pISSN 2384-1095
eISSN 2384-1109

iMRI 2019;23:210-219

https://doi.org/10.13104/imri.2019.23.3.210

iMRI
Investigative Magnetic Resonance Imaging

The Role of Double Inversion Recovery Imaging in Acute Ischemic Stroke

Na Young Choi, Soonchan Park, Chung Min Lee, Chang-Woo Ryu, Geon-Ho Jahng

Department of Radiology, Kyung Hee University Hospital at Gangdong, College of Medicine, Kyung Hee University, Seoul, Korea

Purpose: The purpose of this study was to investigate if double inversion recovery (DIR) imaging can have a role in the evaluation of brain ischemia, compared with diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) imaging.

Materials and Methods: Sixty-seven patients within 48 hours of onset, underwent MRI scans with FLAIR, DWI with b-value of 0 (B0) and 1000 s/mm^2, and DIR sequences. Patients were categorized into four groups: within three hours, three to six hours, six to 24 hours, and 24 to 48 hours after onset. Lesion-to-normal ratio (LNR) value was calculated and compared among all sequences within each group, by the Friedman test and conducted among all groups, for each sequence by the Kruskal-Wallis test. In qualitative assessment, signal intensity changes of DIR, B0, and FLAIR based on similarity with DWI and image quality of each sequence, were graded on a 3-point scale, respectively. Scores for detectability of lesions were compared by the McNemar's test.

Results: LNR values from DWI were higher than DIR, but not statistically significant in all groups ($P > 0.05$). LNR values of DIR were significantly higher than FLAIR within 24 hours of onset ($P < 0.05$). LNR values were significantly different between, before, and after six hours onset time for DIR ($P = 0.016$), B0 ($P = 0.008$), and FLAIR ($P = 0.018$) but not for DWI ($P = 0.051$). Qualitative analysis demonstrated that detectability of DIR was higher, compared to that of FLAIR within 4.5 hours and six hours of onset ($P < 0.05$). Also, the DWI quality score was lower than that of DIR, particularly relative to infratentorial lesions.

Conclusion: DIR provides higher detectability of hyperacute brain ischemia than B0 and FLAIR, and does not suffer from susceptibility artifact, unlike DWI. So, DIR can be used to replace evaluation of the FLAIR-DWI mismatch.

Keywords: Double inversion recovery; Acute ischemic stroke; Magnetic resonance imaging; Diffusion MRI; Brain infarction

Original Article

Received: March 4, 2019
Revised: May 24, 2019
Accepted: June 10, 2019

Correspondence to:
Geon-Ho Jahng, Ph.D.
Department of Radiology, Kyung Hee University Hospital at Gangdong, College of Medicine, Kyung Hee University, #892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea.
Tel. +82-2-440-6187
Fax. +82-2-440-6932
E-mail: ghjahng@gmail.com

INTRODUCTION

In the acute phase of brain ischemia, the best strategy to demonstrate restricted water motion related to cytotoxic edema, is diffusion-weighted imaging (DWI) with magnetic resonance imaging (MRI) (1-3). However, single-shot echo-planar imaging (EPI)-based DWI is limited in detecting acute ischemic stroke in some areas of the brain, because of a magnetic susceptibility artifact and a low spatial resolution (4). Also, it is

an intrinsically low signal-to-noise ratio sequence, caused by a large diffusion-encoding gradient.

Fluid-attenuated inversion-recovery (FLAIR) and T2-weighted (T2W) images, as well as conventional T2-based MRI methods, are usually limited in detecting acute ischemic stroke during the hyperacute phase (2, 3, 5-7), because of insufficient sensitivity to detect cytotoxic edema in the acute phase of infarction (8-10). Additionally, in FLAIR, imaging contrast between white and gray matter is usually more or less poor, because transverse magnetization is highly decayed with a lengthy repetition time (TR) and lengthy echo time (TE). Previous studies reported FLAIR could estimate the age of stroke in patients with unclear stroke onset time, by evaluation mismatch of the ischemic lesion compared to DWI (11, 12).

Double inversion recovery (DIR) MRI sequence is a method to suppress signals from cerebral spinal fluid (CSF) and white matter in the brain simultaneously, by applying two inversion pulses with two different inversion times (TI). This allows the DIR to increase image contrast between gray and white matter (13, 14). So, a brain lesion can be distinguished from normal tissue with a DIR image due to the difference in T1 relaxation time, because DIR imaging contrast depends on T1 relaxation time. Although DIR imaging has been applied to brain diseases such as multiple sclerosis or epilepsy (13, 15-18) and Alzheimer's (19), no study has evaluated the role of DIR imaging in detecting acute ischemic brain lesions.

Since a DIR sequence shows high lesion conspicuity in gray and white matter compared with FLAIR or T2W images (20), the DIR image may provide better detectability of hyperacute ischemic stroke than FLAIR. So, the purpose of this study was to evaluate if DIR can detect acute ischemic stroke, and to compare lesion contrast of DIR images to that of DWI and FLAIR.

MATERIALS AND METHODS

Patient Selection

From September 2006 to May 2008, a total of 101 patients underwent MRI scanning with DWI, FLAIR and DIR sequences due to ischemic symptoms. Among them, we included consecutive patients (n = 76) with ischemic symptoms within 48 hours' symptom onset time, and with diffusion restriction lesions. Patients who had other brain diseases (n = 1; moyamoya disease), or with hemorrhagic infarction (n = 5) and severe motion artifacts (n = 3) were excluded. In the end, 67 patients (41 men and 26 women; mean age = 66.7; range = age 31 to 86), were enrolled in the study. Patients' medical history and demographic information such as age, sex, and duration from symptom onset were obtained. Patients were stratified into four groups based on time after onset of stroke symptoms: Group I (onset ≤ 3 hours), Group II (3 < onset ≤ 6), Group III (6 < onset ≤ 24), and Group IV (24 < onset ≤ 48). Table 1 lists patients' demographic information. The local Institutional Review Board approved a waiver of consent for this retrospective study.

MRI Scanning Protocol

Images were acquired with a 3.0 Tesla MRI scanner (Philips Medical System, Achieva, Best, the Netherlands) using a dedicated 8-element phased array sensitivity-encoding (SENSE) head coil. Imaging protocols included contiguous axial sections of DWI, FLAIR, and DIR. Imaging parameters for the FLAIR sequence were TR/TE/TI =11000/140/2800 ms, slice thickness = 5 mm, field of view (FOV) = 189 × 240 mm^2, and matrix size = 256 × 240, and turbo spin-echo (TSE) factor = 30. Acquisition time for FLAIR was 130 seconds. Imaging parameters for the DWI sequence were TR/TE = 3540/72 ms, slice thickness = 5 mm, FOV = 230 × 230 mm^2, matrix size = 192 × 192, and b-values = 0, and 1000 s/mm^2.

The DIR sequence consisted of two radio frequency (RF) 180° inversion pulses, preceding TSE imaging acquisition (19, 21). The two TI for the DIR sequence was TI_1/TI_2 = 2600/360 ms wherein TI_1 was the time interval from the first to the second 180° inversion pulses, and TI_2 was the time interval from the second 180° inversion pulse, to the 90° excitation pulse. To set the two TIs, we used the null point for the CSF signal (TI_1 = 2650 ms, CSF T1 = 4300 ms), and for white matter (TI_2 = 360 ms, WM T1 = 830 ms) in the human brain, in a 3 Tesla MRI system (22, 23). Effective TE that was time of sampling the center of k-space, with respect to excitation pulse was 100 ms. Additional imaging parameter were: TR = 8000 ms, slice thickness = 5 mm, echo-spacing = 8.3 ms, echo-train length = 11, acquisition matrix = 256 × 256, reconstruction matrix = 512 × 512, FOV = 180 × 180 mm, matrix size = 356 × 256 mm, number of slices = 25, slice thickness = 3 mm, gap between slices = 0.3 mm, TSE factor = 44, SENSE factor = 2, and number of averages = 1. Scan time for the DIR sequence was 140 seconds. The excitation 90° RF pulse was preceded by a fat saturation pulse, and an inferiorly placed saturation slab to minimize flow artifacts.

Imaging Analysis

To identify pathological lesions, images were interpreted by a neuroradiologist (CWR) with 15 years' experience. When multiple diffusion restriction lesions were present in a patient, the largest lesion was selected for further imaging analysis. Diffusion restrictive lesions were classified based on location and size. According to the location, lesions were classified as supratentorial or infratentorial lesions. According to size, lesions were classified as small (less than 2 cm), medium (2 cm to 4 cm) or large (greater than 4 cm) infarcts, based on maximum length of infarction.

Apparent diffusion coefficient (ADC) maps were first calculated, by using the two DWI data with b-values of 0 and 1000 s/mm^2. ADC maps in combination with DWI were used, as a tool to distinguish recent cerebral infarction. In this study, we did not obtain spin-echo T2W images during the acute stages of infarction, to reduce acquisition time. So, DWI with a b-value = 0 s/mm^2 (B0) was regarded as the T2W image.

Quantitative Assessment

Imaging co-registrations among the three different images of DWI, DIR, and FLAIR were performed, using SPM5 software (Statistical Parametric Mapping 5; http://www.fil.ion.ucl.ac.uk/ spm/software/spm5/). So, imaging planes after co-registration were identical, for the four images of DIR, FLAIR, B0, and DWI. To determine signal intensities from infarcted and contra-lateral normal brain areas, volumetric region-of-interests (ROIs) were defined on DWI, at the infarction area and its contra-lateral normal area over several slices using MRIcro software (http://people.cas.sc.edu/rorden/mricro/index.html). Mean values of signal intensities of DIR, FLAIR, B0, and DWI for each patient were obtained from the ROIs.

To explore imaging contrast between normal areas and infracted lesions for each sequence, lesion-to-normal ratio (LNR) value was calculated as the difference of signal intensities between the infarction lesion (L) and the normal area (N), and divided by that of the normal area. So, LNR values were calculated by the formula of 100 (L-N)/N for DIR, FLAIR, B0, and DWI data. Thus, the higher LNR value indicated greater lesion contrast, and increased lesion visualization.

Qualitative Assessment

To investigate potential diagnostic advantages by only visually reviewing images, we qualitatively evaluated conspicuity of the lesion on each image sequence. One neuroradiologist (CWR) blinded to clinical information including the time from stroke onset, graded signal intensity changes from grade 0 to 2 on each of the DIR, FLAIR, and B0 images, in the area corresponding to hyperintensity identified on DWI. Grade 0 was defined, as no signal changes demonstrated on DWI. Grade 1 was defined,

Table 1. Number of Patients by Symptom Onset Time and Lesion-to-Normal Ratio Values in Each Sequence Separated to Onset Times

Characteristics	Group I (n = 18)	Group II (n = 15)	Group III (n = 26)	Group IV (n = 8)	Total (n = 67)	P value
Onset time (hours)	≤ 3	> 3 and ≤ 6	> 6 and ≤ 24	24 < and ≤ 48		
	2.3 ± 0.7	4.9 ± 0.9	15.9 ± 6.1	39.1 ± 10.1	12.6 ± 12.5	
Age (years)	64.5 (54.25-71)	76 (63-82)	69.5 (52.75-75.75)	74 (60.5-81.75)	70 (55-77)	0.197*
Male/Female (n)	8/10	13/2	16/10	4/4	41/26	0.077
Lesion-to-normal ratio (LNR)						
DWI	57.7 (36.3-64.1)	49.4 (25.3-81.7)	67.3 (48.5-90.0)	58.0 (33.1-80.7)	59.6 (37.5-79.0)	0.174*
DIR	29.4 (22.6-46.2)	35.0 (19.3-48.9)	57.8 (35.8-64.2)	48.8 (18.2-59.0)	41.0 (25.1-60.5)	0.098*
FLAIR	13.8 (10.3-27.9)	16.8 (4.7-29.6)	24.6 (16.0-43.0)	18.0 (13.8-31.3)	19.5 (12.7-31.5)	0.090*
B0	15.0 (7.6-17.9)	11.2 (8.7-17.5)	23.6 (13.9-32.8)	13.6 (4.6-22.1)	15.9 (9.6-22.6)	0.007*
P†	< 0.001	< 0.001	< 0.001	< 0.001		

Age and Lesion-to-normal ratio (LNR) are median with interquartile range (Q1-Q3).

Duration from symptom onset time are presented as mean ± standard deviation.

P† tested by Friedman test

P* tested by Kruskal Wallis test

Values in bold indicate statistical significance.

B0 = DWI with b-value = 0 s/mm^2 was regarded as T2W images; DIR = double inversion recovery; DWI = diffusion weighted image with the b-value of 1000 s/mm^2; FLAIR = fluid-attenuated inversion recovery

as subtle hyperintense signal changes and Grade 2 was defined, as definite hyperintense signal changes. All of these subtle and definite signal intensity changes (Grade 1 and Grade 2) were considered positive lesions in each sequence.

Additionally, to evaluate the effect of an artifact or low resolution on diagnosis of acute ischemic stroke, image quality of each sequence was scored. Presence and severity of artifact and overall image quality were subjectively graded on a 3-point scale. Score 3 was defined as no artifact and good image quality, as sufficient in detecting the lesion. Score 2 was defined as scant artifact or low resolution not impairing diagnostic quality, and Score 1 was defined as a considerable artifact that affects evaluation of the lesion. In particular, since the detection of infratentorial lesions using DWI is restricted by geometric distortion from susceptibility artifact, they were separately classified.

Statistical Analysis

Age and gender were compared among the four groups, using the Kruskal-Wallis and Fisher's Exact test, respectively. To compare LNR values among the four different imaging sequences for the four groups, the Friedman test (similar to parametric repeated measures ANOVA) was performed with LNR values as the dependent variable, and sequence types as the independent variable. If any significant difference was found among imaging sequences, then post-hoc analysis was applied, to examine significant differences between sequences. Minimum level of significance was set at a value of Bonferroni-corrected $P < 0.05$, to consider multiple comparison effects. Also, patients were reclassified into two groups according to time of symptom onset (before or after six hours), and we repeated the Friedman test for these two groups (significant level; $P < 0.05$).

To compare LNR values among the four groups, Group I, II, III and IV, for each sequence, the Kruskal-Wallis (similar to one-way ANOVA) test was used, with post-hoc analysis. If any significant difference was found among the groups, then post-hoc analysis was applied, to examine significant differences between the groups using the Mann-Whitney test. Minimum level of significance was set at a value of Bonferroni-corrected $P < 0.05$, to consider multiple comparison effects. Mann-Whitney test was also performed, for comparison among the reclassified two groups (before or after six hours) within each sequence (significant level; $P < 0.05$).

Also, we evaluated the proportion of DWI +, FLAIR + and B0 + results for the following time intervals: within three hours, 4.5 hours, and six hours, respectively. Additionally, for qualitative analysis of acute cerebral infarction, McNemar's test was used to compare detectability of each sequence, especially in patients in the hyperacute stage. A P-value of 0.05 was statistically significant. All analyses were performed, using SPSS software version 24.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Age ($P = 0.197$) and gender ($P = 0.077$), were not significantly different among the four groups. Mean time between onset of ischemic symptom, and MR scanning was 12.6 ± 12.5 hours. Thirty-three patients (48.5%) underwent MR scanning, within six hours of symptom onset. Table 1 summarizes demographic characteristics of patients, according to onset time of acute ischemic stroke in this study. Sixty patients had supratentorial lesions, and only seven patients had infratentorial lesions. A number of lesions in patients according to infarct size, were 28, 14, and 25 for large, medium, and small, respectively.

Representative examples of ischemic lesion images from each sequence are shown in Figures 1 and 2. Figure 1 shows representative MRI images scanned 24 hours, after symptom onset in the case of an age 50 female with an infarction in the right pons. DWI had the highest LNR value, and DWI and DIR show the ischemic lesion in the right pons, clearly compared with FLAIR and B0. Figure 2 shows representative MRI images, collected three hours after symptom onset of an age 71 female patient. There is ischemic infarction, in the right MCA territory. DIR had the highest LNR value in this case.

Comparison of LNR Values among the Five Image Types for Each Group

Figure 3 shows mean LNR values of each sequence within all groups. For all groups within 48 hours of initial stroke symptoms, LNR value of DWI was the highest followed by DIR, FLAIR, and B0. Also, in all groups, the result of the Friedman test showed that LNR values were significantly different among the four sequences ($P < 0.001$) (Table 1).

Table 2 summarizes results of the Friedman test and post hoc analysis with Wilcoxon signed-rank tests for multiple comparisons, between sequences in each group (all of the P values were applied Bonferroni correction). In all groups, LNR values of DIR were not significantly different ($P > 0.05$) to those of DWI. Additionally, LNR values from DIR were statistically significantly higher than those of FLAIR in all

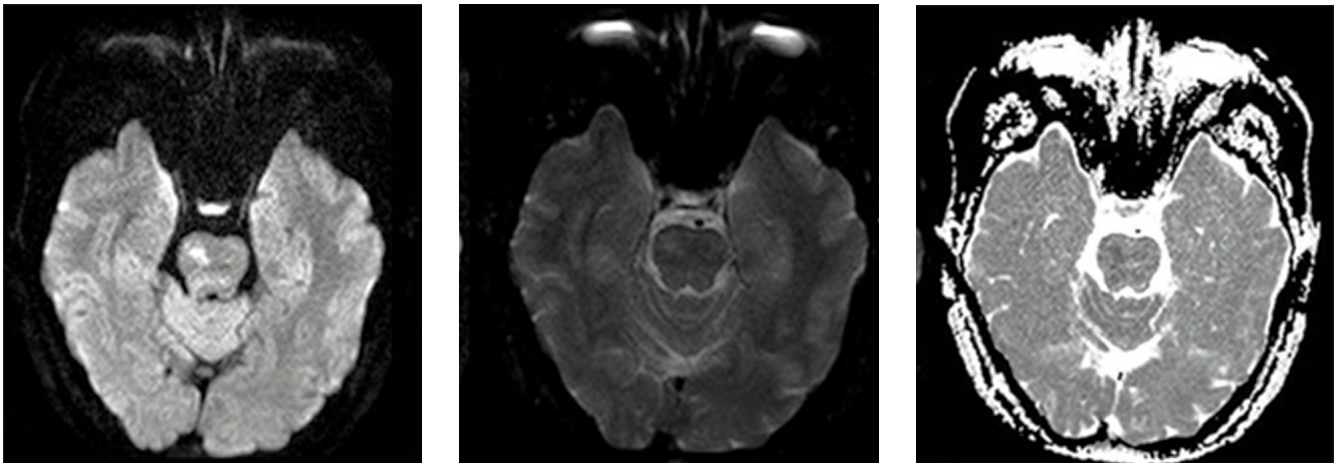
groups except Group IV. Compared with B0, DIR showed statistically significantly high LNR values in Group I and Group III. Within Group IV, within 24 to 48 hours after onset, LNR values among all four imaging sequences were not significantly different from each other ($P > 0.05$).

The result of the Friedman test in the reclassified two groups (before and after six hours onset time), showed that LNR values were significantly different among all sequences ($P < 0.001$). First, LNR values from DWI were significantly higher than those from DIR (Before six hours from onset: $P = 0.015$, after six hours of onset: $P < 0.001$). In patients before or after six hours from stroke onset, LNR values from DIR were significantly higher than those from FLAIR ($P < 0.001$) and B0 (Before six hours from onset: $P = 0.002$, after six hours of onset: $P < 0.001$).

Comparison of LNR Values among the Four Groups for Each Image Type

The result of the Kruskal Wallis test showed that LNR value of only the B0 was significantly different among the four groups ($P = 0.007$). Post-hoc analysis with the Mann Whitney U-test showed that LNR value of the B0 was significantly different, only between Group II and Group III (Bonferroni corrected $P = 0.018$). For other sequences, LNR values were not significantly different among the four groups: DWI ($P = 0.174$), DIR ($P = 0.098$), and FLAIR ($P = 0.090$).

In the two reclassified groups (before and after six hours onset time), LNR values were significantly different between the two groups for B0 ($P = 0.008$), DIR ($P = 0.016$), and FLAIR ($P = 0.018$), but were not significantly different for



a b c

d e

Fig. 1. Representative magnetic resonance imaging (MRI) images scanned 24 hours after symptom onset, in the case of 50 years-old female with infarction in the right pons. Diffusion-weighted imaging (DWI) ambiguously shows the ischemic lesion in the right pons, but double inversion recovery (DIR) depicts the lesion more clearly than the other sequences. From left to right, images are from (a) DWI, (b) DWI with b-value of 0s/mm^2 (B0), (c) Apparent diffusion coefficient (ADC), (d) Fluid-attenuated inversion recovery (FLAIR) and (e) DIR. Note that the LNR values of each sequence are as follow: DWI = 43.5, DIR = 22.7, FLAIR = 9.4, and B0 = 5.8.

DWI (P = 0.051).

Qualitative Analysis

McNemar's test demonstrated that DIR was sensitive to detect brain ischemia, than FLAIR and B0 in patients with acute ischemic stroke within three to six hours after stroke onset. Detection rates of DIR were significantly different from those of FLAIR with 4.5 hour (P = 0.0412) and six hours (P = 0.0412) of onset (Table 3).

According to the qualitative score of each sequence (Table 4), DIR showed fewer artifacts than DWI. Particularly, this was a notable difference in infratentorial lesions known as highly affected by susceptibility artifacts on DWI. Figure 4 shows the difference in qualitative scores between DWI and

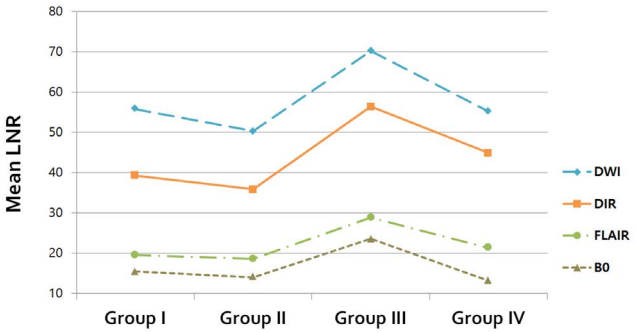
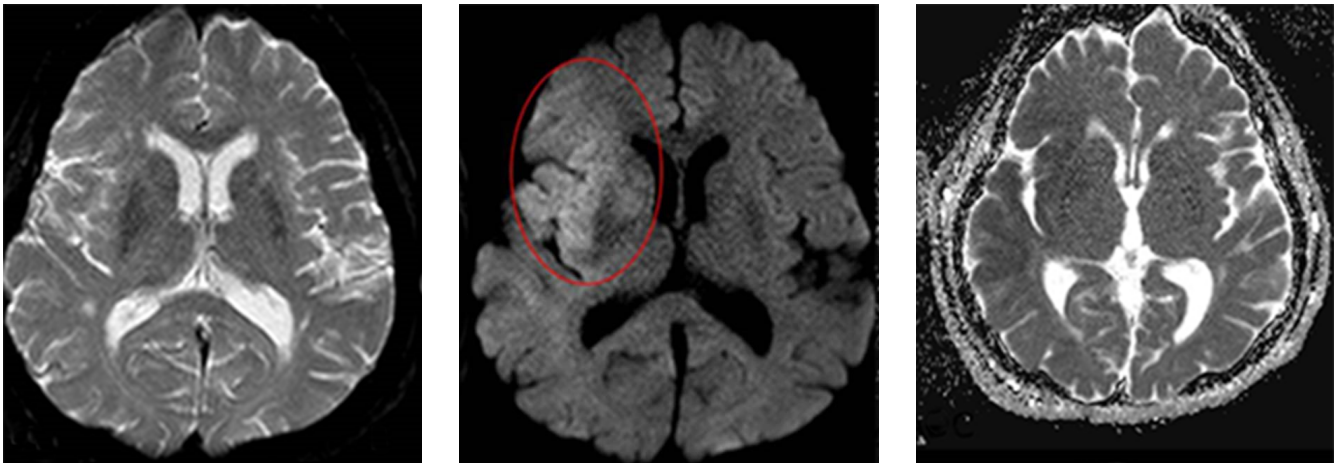
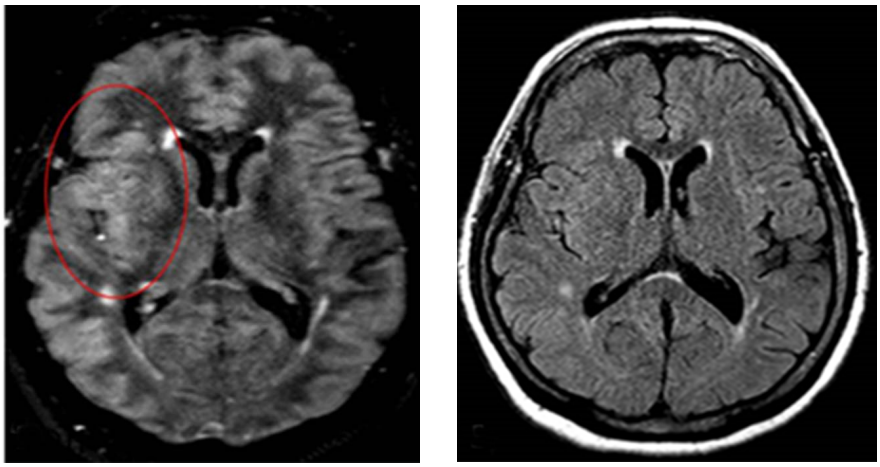


Fig. 3. Graphs of mean lesion-to-normal ratio (LNR) values, of each sequence within all groups (Group I through Group IV).



a b c



d e

Fig. 2. Representative magnetic resonance imaging (MRI) images, collected three hours after symptom onset of 71 years-old female. There is ischemic infarction, in the right middle cerebral artery (MCA) territory. Diffusion-weighted imaging (DWI) depicts the lesion more clearly than the other sequences; Double inversion recovery (DIR) also depicts the lesion better than fluid-attenuated inversion recovery (FLAIR) and DWI with b-value of 0s/mm^2 (B0) sequences. From left to right, images are from (a) B0, (b) DWI, (c) Apparent diffusion coefficient (ADC), (d) DIR and (e) FLAIR. Note that LNR values of each sequence are as follow: DWI = 32.8, DIR = 60.3, FLAIR = 10.2, and B0 = 22.2.

Table 2. The Result of Comparing the LNR Values among the Four Sequences in Each Group

Group (onset, h)	Friedman test	Post-hoc Wilcoxon signed-rank test					
		DWI vs. DIR	DWI vs. FLAIR	DWI vs. B0	DIR vs. FLAIR	DIR vs. B0	FLAIR vs. B0
I (≤ 3)	< 0.001	0.429	0.002	0.002	0.007	0.029	> 0.999
II (> 3 and ≤ 6)	< 0.001	0.106	0.008	0.045	0.012	0.231	> 0.999
III (> 6 and ≤ 24)	< 0.001	0.086	< 0.001	< 0.001	< 0.001	< 0.001	> 0.999
IV (24 < and ≤ 48)	< 0.001	> 0.999	0.117	0.117	0.251	0.117	> 0.999

Each cell shows the P value. Bonferroni-corrected P-values are reported for Post-hoc Wilcoxon signed-rank test. Bold font indicates statistical significance.
B0 = DWI with b-value = 0 s/mm^2 was regarded as T2W images; DIR = double inversion recovery; DWI = diffusion weighted image with the b-value of 1000 s/mm^2; FLAIR = fluid-attenuated inversion recovery; LNR = lesion-to-normal ratio

Table 3. The Predictive Performance of Each Imaging Sequence Based on Diffusion Restrictive Lesion in Patients with Hyperacute Phase of Ischemic Stroke

Onset (hours)	DIR		FLAIR		B0		McNemar (P value)	
	–	+	–	+	–	+	DIR vs. FLAIR	DIR vs. B0
≤ 3	2	16	7	11	12	6	0.0736	0.0044
> 3	1	48	2	47	7	42		
≤ 4.5	2	23	8	17	15	10	0.0412	0.0009
> 4.5	1	41	1	41	4	38		
≤ 6	3	30	9	24	17	16	0.0412	0.0005
> 6	0	34	0	34	2	32		

Positive (+) was defined as Grade 1 plus 2. That is, the patients with subtle or definite signal intensity changes in the region corresponding to the acute ischemic lesion on DWI were included. Negative (–) was defined as no signal intensity change in each sequence (Grade 0 only). Bold font indicates statistical significance.
B0 = DWI with b-value = 0 s/mm^2 was regarded as T2W images; DIR = double inversion recovery; DWI = diffusion weighted image with the b-value of 1000 s/mm^2; FLAIR = fluid-attenuated inversion recovery

Table 4. The Patient Proportion According to the Quality Scores of Each Imaging Sequence

Quality score	DIR	DWI	FLAIR	B0
	Total / Infratentorial lesion (n = 67 / n = 7)			
1 (poor)	2 / 0	4 / 3	3 / 0	6 / 1
2 (fair)	9 / 1	18 / 2	4 / 1	2 / 1
3 (good)	57 / 6	45 / 2	60 / 6	59 / 5

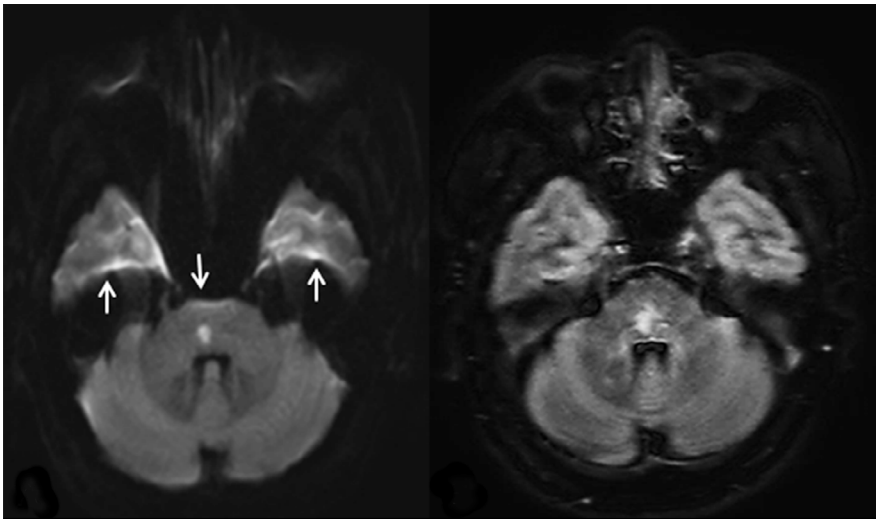
Score 1 was defined as a considerable artifact that affects the evaluation of the lesion. Score 2 was defined as a little artifact or low resolution not impairing diagnostic quality, and score 3 was defined as no artifact and good image quality enough to detect the lesion.
B0 = DWI with b-value = 0 s/mm^2 was regarded as T2W images; DIR = double inversion recovery; DWI = diffusion weighted image with the b-value of 1000 s/mm^2; FLAIR = fluid attenuated inversion recovery

DIR for patients with pontine infarction, and its effect on identification of acute infratentorial brain ischemia.

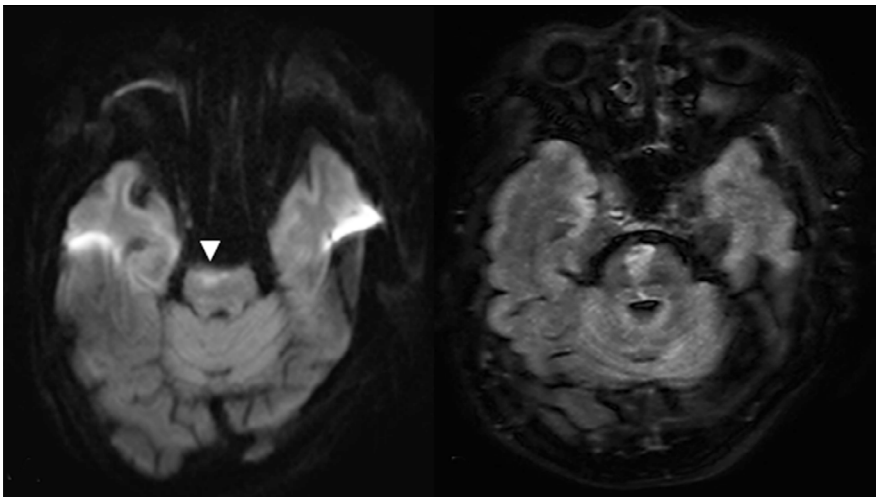
DISCUSSION

Comparison of LNR Values among the Four Image Types for Each Group

In this study, LNR values of DWI were highest in all time-phase. This result is consistent with the previous finding, that DWI is highly sensitive to the early diagnosis of acute cerebral infarction (24). However, LNR values of DIR were not significantly different from those of DWI for all time-phase, and were significantly higher than those of B0 and FLAIR sequences within 24 hours from stroke onset. Also, in our qualitative analysis, DIR shows higher detectability of brain ischemic lesion within six hours of stroke onset than FLAIR and B0. Results suggest that the DIR sequence may be more sensitive than T2W and FLAIR sequences for detecting infarcts, especially at the hyperacute stage (within six hours of onset). Previous studies have showed that conventional MRI sequences such as T2WI and FLAIR are sensitive to subacute brain ischemia (2), but may not detect



a b



a b

Fig. 4. Examples of two patients with infratentorial infarctions, for qualitative assessment of image quality in each sequence. Top row: An age 50 male who underwent magnetic resonance imaging (MRI) scan at 20 hours after left ataxia. A typical susceptibility artifact (white arrows) is visible on (a) diffusion-weighted imaging (DWI), without affecting diagnosis of a small (< 2 cm) hyperintense lesion in the right pons (Score 2). In (b) double inversion recovery (DIR), a lesion is identified at a location corresponding to that of DWI, without anatomic distortion (Score 3). Bottom row: Images of an age 81 female presenting left side weakness and speech disturbance, were obtained within 48 hours after symptom onset. (a) DWI shows considerable geometric distortion by susceptibility artifact, leading to underestimation of right paramedian pontine infarction (arrowhead) (Score 1). Also, itself may be mistaken for an artifact. In contrast, (b) DIR shows definite high signal intensity lesion in the right pons (Score 3).

an ischemic lesion within few hours of onset (3, 5-7).

Additionally, in our visual assessment of image quality for each sequence, DIR showed better image quality in detecting acute ischemic stroke compared to DWI, especially in infratentorial lesions. Although DWI is the standard technique to detect acute ischemic stroke, evaluation of regions of the air-bone interface including infratentorial lesion, is limited by susceptibility artifact and low spatial resolution in clinical practice (4, 25).

A DIR sequence may significantly improve signal contrast of brain tissue by applying two inversion pulses, and may be less sensitive to susceptibility-related artifacts than DWI. So, DIR can serve as complementary sequence in identifying hyperacute infarction, without signal changes of FLAIR in areas that are difficult to detect because of poor image quality in DWI.

Inversion recovery (IR) sequences can be used to nullify the signal of a tissue by appropriately selecting the TI, and the additional inversion pulse allows two tissues to be nullified simultaneously. In this study, the DIR sequence used two 180-degree inversion times to null signals from CSF and white matter, and resulted in superior contrast between gray and white matters which were limited in other sequences (13, 15-18, 26). Most of ROIs were composed of white matter lesions, although we did not accurately identify it as either gray or white matter lesions. Failure to nullify or suppress the white-matter signal, resulted in high signal intensity on the DIR sequence. This phenomenon is supposedly caused by T1 shortening usually because of edema or demyelination in white matter, similar

with characteristics of FLAIR which reflects minimal change of the CSF in patients with subarachnoid hemorrhage or meningitis (27). Thus, the DIR sequence could be used as an effective tool, for detecting hyperintense lesions in the brain.

Comparison of LNR Values among the Groups for Each Image Type

Our results for comparing LNR values in each sequence showed, that only B0 could discriminate the acute ischemic lesion among the four groups. However, when we re-grouped more simply based on before or after six hours of onset, DIR (P = 0.016) and FLAIR (P = 0.018) also showed discrimination of acute infarcts, in addition to B0 (P = 0.008). Previous studies have revealed that DWI-FLAIR mismatch, which is ischemic lesions detected with DWI but not with FLAIR, can predict onset time in acute ischemic stroke with uncertain time of symptom onset (11, 12).

Our study showed that DIR was similar or superior to FLAIR, in detecting hyperacute ischemic lesions (within six hours of ischemic stroke onset). Also, in visual assessments, lesion conspicuity looks higher in DIR images than in B0 and FLAIR images, within three hours, three to 4.5 hours, and six hours of onset. There is a considerable time gap between lesion detection with DWI, and detection by B0 and FLAIR. Although relationships between onset times of ischemic stroke and signal changes in the DIR sequence require further studies, it is expected that the DIR sequence will yield additional information in predicting hyperacute infarcts, not clearly identified in DWI and FLAIR.

Limitations

This study had several limitations. First, the number of patients enrolled in our study was small. There were only seven patients with infratentorial lesion. So, findings may be insufficient to demonstrate that DIR plays a complementary role in diagnosing acute ischemic stroke, especially in evaluating infratentorial lesions with limited diagnostic value on DWI. Additional studies with a larger number of patients are warranted, for better understanding of the usefulness of DIR in diagnosing acute ischemic stroke. Second, we draw ROIs manually by one person (CWR). This may cause subjective assessment of data. So, multiple readers should perform data analyses. Third, DIR and FLAIR images for each patient, were co-registered and resliced into B0 images. Mis-coregistrations among images may miscalculate LNR values from ROIs. Finally, in routine brain imaging for acute ischemic stroke, FLAIR and DIR requires additional scan time. Scan times in this study were 140 seconds for DIR, and 130 seconds for FLAIR. So, the major obstacle for application of DIR or FLAIR in hyperacute stroke patients is the scan time issue.

In conclusion, in quantitative and qualitative analyses, DIR was superior to FLAIR in distinguishing hyperacute brain ischemia within six hours of symptom onset. DIR also showed better image quality in the infratentorial area, whereas DWI was limited in evaluating brain lesion. So, DIR can be applied to enhance evaluation of the FLAIR-DWI mismatch.

Acknowledgments

The authors are grateful to Ms. Soo Jin Kim for statistical assistance in this study. This study was supported by the Convergence of Conventional Medicine and Traditional Korean Medicine R&D program funded by the Ministry of Health & Welfare through the Korea Health Industry Development Institute (KHIDI) (HI16C2352).

REFERENCES

1. Benveniste H, Hedlund LW, Johnson GA. Mechanism of detection of acute cerebral ischemia in rats by diffusion-weighted magnetic resonance microscopy. Stroke 1992;23:746-754
2. Brant-Zawadzki M, Atkinson D, Detrick M, Bradley WG, Scidmore G. Fluid-attenuated inversion recovery (FLAIR) for assessment of cerebral infarction. Initial clinical experience in 50 patients. Stroke 1996;27:1187-1191
3. Gauvrit JY, Leclerc X, Girot M, et al. Fluid-attenuated inversion recovery (FLAIR) sequences for the assessment of acute stroke: inter observer and inter technique reproducibility. J Neurol 2006;253:631-635
4. Le Bihan D, Poupon C, Amadon A, Lethimonnier F. Artifacts and pitfalls in diffusion MRI. J Magn Reson Imaging 2006;24:478-488
5. Lutsep HL, Albers GW, DeCrespigny A, Kamat GN, Marks MP, Moseley ME. Clinical utility of diffusion-weighted magnetic resonance imaging in the assessment of ischemic stroke. Ann Neurol 1997;41:574-580
6. Sorensen AG, Buonanno FS, Gonzalez RG, et al. Hyperacute stroke: evaluation with combined multisection diffusion-weighted and hemodynamically weighted echo-planar MR imaging. Radiology 1996;199:391-401
7. Perkins CJ, Kahya E, Roque CT, Roche PE, Newman GC. Fluid-attenuated inversion recovery and diffusion- and perfusion-weighted MRI abnormalities in 117 consecutive

patients with stroke symptoms. Stroke 2001;32:2774-2781
8. Alexander JA, Sheppard S, Davis PC, Salverda P. Adult cerebrovascular disease: role of modified rapid fluid-attenuated inversion-recovery sequences. AJNR Am J Neuroradiol 1996;17:1507-1513
9. Reidel MA, Stippich C, Heiland S, Storch-Hagenlocher B, Jansen O, Hahnel S. Differentiation of multiple sclerosis plaques, subacute cerebral ischaemic infarcts, focal vasogenic oedema and lesions of subcortical arteriosclerotic encephalopathy using magnetisation transfer measurements. Neuroradiology 2003;45:289-294
10. Ricci PE, Burdette JH, Elster AD, Reboussin DM. A comparison of fast spin-echo, fluid-attenuated inversion-recovery, and diffusion-weighted MR imaging in the first 10 days after cerebral infarction. AJNR Am J Neuroradiol 1999;20:1535-1542
11. Thomalla G, Cheng B, Ebinger M, et al. DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4.5 h of symptom onset (PRE-FLAIR): a multicentre observational study. Lancet Neurol 2011;10:978-986
12. Aoki J, Kimura K, Iguchi Y, Shibazaki K, Sakai K, Iwanaga T. FLAIR can estimate the onset time in acute ischemic stroke patients. J Neurol Sci 2010;293:39-44
13. Wattjes MP, Lutterbey GG, Gieseke J, et al. Double inversion recovery brain imaging at 3T: diagnostic value in the detection of multiple sclerosis lesions. AJNR Am J Neuroradiol 2007;28:54-59
14. Jahng GH, Stables L, Ebel A, et al. Sensitive and fast T1 mapping based on two inversion recovery images and a reference image. Med Phys 2005;32:1524-1528
15. Geurts JJ, Pouwels PJ, Uitdehaag BM, Polman CH, Barkhof F, Castelijns JA. Intracortical lesions in multiple sclerosis: improved detection with 3D double inversion-recovery MR imaging. Radiology 2005;236:254-260
16. Rugg-Gunn FJ, Boulby PA, Symms MR, Barker GJ, Duncan JS. Imaging the neocortex in epilepsy with double inversion recovery imaging. Neuroimage 2006;31:39-50
17. Calabrese M, De Stefano N, Atzori M, et al. Detection of cortical inflammatory lesions by double inversion recovery magnetic resonance imaging in patients with multiple sclerosis. Arch Neurol 2007;64:1416-1422
18. Nelson F, Poonawalla AH, Hou P, Huang F, Wolinsky JS, Narayana PA. Improved identification of intracortical lesions in multiple sclerosis with phase-sensitive inversion recovery in combination with fast double inversion recovery MR imaging. AJNR Am J Neuroradiol 2007;28:1645-1649
19. Jahng GH, Lee DK, Lee JM, Rhee HY, Ryu CW. Double inversion recovery imaging improves the evaluation of gray matter volume losses in patients with Alzheimer's disease and mild cognitive impairment. Brain Imaging Behav 2016;10:1015-1028
20. Bedell BJ, Narayana PA. Implementation and evaluation of a new pulse sequence for rapid acquisition of double inversion recovery images for simultaneous suppression of white matter and CSF. J Magn Reson Imaging 1998;8:544-547
21. Turetschek K, Wunderbaldinger P, Bankier AA, et al. Double inversion recovery imaging of the brain: initial experience and comparison with fluid attenuated inversion recovery imaging. Magn Reson Imaging 1998;16:127-135
22. Redpath TW, Smith FW. Technical note: use of a double inversion recovery pulse sequence to image selectively grey or white brain matter. Br J Radiol 1994;67:1258-1263
23. Boulby PA, Symms MR, Barker GJ. Optimized interleaved whole-brain 3D double inversion recovery (DIR) sequence for imaging the neocortex. Magn Reson Med 2004;51:1181-1186
24. Hacke W, Warach S. Diffusion-weighted MRI as an evolving standard of care in acute stroke. Neurology 2000;54:1548-1549
25. Benameur K, Bykowski JL, Luby M, Warach S, Latour LL. Higher prevalence of cortical lesions observed in patients with acute stroke using high-resolution diffusion-weighted imaging. AJNR Am J Neuroradiol 2006;27:1987-1989
26. Cotton F, Rambaud L, Hermier M. Dual inversion recovery MRI helps identifying cortical tubers in tuberous sclerosis. Epilepsia 2006;47:1072-1073
27. Noguchi K, Ogawa T, Inugami A, et al. Acute subarachnoid hemorrhage: MR imaging with fluid-attenuated inversion recovery pulse sequences. Radiology 1995;196:773-777