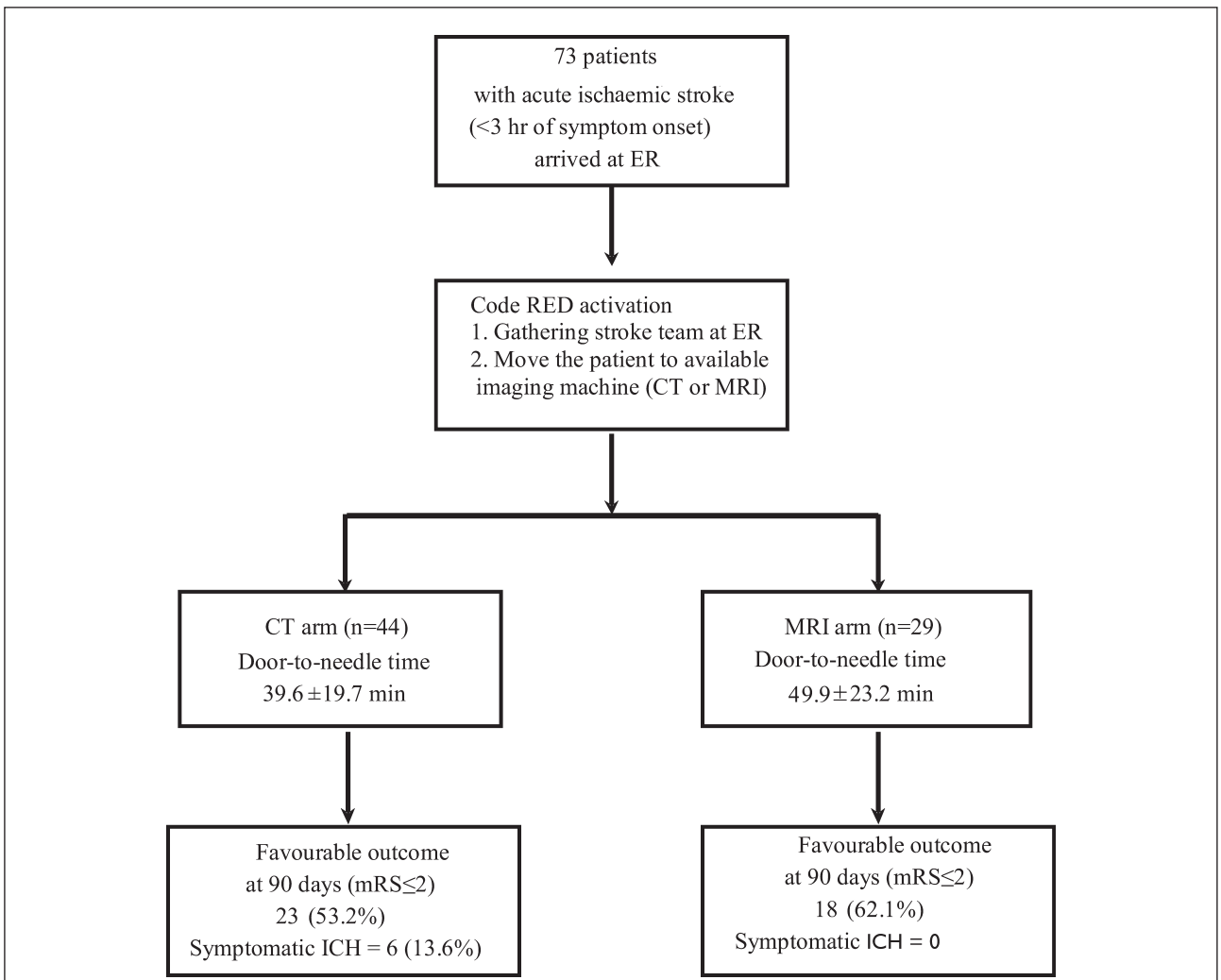
	No haemorrhage N=67	Haemorrhage N=6	p
Age (years)	63.2±11.0	68.2±14.0	0.30
Male	44 (65.7%)	4 (66.7%)	0.30
Door-to-needle time (min)	44.5±22.0	35.0±14.1	0.31
NIHSS	12.9±4.7	19.7±2.7	0.00
Large artery atherosclerotic infarction	35 (52.2%)	3 (50.0%)	0.23
Recanalization	45 (67.2%)	2 (33.3%)	0.17
Serum glucose (mmol/dL)	8.7±5.0	10.1±5.0	0.5
CT based diagnosis	38 (56.7%)	6 (100%)	0.08

mRS=modified Rankin Score; NIHSS=National Institutes of Health Stroke Scale

Table 3. Differences of clinical and laboratory findings between patients having favourable outcome (mRS ≤2) and those having poor outcome (mRS >2) after 90 days

	Good (mRS-90, 0-2) N=41	Poor (mRS-90, 3-6) N=32	p
Age	60.9±10.9	67.0±10.8	0.02
Male	30 (73.2 %)	18 (56.3 %)	0.13
Door-to-needle time (min)	43.2±21.1	44.3±22.6	0.84
CT based (Angio CT)	23 (56.1%)	21 (65.6%)	0.41
Serum glucose (mmol/dL)	7.6±2.4	10.2±6.7	0.04
NIHSS	11.5±4.5	15.9±4.4	0.00
Recanalization	40 (97.6%)	7 (21.9%)	0.00
Symptomatic intracerebral haemorrhage	1 (2.4%)	5 (15.6%)	0.08

mRS=modified Rankin Score; NIHSS=National Institutes of Health Stroke Scale



ER=emergency room; ICH=intracerebral haemorrhage; mRS=modified Rankin Score

Figure 1. Flow chart of the case distribution and management sequence.

Discussion

A central alerting system could produce an average door-to-needle time of 43 minutes as measured from the time of arrival at the emergency department of the patient with a suspected ischaemic stroke to the commencement of IV t-PA, and this was within 60 minutes as recommended by the National Stroke Association. Out of a total of 73 patients, only 12 cases (16.4%) exceeded this recommended door-to-needle time frame and that was an excellent result. Our findings suggest that even an elementary central alerting system can be very helpful in achieving a good door-to-needle time.

Although the use of MRI would prolong the door-to-needle time by an average of 10 minutes compared to the use of CT, the MRI group had a better outcome during the 90-day assessment (8.8% lower mRS) though the difference was not statistically significant. The frequency of severe ICH was 13.6% lower in the MRI group (p=0.08). These findings suggest that t-PA treatment based on MRI findings may be a safer option than those based on CT findings.

A patient who may benefit from t-PA has to face various obstacles before receiving this needed treatment. One of the most important barrier is processing delays within the hospital.[8,11] Door-to-needle time is a measure commonly used in t-PA studies.[12,13] However, many t-PA studies to date have used CT as diagnostic workup modality rather than MRI because CT can be completed in only 10 minutes but MRI study may require 30 minutes. To achieve the desirable door-to-needle time, CT would seem to offer certain advantage over MRI and it explains why the current guidelines recommend CT as the standard imaging modality.

However, recent studies have reported some advantages in using MRI.[14-16] MRI diffusion images provide clear information about the extent of any cerebral infarction within 10 minutes of the initial manifestation of symptoms; however a CT examination cannot provide this information until at least 24 hours after the onset of the stroke. The size of the stroke has important implications on the prognosis. A recent study found that the risk of cerebral haemorrhage was proportional to the size of the ischaemic stroke. We found that the rate of severe ICH in patients receiving t-PA was lower in the MRI group than the CT group. Although there was no statistical difference in the baseline NIHSS between the two groups, the CT group had more severe neurological deficit than the MRI group. This difference might have led to the difference of ICH rate observed between the two groups.

We presume that MRI must have excluded most of the large size infarcts from using IV t-PA because of its better ability to estimate the real size of ischaemic lesions within 3 hours compared to CT. So the benefit of performing MRI before t-PA is more applicable to patients who have more benign neurological severity. Using MRI, therefore, may help to select patients at lower risk of complications for t-PA use. The unfavourable increase in door-to-needle time created by using MRI has to be weighed against this potential benefit.[17,18]

In our study, we achieved a door-to-needle time of 49.9 min in the MRI group by using a central alerting system, called "code RED", which has been operated in our hospital since 2006. Prior to 2006, an acute ischaemic stroke patient who came to the Emergency Center would typically be seen by a single doctor who was responsible for all the patient's care, such as taking the history, performing the physical examination, making the provisional diagnosis, identifying contraindications to t-PA use, arranging brain imaging, getting consent from the patient and commencing treatment. The code RED system allows effective patient processing by concentrating at least four ischaemic stroke professionals in the Emergency Center immediately after a patient is identified as a potential candidate for t-PA use.

In our study, 6 patients (13.6%) in the MRI group exceeded the door-to-needle time limit of 60 minutes. When we analysed the causes of the holdup, however, we found that they were due to delay in activating the alerting system rather than delay in securing a MRI.

Those 12 patients who had exceeded the recommended door-to-needle time had the problem of failure to detect the stroke earlier in the Emergency Center. The fact that there were many patients visiting our ER and what was worse, that they usually came at the same time might be the reasons affecting the ER doctors, confusing the stroke symptoms with other similar diseases. Very often, the time delay caused by this failure was longer than that on arranging a MRI examination. Therefore it seems that improving the management system is as important as improving the arrangement of MRI with respect to the reduction of door-to-needle time.

The rate of severe ICH was significantly higher in the CT group. In fact, no MRI patients had an ICH, which suggests that MRI may offer a safety advantage over CT. Work is being done to investigate on whether the use of MRI diffusion perfusion images could allow t-PA to be safely given to patients presenting more than 3 hours after the onset of stroke.[14]

Acute ischaemic stroke is an important disease and calls for careful and expedited management in the emergency room as both morbidity and mortality are affected by the initial medical attention. In terms of outcome, the most important treatment is to provide IV t-PA within 3 hours from the onset of stroke symptoms. Rapid patient processing is therefore needed, but techniques for reducing treatment complications, such as ICH, are also important. Our findings suggest that MRI can be helpful, provided that there is a system in place to keep door-to-needle time within the recommended 60-minute time frame. The code RED system described here is a simple central alerting system that is effective in reducing treatment delay.

Limitations

This was a small retrospective study with all the biases resulting from that approach. A larger prospective randomised study is required to validate the results.

Conclusion

Stroke patients receiving CT investigation before t-PA has a significantly shorter door-to-needle time than patients receiving MRI examination. However, MRI patients may have a lower rate of ICH and are likely to have a better outcome at 90-day post-stroke. The use of a central alerting system helps to ensure that most patients would have a door-to-needle time within the recommended time frame of 60 minutes. Delays in detecting stroke patients and activating the system result in patients not being treated timely.

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