J Korean Soc Radiol 2009 ; 60 : 71-77

Detecting Cerebral Microbleeds on Susceptibility-Weighted MR Imaging: Comparison with the Conventional MR Imaging Sequences[1]

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Purpose: The purpose of our study was to compare the susceptibility-weighted imaging (SWI) with the conventional MR imaging sequences for their ability to detect cerebral microbleeds.

Materials and Methods: We studied 17 patients (9 men and 8 women, mean age: 58 years) with microbleeds. The gradient-recalled echo T2*-weighted imaging (GRE), the T2-weighted imaging (T2WI), the fluid-attenuated inversion recovery (FLAIR) imaging and the SWI were obtained from all the subjects. The number of microbleeds was counted on each MR imaging sequence. We also compared the number of detected microbleeds (%) of each imaging technique with that of SWI being 100%. The Friedman ANOVA Test was used for statistical analysis and a p value of less than 0.05 was considered statistically significant.

Results: The number of detected mircobleeds on each imaging technique (%, mean $\pm$ standard deviation), as compared to that detected on SWI as 100%, was as follows: GRE vs. SWI (64.9 $\pm$ 19.3 vs. 100, p =0.001), T2WI vs. GRE (16.9 $\pm$ 17.7 vs. 64.9 $\pm$ 19.3, p = 0.001), and T2WI vs. FLAIR (16.9 $\pm$ 17.7 vs. 13.8 $\pm$ 17.7, p = 0.027).

Conclusion: SWI demonstrates a significantly higher sensitivity for detecting microbleeds as compared to that of GRE and the other conventional MR imaging sequences.

Index words : Susceptibility artifact
Magnetic resonance (MR)
Brain ischemia
Cerebral hemorrhage

Cerebral microbleeds have been defined as small, spontaneous, homogeneous, round foci of low signal intensity on the gradient-recalled echo (GRE) imaging sequence (1, 2). The prevalence of microbleeds in healthy adults is about 5% (2). Microbleeds may be a marker for cerebral microangiopathy and small vessel disease, and they may be a prognostic indicator for potential future bleeding, and especially for patients with ischemic or hemorrhagic stroke and intracerebral hemorrhage (3-6). There have been many studies on microbleeds that have used MR imaging (2-7). Among the various MR imaging sequences, the GRE sequence has been regarded as the most reliable technique for detecting microbleeds (2, 3, 7).

Susceptibility-weighted MR imaging (SWI) is a tech-

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Received September 1, 2008 ; Accepted October 22, 2008
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nique that exploits the magnetic susceptibility effects of tissues (8). The susceptibility difference between tissues is a new kind of contrast that is different from the spin density, T1-, or T2-weighted imaging. The SWI technique uses a fully velocity compensated, RF spoiled, high-resolution and three dimensional modified gradient echo T2*-weighted sequence (9–11). Because SWI allows for the improved detection of paramagnetic blood products, the venous vasculature and the iron content in the brain, it would increase the sensitivity for detecting microbleeds (3, 8).

To date, most of the studies have used the 2D GRE sequences for the detection of cerebral microbleeds. These sequences have been considered as a gold standard for the study of microbleeds. However, SWI has rarely been used for the evaluation of cerebral microbleeds in healthy adults (3). Further, no study has compared the impact of various imaging sequences on the prevalence or the number of microbleeds detected in the brain. Thus, we tried to evaluate the sensitivity of SWI for detecting silent microbleeds in healthy adults and patients with minor neurological abnormalities, as compared with GRE and the other conventional MR imaging sequences.

Materials and Methods

We retrospectively reviewed the MR images that were obtained from 227 consecutive patients from December 2006 to March 2007. Among those patients, only 61 patients were found to have microbleeds on SWI. Among these 61 patients with microbleeds, the patients with hemorrhage related symptoms (n = 26), hemorrhagic infarction (n = 2), a past history of trauma (n = 9) or cavernous angioma (n = 1), and the patients who did not undergo two dimensional GRE sequence imaging (n = 6) were excluded. Seventeen patients were finally included in the study. They were 9 males and 8 females ranging in age from 39 to 88 years (mean age: 58 years). They were referred to our department for the evaluation of headache (n = 3), optic nerve anomaly (n = 1), transient ischemic attack (n = 9), acute amnesia (n = 1), disorientation (n = 1) and for a routine check (n = 2).

MR imaging of the brain was conducted on a 1.5-Tesla scanner (Magnetom Avanto; Siemens Erlangen, Germany) with a 12 channel head matrix coil. We obtained the routine MR sequences with a 5 mm slice thickness, a 1.5 mm interslice gap and a 220×220 mm field of view (FOV). The routine MR sequences included the axial T2W images (TR/TE = 3850/96 msec, matrix = 229×384), the axial FLAIR images (TR/TE = 8500/100 msec, matrix = 229×384) and the axial 2D GRE images (TR/TE = 519/21.8 msec, flip angle (FA) = 20°, matrix = 187×320). We included the T2WI and T2 FLAIR pulse sequences in this study because we want to determine how many microbleeds can be depicted on these imaging sequences.

The SWI technique used the 3D FLASH sequence in the axial plane with the following parameters: TR/TE = 49/40 msec, number of excitations = 1, FA = 15°, low bandwidth = 78 Hz/pixel, slice thickness = 5 mm, interslice gap = 1.5 mm, matrix = 180×256, FOV= 193 ×220 mm and a voxel size of 1.1×0.9 8×5.0 mm^3. A parallel imaging technique was used with a GRAPPA 2 reduction factor and the acquisition time was 3 minutes 46 seconds. The SW images were created using the magnitude and phase data sets (8). The phase images were high pass filtered to create the normalized phase mask. The phase mask was multiplied 4 times with the original magnitude image. A minimum intensity projection over two slices was performed to display the final SWI data. This process was done via the Siemens Vision software.

We considered a round area of marked, homogeneous low signal intensity on SWI that was less than 8 mm as a microbleed. We excluded dark areas in the cortical sulci to avoid confusion with the flow void from the cerebral

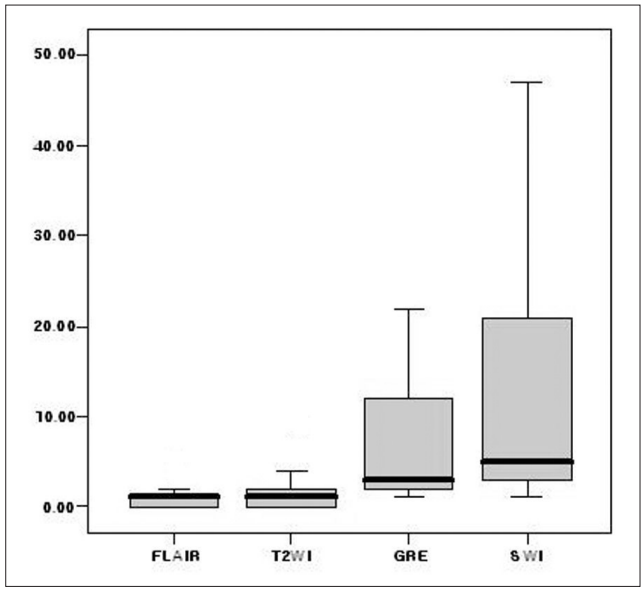


Fig. 1. Comparison of the number of microbleeds detected on each MR imaging sequence. SWI demonstrates significantly higher sensitivity for the detection of microbleeds than did the GRE sequence (p =0.001).

vessels. In addition, the subcortical and symmetric basal ganglia hypointense lesions that were likely to represent focal calcification were also excluded.

The number of microbleeds was counted on the SWI, GRE, T2WI and FLAIR images by two neuroradiologists who were "blinded" to patients' clinical information. The evaluation process was done by these two neuroradiologists working in consensus. The number of microbleeds detected on SWI and the other routine MR imaging sequences was compared with using the non-parametric Friedman ANOVA Test. For post-hoc comparisons, we used the Wilcoxon signed-rank test to determine whether there were differences between the pairs of the group means in order to understand the nature of a significant ANOVA value. We also set the number of microbleeds on SWI as 100% and we calculated the relative percentage from the number of microbleeds detected on the other sequences in each individual. Statistical analysis was performed with SPSS and a p value less than 0.05 was considered as statistically significant.

Results

The mean values of the total number of microbleeds on each MR imaging sequence are summarized in Table 1 and Figure 1. The number of microbleeds on SWI varied from 1 to 47 (mean ± SD = 11.5 ± 12.6) in all the subjects. The number of microbleeds detected on SWI

Table 1. Comparison of the Number of Microbleeds

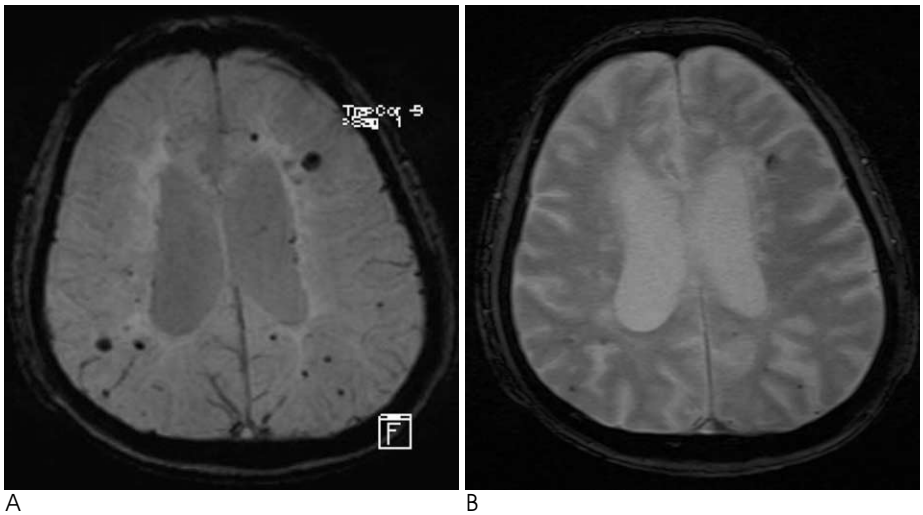
MRI Sequences	No. of Subjects	Minimum	Maximum	Mean	SD
FLAIR	17	0	7	1.2	1.9
T2WI	17	0	9	1.8	2.4
GRE	17	1	22	6.1	6.9
SWI	17	1	47	11.5	12.6

FLAIR: Fluid-attenuated inversion recovery,
T2WI: T2-weighted imaging, GRE: Gradient-recalled echo imaging,
SWI: Susceptibility-weighted imaging

Table 2. Comparison of the Relative Percentages of Microbleeds Detected on the Conventional MR Imaging Sequences with that on the SWI (100%)

MRI Sequences	No. of Subjects	Minimum	Maximum	Mean	SD
FLAIR	17	0.0	50.0	13.8	17.7
T2WI	17	0.0	50.0	16.9	17.7
GRE	17	33.0	100.0	64.9	19.3
SWI	17	100.0	100.0	100.0	0.0

FLAIR: Fluid-attenuated inversion recovery,
T2WI: T2-weighted imaging, GRE: Gradient-recalled echo imaging,
SWI: Susceptibility-weighted imaging



A B

Fig. 2. Axial images obtained with a 1.5 T scanner in a 72-year-old man with headache.
A. Susceptibility-weighted imaging. Multiple microbleeds are seen in the bilateral frontal and parietal lobes.
B. Gradient echo imaging. Fewer microbleeds are seen in the bilateral frontal and parietal lobes, as compared to the susceptibility-weighted imaging.

Table 3. *p* Values for the Number of Microbleeds and the Relative Percentages between the Imaging Sequences

	p-value of No. of Microbleeds	*p*-value of Relative Percentages
T2WI-FLAIR	0.023	0.027
GRE-T2WI	0.001	0.001
SWI-GRE	0.001	0.001

FLAIR: Fluid-attenuated inversion recovery,
T2WI: T2-weighted imaging, GRE: Gradient-recalled echo imaging,
SWI: Susceptibility-weighted imaging

was significantly higher than those detected on the GRE sequence (p = 0.001) (Fig. 2). GRE was more sensitive than the T2WI and FLAIR sequences for detecting microbleeds (p = 0.001). The numbers of microbleeds detected on the T2WI and FLAIR sequences were not significantly different (p = 0.023).

We set the mean number of microbleeds detected on SWI as 100% and we calculated the relative percentages from the number of microbleeds on the other routine MR sequences. GRE showed significantly higher performance for the detection of microbleeds than did the T2WI and FLAIR sequences. However, the GRE sequence demonstrated only 64.9% of the microbleeds, as compared with SWI (Table 2 and Fig. 3).

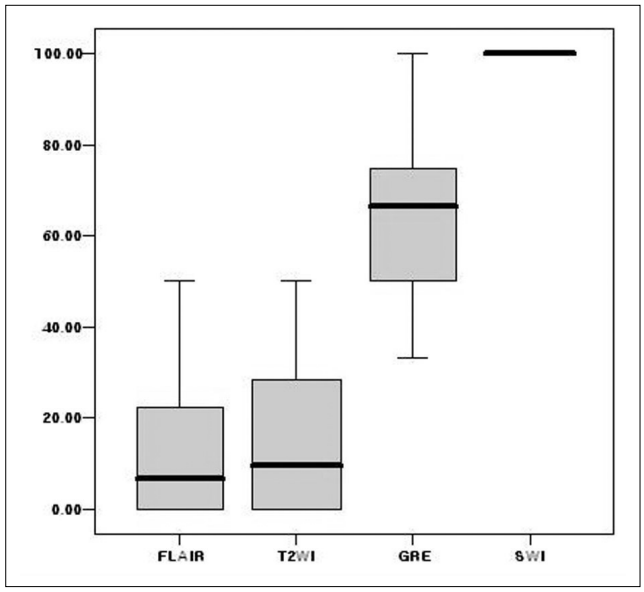


Fig. 3. Comparison of the relative percentages of the microbleeds detected on the conventional MR imaging sequences with that seen on SWI (100%). The GRE sequence detects only 64.9% of the microbleeds as compared to SWI (p = 0.001).

Discussion

The spontaneous, small, homogeneous, round foci of low signal intensity in the brain that are detected on the GRE sequence are considered to be microbleeds. The range of the diameter of these microbleeds has been defined as 2–10 mm in most of the previous studies of microbleeds. Although microbleeds have characteristic imaging findings, sometimes it is hard to differentiate them from flow voids in the pial blood vessels in the cortical sulci and from type IV cavernous malformations, hemorrhagic transformations of cerebral infarcts and the symmetrical hypointensities in the globi pallidi due to iron deposition or calcification (2).

Advanced age, diabetes mellitus and hypertension have been regarded as the most important risk factors for microbleeds (12, 13). Microbleeds may also be caused by cerebral amyloid angiopathy (14, 15), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (16), Binswanger's disease (17), traumatic brain injury (18, 19) and primary angiitis of the CNS (20).

The prevalence of microbleeds is about 5% in healthy adults. However, the prevalence is dramatically increased in patients with various underlying cerebral abnormalities. For patients with ischemic stroke and nontraumatic intracerebral hemorrhage, the prevalence is about 34% and 60%, respectively (2).

Koennecke (7) reviewed the published literature and concluded that cerebral microbleeds might indicate a higher risk of future intracerebral hemorrhage and they may be a marker of cerebral small-vessel disease and cerebral amyloid angiography. However, more prospective data is required in order to confirm these assumptions. The association between microbleeds and the risk of hemorrhagic transformation following intravenous administration of tissue plasminogen activator (tPA) for treating acute ischemic stroke has also been explored in several studies. These studies suggested that microbleeds increased the risk of future hemorrhagic transformation of cerebral infarction or ICH (21–24). However, a recent multicenter study (BRASIL) (25) with 570 ischemic stroke patients who were treated with intravenous tissue plasminogen activator reported that the proportion of patients with symptomatic intracerebral hemorrhage was 5.8% for the patients with microbleeds and it was 2.7% for the patients without microbleeds. The BRASIL study claimed that the estimated risk of hemorrhage in the presence of microbleeds is unlikely to exceed the benefit of thrombolytic treatment. It is still debatable whether microbleeds will increase the risk of

future hemorrhagic transformation.

The susceptibility difference between tissues is a new kind of contrast imaging that is different from the spin density, T1- or T2-weighted imaging (9, 10). SWI is a high-spatial-resolution 3D gradient echo imaging technique that's extremely sensitive to susceptibility changes by setting a long TE (9, 26). The susceptibility effects of iron content increase the distortion of a focal magnetic field, which results in the accentuation of the loss of signal intensity from rapid spin dephasing on the magnitude images of SWI (8). The minimum intensity projection images exaggerate the low signal intensity of veins, hemosiderin deposition or the iron content, and they minimize the high signals of the brain tissue (10). It has been reported that the signal intensity loss caused by susceptibility effects from extravascular deoxyhemoglobin, methemoglobin, hemosiderin and iron content is more accentuated on SWI than on the conventional T2WI and GRE sequences (8, 10, 11, 27).

To date, only a few studies have evaluated the sensitivity of SWI for the detection of microbleeds in patients with various intracerebral hemorrhagic abnormalities (3, 28). Akter et al. (3) reported that SWI detected the greatest number of small hypointense foci less than 5 mm in diameter and SWI depicted twice as many lesions as the GRE sequence in patients with intracerebral hemorrhagic complications. Tong et al. (28) reported that hemorrhagic lesions in patients with post-traumatic brain injury were detected 4 to 6 times greater on SWI as compared with that detected on that on the conventional GRE. In our study, we found that SWI detected approximately 1.5 times more microbleeds than did the GRE sequence. The previous studies showed that their SWI detected even more lesions than our SWI did. We believe that the difference of the study subjects may have affected the results. They evaluated patients with post-traumatic brain injury and the patients with various hemorrhagic lesions, including cavernous angiomas, tumors, hypertensive microangiopathy, angiitis etc. Yet in our study, we only included healthy adults and patients with minor neurologic abnormalities to avoid the influence of large intracerebral hemorrhagic lesions on the sensitivity to detect microbleeds on MR imaging sequences. Many of our study subjects had only one hypointense hemorrhagic focus, which could be detected either on the SWI and GRE sequences. The small number of microbleeds in each healthy subject of our study may have influenced the detection of microbleeds on SWI.

There were some limitations in our study. First, we did not perform quantitative analysis using the contrast-to-noise ratio (CNR) in each hypointense focus. Akter et al. (3) reported that the CNR of lesions was significantly higher for SWI than that for the GRE sequence. Second, the spatial resolution of SWI ($1.1 \times 0.9 \times 5.0$ mm^3 in voxel size) was not high enough as compared with a previous study with a voxel size of $1.0 \times 0.5 \times 2.0$ mm^3 (28). The difference in the spatial resolution may have affected the sensitivity of SWI for detecting microbleeds. Finally, other than old microbleeds, there could have been another factors that influenced the susceptibility effects, such as calcification, non-hemorrhagic iron deposition and vascular deoxyhemoglobin. Although we could differentiate those factors from microbleeds by using our knowledge of the anatomical distribution, it may have been possible for the factors listed above to influence the sensitivity for detecting true old microhemorrhagic lesions on SWI and the GRE sequences.

In conclusion, SWI showed significantly higher sensitivity for the detection of microbleeds as compared to GRE and the other conventional MRI imaging sequences. The GRE sequence, which was previously considered to be the gold standard for the study of microbleeds, detected only 64% of the total microbleeds. We now believe that SWI is the best technique for detecting microbleeds in the brain.

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자화율 강조 자기공명영상에서의 미세 뇌출혈: 고식적인 자기공명영상 기법과의 비교[1]

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목적: 본 연구의 목적은 미세 뇌출혈을 발견하는데 있어 자화율 강조 자기공명영상과 고식적인 자기공명영상 기법을 비교하는 것이었다.

대상과 방법: 미세 뇌출혈을 가진 17명의 환자를 대상으로 하였다. 모든 대상군에서 경사 에코 T2* 강조 영상(GRE), T2 강조 영상(T2WI), 액체감약반전회복(FLAIR), 그리고 자화율 강조 자기공명영상(SWI)들을 얻었다. 각각의 자기공명영상 기법에서 미세 뇌출혈의 개수를 세었다. 또한 자화율 강조 자기공명영상에서 발견된 미세 뇌출혈의 개수를 100%로 한 다른 자기공명영상 기법에서의 비교값(%)을 계산하였다. 통계학적 분석은 Friedman ANOVA Test를 이용하였고 p value가 0.05 미만일 때 통계학적으로 유의한 것으로 생각했다.

결과: 자화율 강조 자기공명영상(100%)에 대한 비교값(%, mean ± standard deviation)은 다음과 같다: 경사 에코 대 자화율 강조 영상(64.9 ± 19.3 대 100, p = 0.001), T2 강조 영상 대 경사 에코(16.9 ± 17.7 대 64.9 ± 19.3, p = 0.001), 그리고 T2 강조 영상 대 액체감약반전회복(16.9 ± 17.7 대 13.8 ± 17.7, p = 0.027).

결론: 자화율 강조 자기공명영상은 경사에코와 다른 고식적인 자기공명영상 기법과 비교하여 미세 뇌출혈의 발견하는데 있어 유의하게 높은 민감도를 보인다.