CASE SERIES

Tissue Window versus Time Window? A Review of Patients Receiving Extended Hours Thrombolysis Guided By DWI-FLAIR Mismatch : Case Series

Anna Misya'il Abdul Rashid[1,3], Mohamad Syafeeq Faeez Md Noh[2], Abdul Hanif Khan Yusof Khan[1], Wei Chao Loh[1], Janudin Baharin[1], Azliza Ibrahim[1], Liyana Najwa Inche Mat[1], Wan Aliaa Wan Sulaiman[1], Fan Kee Hoo[1], Hamidon Basri[1]

[1] Department of Neurology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400, Serdang, Selangor, Malaysia.
[2] Department of Radiology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400, Serdang, Selangor, Malaysia.
[3] Institut Penyelidikan Penuaan Malaysia (MyAgeing™), Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia.

ABSTRACT

Introduction: Intravenous thrombolysis (IVT) is the gold standard for the treatment of patients with acute ischemic stroke (AIS) presenting within four and a half hours of onset. However, development of new thrombolytic agents and advanced imaging has led to extended time for thrombolysis based on advanced imaging. Here we describe four patients who presented in the extended hours; that benefitted from thrombolysis. **Case series:** We advocate magnetic resonance imaging (MRI) for AIS, that includes diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC), fluid attenuated inversion recovery (FLAIR), susceptibility weighted imaging (SWI), and magnetic resonance angiography (MRA). We included four patients who were more than 18 years old, with National Institute of Health Stroke Scale (NIHSS) of six or more, presenting between four and a half to nine hours after stroke onset with no contraindications for intravenous thrombolysis. The imaging criteria used to determine eligibility for IVT is evidence of DWI-FLAIR mismatch on MRI. If FLAIR detects no signal change in the area of stroke on DWI, it is then termed DWI-FLAIR mismatch, or FLAIR-negative – indicating high probability that the brain tissue is still viable, and that patients are good candidates for IVT. **Conclusion:** For patients with AIS who present within nine hours, DWI-FLAIR mismatch serves as an excellent surrogate marker of salvageable brain tissue, allowing a greater proportion of patients benefiting from this life-saving therapy. Our experience also shows that with careful patient selection, treatment with IVT can safely be given without an increased risk of bleeding or mortality.

Keywords: Acute ischemic stroke (AIS), Thrombolysis, Magnetic resonance imaging (MRI), Diffusion weighted imaging (DWI), Fluid attenuated inversion recovery (FLAIR)

Corresponding Author:
Anna Misya'il Abdul Rashid, MMED
Email: annamisyail@yahoo.com
Tel:+6012-9831915

INTRODUCTION

The recent years have seen a tremendous shift in the management of acute ischemic stroke (AIS) with current guidelines approving the use of intravenous thrombolysis (IVT) up to four and a half hours from symptom onset and endovascular thrombectomy (EVT) up to 24 hours from symptom onset in the presence of large vessel occlusion (LVO) (1-2). However, a huge subset of patients who do not have clinical or imaging evidence of LVO often present outside the thrombolysis window of four and a half hours which precludes them from receiving potentially life changing therapy with IVT. In the setting of Asian countries, this delay in time of presentation is largely due to logistics reasons, where IVT is only available in certain tertiary centers (3). We wish to share our experience in successfully treating a series of patients who presented out of the thrombolysis window with the guidance of advanced magnetic resonance imaging (MRI).

Our center is a comprehensive stroke center that specializes in hyperacute stroke treatment. The layout of the hospital system is pivotal in order to create a network among satellite hospitals nearby, and to receive cases of acute stroke requiring the appropriate treatment. As such, our first line imaging is via a three Tesla (3T) MRI system. Our stroke protocol includes diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC), fluid attenuated inversion recovery (FLAIR), susceptibility weighted imaging (SWI), and magnetic

resonance angiography (MRA). In this case series, we included four patients who were more than 18 years old, with National Institute of Health Stroke Scale (NIHSS) of six or more, presenting between four and a half to nine hours after stroke onset with no contraindications for IVT. The imaging criteria used to determine eligibility for IVT is evidence of DWI-FLAIR mismatch on MRI. DWI is the earliest sequence to detect acute stroke following cytotoxic edema due to hypoperfused brain tissue. The FLAIR sequence detects the presence of vasogenic edema due to destruction of the blood brain barrier, following cytotoxic edema. If FLAIR detects no signal change in the area of stroke on DWI, it is then termed DWI-FLAIR mismatch, or FLAIR-negative – indicating high probability that the brain tissue is still viable, and that patients are good candidates for IVT. The patients in this case series presented to our center from March 2020 to December 2020. The radiographical images and sociodemographic data were reviewed from the hospital electronic medical records and information was retrieved for the preparation of this manuscript.

CASE SERIES

PATIENT 1

The first patient was a 71-year-old female with hypertension and dyslipidemia. She presented with right sided body weakness and vomiting at five hours post stroke onset. The NIHSS score was ten. MRI revealed an acute left hemipontine infarct with DWI-FLAIR mismatch (Fig. 1A-1B). MRA showed no LVO. She was given IVT with tenecteplase (TNK) 0.25mg/kg. The NIHSS score improved from ten to five, and she remained stable until discharge. A computed tomography (CT) scan of the brain at 24 hours did not show intracerebral hemorrhage (ICH), and she was started on antiplatelet therapy. At three months, her NIHSS score significantly reduced to three with a modified Rankin scale (MRS) of one.

PATIENT 2

The second patient was a 62-year-old male with diabetes mellitus, hypertension, ischemic heart disease and atrial fibrillation. He presented with right sided body weakness at five and a half hours after stroke onset with a NIHSS score of 14. MRI showed a left parietal acute infarct with DWI-FLAIR mismatch (Fig. 2A-2B). MRA showed no LVO. IVT with TNK 0.25mg/kg was administered. The patient showed clinical improvement as early as day two post thrombolysis, and his NIHSS score was zero at day four. A repeat brain CT at 24 hours did not show ICH, and he was subsequently started on anticoagulant therapy at day six due to atrial fibrillation. He remained neurologically well at three months follow up with NIHSS of zero and MRS of one.

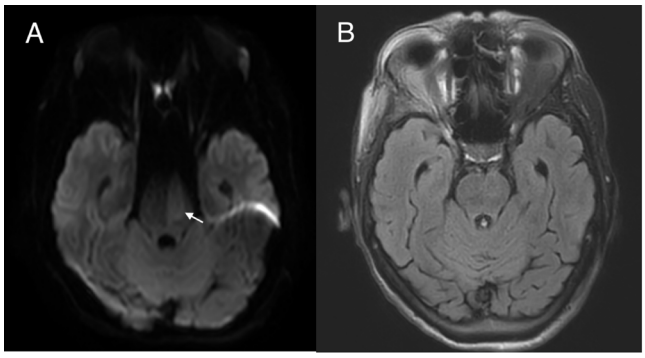

Figure 1: A – Axial DWI image (b=1000) showing a left hemipontine acute infarct (white arrow). B – Axial FLAIR image at the same level shows no abnormal high signal intensity (FLAIR-negative).

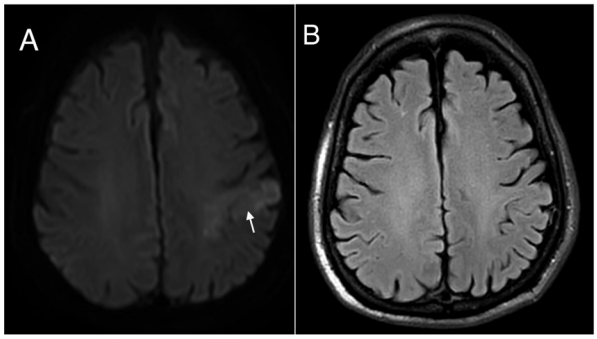

Figure 2: A – Axial DWI image (b=1000) showing a left parietal region acute infarct (white arrow). B – The corresponding axial FLAIR image shows no increased signal at the same region (FLAIR-negative).

PATIENT 3

The third patient was a 78-year-old female with underlying hypertension, dyslipidemia, atrial fibrillation and osteoarthritis that was not on treatment. She presented with right sided body weakness and aphasia at six hours after onset of stroke with a NIHSS of 17. MRI showed left parietal acute infarct with DWI-FLAIR mismatch (Fig. 3A-3B) while MRA showed distal M2 occlusion (Fig. 3C). She was given IVT with TNK 0.25mg/kg and underwent cerebral angiography, anticipating the need for EVT due to the distal occlusion. However, there was full recanalization with IVT and no thrombus was aspirated. Thrombolysis in Cerebral Infarction (TICI) score post procedure was three. She had early neurological recovery (ENR) with NIHSS improving to 11 within 24 hours and subsequently improved to five upon discharge. Repeat brain CT did not show evidence of ICH, and she was started on anticoagulation therapy at day 15 due to atrial fibrillation. At three months follow up, she remained well with NIHSS of three and MRS of three (this was confounded by other factors associated with old age, such as osteoporosis and osteoarthritis, thus her mobility was limited and she required a walking aid).

PATIENT 4

The fourth patient was a 58-year-old male with underlying diabetes mellitus, hypertension and dyslipidemia who presented with left sided weakness at six and a half hours post symptom onset and a total NIHSS of ten. MRI showed right pre and post central gyrus acute infarct with DWI-FLAIR mismatch (Fig. 4A-4B). MRA showed

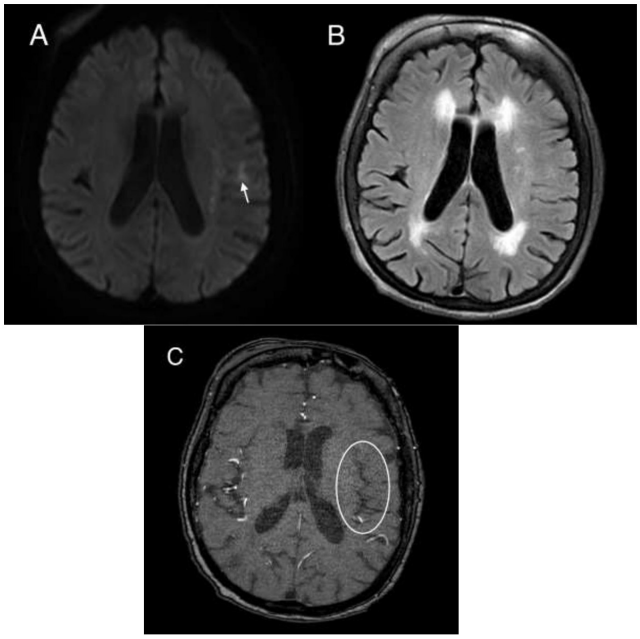

Figure 3 : A – Axial DWI image (b=1000) shows a left parietal region acute infarct (white arrow). B – The corresponding axial FLAIR image shows no increased signal at the same region (FLAIR-negative). C – Absence of signal within the vessels at the left M2 region (white circle) compared to the contralateral side, secondary to occlusion.

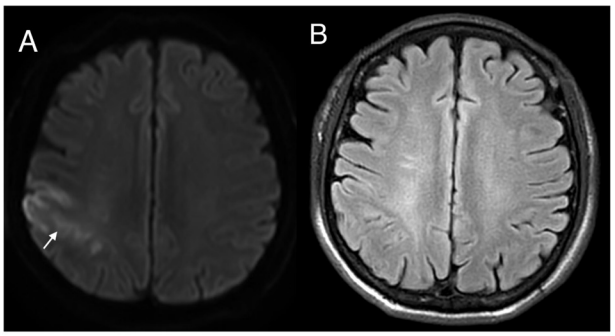

Figure 4: A – Axial DWI image (b=1000) showing right sided pre- and post-central gyrus acute infarct (white arrow). B – Axial FLAIR image at the same region shows no signal abnormality (FLAIR-negative).

no LVO, thus he was given IVT with TNK 0.25mg/kg. He had ENR with NIHSS improving to five within 24 hours and subsequently four upon discharge. A repeat CT of the brain at 24 hours showed no ICH and antiplatelet was started. At three months follow up, he remained well with NIHSS of zero and MRS of zero.

The baseline characteristics and summary of these patients are presented in Table I.

Table I: Baseline patient characteristics

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	71	62	78	58
Sex	Female	Male	Female	Male
Comorbidities	Hypertension Dyslipidemia	Diabetes mellitus Hypertension Ischemic heart disease Atrial fibrillation	Hypertension Dyslipidemia Atrial fibrillation Osteoarthritis	Diabetes mellitus Hypertension Dyslipidemia
NIHSS	10	14	17	10
MRS pre stroke	0	0	1 (mild disability due to osteoarthritis)	0
Area of stroke	Posterior circulation	Anterior circulation	Anterior circulation	Anterior circulation
TOAST	SVO	Cardioembolic	Cardioembolic	SVO
Time to presentation, hours	5	5.5	6	6.5
MRI findings	left hemipontine infarct	left parietal infarct	left parietal infarct	Right pre and post central gyrus infarct
DWI-FLAIR mismatch	mismatch	mismatch	mismatch	mismatch
Door to needle (DTN), mins	38	33	56	41
MRA findings	No LVO	No LVO	M2 occlusion	No LVO
CT brain at 24 hours	Acute left hemipontine infarct, no hemorrhagic transformation. No ICH	Non evolving left parietal acute infarct, no hemorrhagic transformation or midline shift. No ICH	Non evolving left parietal acute infarct, no hemorrhagic transformation or midline shift. No ICH	Non evolving right pre and post central gyrus acute infarct, no hemorrhagic transformation or midline shift. No ICH
NIHSS at discharge	5	0	5	4
MRS at discharge	3	1	3	3
NIHSS at 3 months	3	0	3	0
MRS at 3 months	1	1	3	0

TOAST : Trial of Org 10172 in Acute Stroke Treatment
SVO : small vessel occlusion

DISCUSSION

Although current guidelines do not support the routine use of IVT for AIS patients presenting outside of the four and a half hours' time window,(1,4-5) there is robust literature suggesting that advanced neuroimaging is able to guide the selection of a subset of patients whom are expected to gain the most benefit from IVT based on the concept of "tissue window" as opposed to elapsed time from symptom onset; or time window (5,6).

Recent studies have focused on the treatment of stroke of unknown onset, which occurs in about 28% of patients, and those who wake up with symptoms of stroke (7,8). In these studies, patients within four and a half to nine hours from stroke onset or who woke up with stroke with potentially salvageable brain tissue as evidenced by advanced imaging had better functional outcome when treated with IVT (9,10). This provides valuable insight that each patients' treatment should be individualized based on each person's unique ability to tolerate ischemia or neuronal loss. Each human brain is different, with different levels of neuroplasticity, different variations in cerebral blood flow reserve, as well as collateral blood supply. Therefore, time window should not be the only parameter when deciding treatment. The concept of tissue window may potentially identify patients who would greatly benefit from therapy, despite a later presentation.

The concept of DWI-FLAIR mismatch has become of interest in recent years to identify patients who would benefit from IVT. The pathophysiology of brain damage is a dynamic process that begins with alterations of water diffusion and can be detected on DWI as early as three minutes from the onset of ischemia(11). FLAIR imaging on the other hand is a response to the initial insult causing a break in the blood brain barrier, with ensuing vasogenic edema (12). DWI-FLAIR mismatch is defined as an ischemic DWI lesion with no corresponding signal change on FLAIR sequence (FLAIR-negative); the opposite is said to occur when there is corresponding signal change on FLAIR in the area of ischemia on DWI (FLAIR-positive) (13).

This mismatch serves as a surrogate marker of reversible ischemia and salvageable brain tissue. Many studies have shown that FLAIR-negative patients have lesser complications such as symptomatic ICH and is associated with good outcome at three months (14,15). By taking this evidence into consideration, we decided to use the concept of DWI-FLAIR mismatch to identify a group of patients with disabling neurological symptoms, defined as NIHSS more than six, that would have been excluded from IVT should they be treated strictly according to time window. Instead, availability of MRI and the presence of DWI-FLAIR mismatch (FLAIR-negative) gave us the confidence to treat these patients with IVT, which proved to be of excellent benefit. Neurological improvement was seen in three of the four patients as early as days post stroke, with definite improvement of all four patients at three months follow up. They were able to achieve MRS of zero to one, and were able to return to work and activities of daily living. The only outlier was patient three, who is in the geriatric age group, whose MRS is three at three months (she required the use of a walking aid due to osteoarthritis and osteoporosis).

Furthermore, we did not encounter ICH on repeat brain CT of these patients, despite delivering IVT beyond the time window. This suggests that with proper patient selection based on specific criteria on advanced imaging, the delivery of thrombolytic therapy is potentially life changing in certain patients, without any added risk.

Many centers would contemplate the use of MRI as first line imaging due to the scanning time. However, in our center, we were able to complete DWI, ADC, FLAIR, SWI and MRA within approximately ten minutes. The scanning time for DWI/ADC and FLAIR is five minutes in total, which enabled us to identify DWI-FLAIR mismatch swiftly prior to the decision on administering IVT without the need to wait for MRA. As opposed to perfusion weighted imaging (PWI)-DWI mismatch, or advanced perfusion imaging that require trained neuroradiologists to interpret the imaging findings, the concept of DWI-FLAIR mismatch is relatively easy to comprehend with good inter-reviewer agreeability (16,17). Furthermore, the simplicity with which to recognize DWI-FLAIR mismatch on MRI excludes the need for automated software to guide treatment, as these software may be expensive and costly.

In this series of patients, we chose TNK as the desired thrombolytic agent due to advantages associated with the drug's characteristics, and ease of administration (18). As opposed to alteplase that requires intravenous maintenance over one hour after an initial bolus, TNK only requires one bolus dose owing to its greater fibrin specificity and increased resistance to plasminogen activator inhibitor one activity, thus providing more rapid thrombolysis with a longer half-life (19). Similar studies have shown significant benefit with TNK compared to alteplase with no increased risk of ICH or mortality (20). The marked improvement seen in our patients corroborate the findings of these studies.

We realize that the results of this case series may not be generalized to the general population due to a very small patient number and that the evidence supporting the use of TNK in extended hours is scarce and most randomized controlled trials are still ongoing. Thus, in our centre, we counselled patients for the off-label use of TNK prior to administration and an informed consent was attained. More importantly, we did not observe any serious adverse events with administering TNK in the extended hours, which proves an added advantage for

patients whom would be precluded from treatment if time window alone was used to guide the decision on IVT.

We would like to stress the importance of proper patient selection based on the concept of tissue window as opposed to time window alone, might increase the proportion of patients benefiting from IVT, whom otherwise would be excluded when following a strict time window. This in turn provides patients a chance to return to their normal daily routines faster, and reduces the length of hospital stay and in-patient rehabilitation costs. Therefore, bigger randomized controlled studies will be necessary to confirm our findings.

CONCLUSION

For patients with AIS who present between four and a half to nine hours, the use of advanced imaging, namely MRI with DWI-FLAIR mismatch serves as an excellent surrogate marker of salvageable brain tissue, and thus is able to guide administration of extended hours thrombolysis (which would normally strictly be allowed within the four and a half hours' time window). This allows a greater proportion of patients benefiting from this life-saving therapy. Our experience also shows that with careful patient selection, treatment with IVT can safely be given without an increased risk of bleeding or mortality.

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