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Comparison Between Immediate and Delayed Imaging after Gadolinium Chelate Injection for Detecting Enhanced Lesions in Multiple Sclerosis

Background/Objective: Magnetic resonance imaging (MRI) is a noninvasive and valuable method in the diagnosis of Multiple Sclerosis (MS). Compared with other modalities, the sensitivity of MRI for detection of the lesion increases using magnetization transfer (MT) and delayed imaging. Our aim was to compare the two methods in detecting MS lesions.

Patients and Methods: In this double-blind clinical trial, twenty-one patients with the definite diagnosis of MS referred to Poursina Hospital, Rasht were included. Two radiologists evaluated all the images. First, images without contrast were conducted, then 0.1 mmol/kg contrast material (Dotarem, single dose) was injected and after 30 minutes, T1W and MT images were obtained. Seventy-two hours later, T1W images were obtained immediately after injection of 0.2 mmol/kg contrast material (double dose). The data were analyzed using Fisher's and McNemar tests by SPSS for Windows.

Results: Delayed magnetization transfer showed 44 enhanced lesions using MT (69.84%) and 29 lesions using T1 (46.03%). In addition, the number of enhanced lesions in the delayed method were significantly more than those in the immediate method (p value=0.003).

Conclusion: The use of single dose in combination with MT and delayed images after 20-30 minutes enables us to detect more enhanced lesions.

Keywords: Magnetic Resonance, Magnetization Transfer, Multiple Sclerosis, Delay

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Introduction

Multiple Sclerosis (MS) is a disabling disease that causes inflammatory demyelination of the central nervous system.[1] The main cause of the disease is unknown but factors such as autoimmune reaction, viral infections, genetics, race, family history and geographic location are effective in the etiology. MS is 1.7 times more common in women than men.[2,3] MS is associated with complications such as blurred vision, spastic paralysis, sphincter disorder, sexual dysfunction particularly in men, bedsores and superimposed infections. Furthermore, lack of physical interaction and in advanced cases, brain atrophy, severe speech disorders, sensory disturbance and depression are common.[4] MS is the main cause of disability in young adults. The clinical syndrome of the disease occurs as a recurrent disorder with heterogeneous appearance.[5]

Diagnosis of MS is based on history, physical examination, imaging, CSF analysis and evoked potential assessment. Magnetic resonance imaging (MRI) is one of the noninvasive methods in the diagnosis of the disease. Brain MRI is more valuable than other modalities in the diagnosis of MS[6,7] and MRI is the most useful diagnostic assessment tool in this disease, in which the plaques in CNS will be revealed. Abnormal MRI is seen in 90-95% of MS patients. MRI is a sensitive evaluation

method for MS and the specific tool in the assessment of MS plaques is magnetization transfer (MT) sequence in which using contrast media increases the sensitivity for the detection of the enhanced lesions.

Magnetization transfer (MT) is the usage of great radio frequency pulses, which reduce white mater signal intensity in T1-weighted images. Using intravenous gadolinium does not affect the T1 shortening, which indicates that magnetization transfer will increase the severity and resolution of the contrast.

Some studies revealed that in order to determine MS lesions, using triple doses of contrast has higher sensitivity than using the standard dose.[8-10] In addition, other studies have shown that the best dose of contrast material for showing active lesions is the double dose of contrast material and lesions which enhanced with triple doses of contrast will have milder pathologic processes. Therefore, using triple doses of contrast does not give more information about the severity of pathology and is not cost-effective, so its application is limited.[11-13] Furthermore, some studies have shown that the peak of MS lesion enhancement will be at 20-30 minutes after contrast injection.[14-15]

The contrast material used in this survey is Dotarem (meglumine gadoterate), which is excreted by the kidneys and has a half-life of 9 hours. Therefore, injection of the second dose 72 hours after the first dose has no cumulative effects. The only important reported side-effect of gadolinium products, which is very infrequent, is nephrogenic systemic fibrosis (NSF) in patients with acute or chronic renal failure. Dotarem is a macrocyclic ionic chelate of gadolinium with high thermodynamic and kinetic stability, which has been used in more than 20 million patients so far.

Note that the contrast material used in this procedure is more expensive and results in more side-effects in the case of double dose injection. However, using MT and T1 (single dose) is cost-effective with fewer complications, so the aim of this study was to compare immediate (T1) and delayed imaging (T1 and MT) after gadolinium chelate injection for detecting potentially enhancing lesions in multiple sclerosis.

Patients and Methods

In this clinical trial, 21 patients with the definite diagnosis of MS according to Mc Donald's criteria who required contrast enhanced MRI were studied to determine the status of disease activity (relapse) and the effects of treatment. Consent letter was acquired and renal function tests were performed. Exclusion criteria were renal failure, pregnancy and the presence of foreign ferromagnetic bodies. First, images without contrast were obtained in Poursina hospital using 1-Tesla Philips MRI machine including T1-weighted with magnetization transfer, T1-weighted spin-echo, T2, FLAIR and proton density sequences.

Then, 0.1 mmol/kg (single dose) contrast material (Dotarem, Gurbert, France) was injected to each patient and after 30 minutes, T1W and MT images were obtained (Method A). Since 80% of Dotarem is exerted in the urine within 6 hours and 96% within 24 hours after injection, the next imaging was performed 72 hours after the first dose of contrast material injection to avoid any cumulative effects. After 72 hours, 0.2 mmol/kg of Dotarem (double dose) was injected and T1W images were obtained immediately (Method B). Each image was randomly coded, having no information about the patient's data, dose of contrast material, imaging time and use of magnetization transfer. First images, with and without contrast material, were studied by two radiologists separately to detect enhanced lesions. In case of controversy, images were studied again by each radiologist to achieve agreement.[16] To avoid false negative enhanced lesions, an enhanced lesion was identified as a definite area of increased signal intensity compared with the normal white mater. Enhanced vessels and image artifacts with or without simultaneous injection were studied. Then, the total number of enhanced lesions detected by method A (single dose=T1W and MT) and method B (double dose=T1W) along with the total number of enhanced lesions were defined and all the common lesions found in each method were evaluated separately. Data were analyzed using Kappa, Fisher's and Mc Nemar tests in SPSS.

Results

Magnetic resonance images of 21 patients showed enhanced lesions in all methods, in which 13 lesions were seen in common in all methods (20.6%). Using a single dose of contrast, delayed magnetization transfer (MT) showed 44 enhanced lesions (69.84%), of which 13 lesions were in common with other methods and 31 lesions were specifically detected in this sequence; T1

showed 29 lesions (46.03%), of which 13 lesions were in common with other methods and 16 lesions were seen specifically in this sequence. Moreover, 16 lesions (25.3%) were detected by the immediate method with double dose contrast, of which 13 lesions were seen in all sequences and 3 lesions (18.7%) specifically in this sequence.

The number of enhanced lesions in the delayed method using T1 and magnetization transfer were significantly more than their number in the immediate method after double dose (p value=0.003) (Fig. 1), and the number of enhanced lesions in the immediate method with double dose in comparison with the other two groups was significantly low (p value=0.000), while comparison between enhanced lesions in the delayed method using magnetic transfer and total lesions in all methods showed no significant differences. (p value=0.501). In addition, comparison

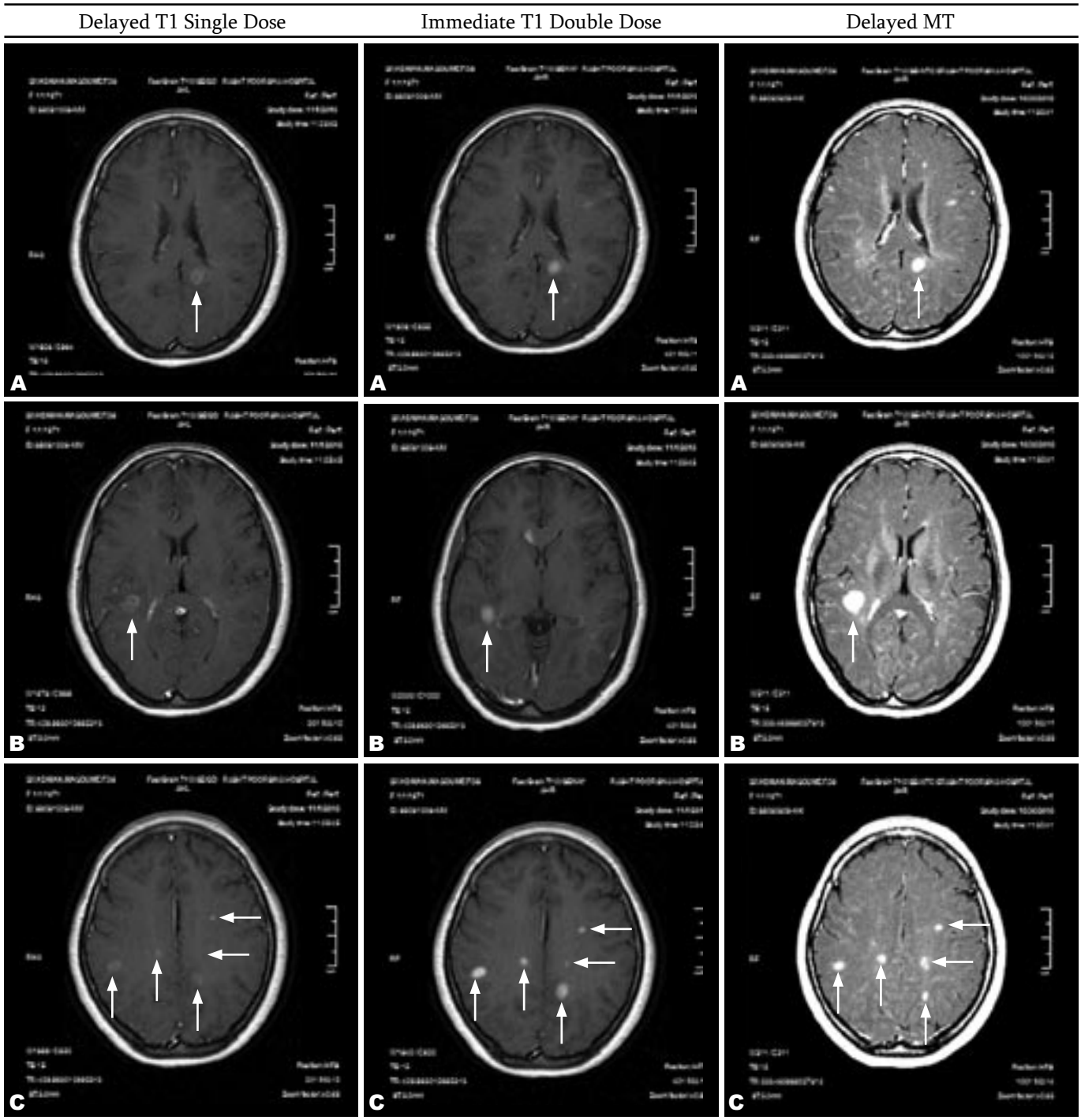

Fig. 1. Comparison between the number of enhanced lesions in the delayed T1 single-dose, immediate T1 double-dose and delayed method in three different patients **(A-C)**. As demonstrated, the number of enhanced lesions in the delayed method are significantly more than the immediate method.

between the number of lesions in the immediate method with double dose and the number of lesions in all methods did not show significant difference (p value=0.501).

Furthermore, MRI images of five patients did not show any difference in any of the protocols performed. There was no agreement between different methods (Kappa=0.03) and regarding the results of Mc Nemar test, disagreements were observed in methods.

Discussion

This survey showed that in MS patients, magnetization transfer 30 minutes after injection of 0.1 mmol/kg (single dose) of contrast material significantly increases the sensitivity in determining enhanced lesions compared with immediate imaging after injection of 0.2 m mol/kg (double dose) contrast material.

This finding was similar to the results obtained by other researchers. Uysal et al.[15] showed that in MS patients with an active disease, using a double dose of contrast material increases the number of enhanced lesions, and a 5-minute interval after injection of contrast material is more effective for determination of the lesions. Filippi et al.[17] showed the sensitivity of MRI in the diagnosis of MS lesions will be increased by delayed injection of the contrast material. Gasperini et al.[16] revealed that using a double dose of contrast had the same sensitivity as using triple dose in the determination of active MS lesions. However, Silver et al.[18] reported that using the triple-dose of contrast material and the delayed method in determining recurrence and evaluation of treatment could be more sensitive than using the double-dose. Bastianello et al.[19] showed that there is no difference in the ability to demonstrate lesions between triple-dose contrast material with and without MT.

In the present study, the number of enhanced lesions determined with the immediate imaging method after the double-dose of contrast material (0.2 mmol/kg) was significantly lower than the total lesions determined with the methods of immediate and delayed. Most studies also reported that immediate method of imaging had less sensitivity in showing aggravated lesions.[15,17,18,20]

There was no agreement between the delayed method using MT and T1 and the immediate imaging method using double dose (Kappa=0.03). However, the study of van Wasberghe et al.[20] showed that injection of triple-dose contrast material in MS patients using a magnetization transfer sequence had a higher sensitivity than injection of the usual dose.

It seems that using magnetization transfer imaging with 30 minutes delay after injection of contrast material will increase the intensity and clarity of lesions with contrast enhancement, while using immediate magnetization transfer in imaging separately would possibly not show significant difference in revealing lesions.

It also seems that appropriate delay between injection and imaging is effective in demonstrating enhanced lesions.

In addition, the combination of time delay and magnetization transfer usage increases the sensitivity of MRI in multiple sclerosis and this method will be more effective than increasing doses of contrast material.

Considering the results obtained in this project and the lack of bias, it seems that the delayed imaging method with 30 minutes interval after 0.1 mmol/kg injection of Gadolinium and using magnetic transfer will have high sensitivity in identifying enhanced lesions in MS patients, which is also more cost-effective due to the reduced dose of contrast material.

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