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Comparison of Gadovist and Magnevist in Brain Magnetic Resonance Imaging of Multiple Sclerosis Patients with an Acute Attack

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Abstract

Background: The use of an appropriate contrast agent performs a major role in brain magnetic resonance imaging (MRI) of multiple sclerosis (MS) patients.

Objectives: The present study aimed to make a comparison between the diagnostic values of Gadovist and Magnevist considering the successive imaging times in contrast-enhanced brain MRI of MS patients.

Methods: A total of 62 relapsing-remitting MS patients (56 females, mean age of 31 years) were enrolled in the present study. All of them underwent two sessions of standard contrast-enhanced brain MRI upon enrollment and 48 h later. The participants were randomly assigned to each contrast agent. T1-weighted (T1W) images were taken 30 sec, as well as 5, 10, 15, and 30 min after the contrast injection. For all of the images, two neuro-radiologists who were blinded to the contrast type counted the number of plaques in the brain. In addition, for the enhanced plaques larger than 10 mm, the signal intensity (SI) was determined using its region of interest.

Results: The mean plaque number significantly increased from 30 sec to 15 min for both contrasts separately (P<0.001). Nonetheless, the slight increases in the mean plaque number from 15-30 min for both Gadovist and Magnevist were not statistically significant (both P-Values>0.25). The mean plaque number in the Gadovist group was higher, compared to that in the Magnevist group at both 15 and 30 min, and the differences were statistically on the borderline (both P-Values=0.07). The mean SI of enhanced plaques gradually increased in the course of imaging in both contrast groups. Except for 30 sec, in all other time sessions, the mean SI was higher in Gadovist-enhanced MR images, compared to Magnevist-enhanced MR images (P<0.01).

Conclusion: As evidenced by the obtained results, Gadovist showed a relatively better diagnostic value for brain MRI of MS patients. Furthermore, the findings suggested that it is cost-effective to take MRI only up to 15 min (instead of 30 min) after contrast injection in both agents.

Keywords: Contrast media, Image enhancement, Magnetic resonance imaging, Multiple sclerosis

1. Background

Multiple sclerosis (MS) is a chronic demyelinating nervous system disease, most commonly affecting young women. In general, MS prevalence has dramatically increased up to 10% in the last five years, affecting 2.3 million people worldwide (1-4). This disease is usually progressive and disables the patients after a few years (5, 6). Therefore, this disease leads to major problems and imposes a heavy economic burden on patients and society. The imaging criteria of MS have drastically changed over the last two decades. An important element of McDonald criteria 2017 is now the evaluation of dissemination in space (the development of lesions in distinct anatomical locations) and time (the development or appearance of new lesions over time) in the central nervous system (CNS)(7-10).

Regarding the McDonald criteria for MS diagnosis, the demonstration of plaques in the acute phase is required. Furthermore, the determination of plaque burden and the extent of damage is of utmost importance in the treatment plan and prognosis. The diagnosis of MS is supported by detecting brain plaques in contrast-enhanced magnetic resonance imaging (MRI) (11-14). Some features of these plaques are different in MRI regarding various shapes of MS plaques in different phases of disease attack. Therefore, various techniques are required to detect lesions in different phases of the disease. In the acute phase, although lesions show inflammation and contrast enhancement, their detection is sometimes challenging; consequently, any method that can improve the sensitivity of plaque detection can help the early diagnosis of plaques (15, 16).

There are various contrast agents that have been

introduced and used for MR, including Dotarem (Gadoterate meglumine, Guerbet) and Omniscan (Gadodiamide, GE Healthcare). In 1988, Bayer Schering Pharma company introduced the first gadolinium-based MRI contrast agent, Magnevist (Gadopentetate dimeglumine, Bayer), which developed and improved the usefulness of MRI. Researches in this field continued and markedly progressed in later years. Recently, a high-concentrate extracellular contrast agent called Gadavist® 1.0 (Gadobutrol, Bayer) with macrocyclic and nonionic features was introduced by Bayer Schering Pharma for MRI scan (17-22).

Magnevist is contraindicated in neonates up to 4 weeks of age due to their immature renal function. It also increases the risk of Nephrogenic Systemic Fibrosis (NSF) in patients with renal insufficiency, as compared to macrocyclic gadolinium-based contrast agents (22). The safety and efficacy of Gadovist at a dose of 0.1 mL/kg have been established in children of all ages, including term newborns (21). Gadovist is also suitable for perfusion studies for the diagnosis of stroke, detection of focal cerebral ischemia, and tumor perfusion (21). Therefore, it seems necessary to assess the power of Gadovist in the diagnosis of acute-phase lesions, in comparison with other contrast agents.

In a previous study conducted by Uysal et al. in 2007 (7), the authors compared Gadovist with Magnevist and reported that Gadovist enhanced more lesions at different times. Nevertheless, they did not measure the signal intensity of the lesions for each contrast agent at different times. To the best of our knowledge, no studies so far have investigated the results of serial images after the injection of Gadovist or Magnevist at different time intervals.

2. Objectives

The present study aimed to compare the diagnostic values of Gadovist and Magnevist as standard contrast agents among MS patients with acute attacks.

3. Methods

3.1. Patients and design

A number of 62 relapsing-remitting MS patients with an acute attack (56 females and 6 males) with a mean age of 31 years were enrolled in the current study. All patients signed a written informed consent after the detailed explanation. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences. This prospective single-center study was conducted from December 2012 to August 2013. The patients and neuro-radiologists were blinded to the contrast agent's allocation. A 1.5 Tesla MR scanner (Signa, GE Healthcare, Milwaukee, WI, USA) with a 16-channel phased-array head coil was used for the purpose of the study. The T1 Spin Echo [SE] was acquired in an axial orientation with 3mm slice thickness[ST], field of view[FOV]24*24 cm, 40 slices, repetition time [TR]560 msec, echo time [TE]12 msec, matrix size 256*192, scan time 2 min and 57 sec.

Gadovist and Magnevist were administered based on the randomization protocol (Block randomization). Since 93% of gadolinium is excreted within 24 h after injection and also to eliminate the effects of the first gadolinium injection on the second contrast imaging session, the second imaging was performed after 48 h of the first imaging with the other contrast agent (7). Magnevist was injected with a dose of 0.5 mol/L (0.2 mmol of gadolinium per kilogram of body weight), while Gadovist was formulated at a higher concentration of 1.0 mol/L (0.1 mmol of gadolinium per kilogram of body weight).

3.2. Image analysis

The images were separately evaluated by two expert neuro-radiologists (H.H., M.M., with 15 and 5 years of experience, respectively). The timing of T1W images after injection was 30 sec, as well as 5, 10, 15, and 30 min. Firstly, all images were visually assessed to detect the number of enhanced plaques. Thereafter, the signal intensity (SI) was determined using region of interest (ROI) in workstations by two neuro-radiologists for all enhanced plaques greater than 10 mm in size. This measurement was undertaken on the contrast-enhanced T1-weighted images for each patient at each interval. In the second session, the ROI curves were placed on the same lesions that were taken in the first session, and SI were measured.

Finally, a comparison was made between the mean numbers of enhanced plaques in different time series using both contrast agents, as well as the mean SI of lesions at each session. The difference between the two contrast agents for the detection of lesion (plaque) enhancement in T1 weighted images was also assessed. The data were analyzed in SPSS software (version 18). A p-value less than 0.05 was considered statistically significant.

4. Results

We counted the number of plaques in the T1W sequence in different anatomical parts and calculated the total number of brain plaques. This calculation was separately performed in all successive time sessions (30 sec, as well as 5, 10, 15, and 30 min) for Gadovist and Magnevist. Thereafter, the results were compared among successive time sessions for each contrast agent. In addition, the number of plaques in similar time sessions was compared between Gadovist and Magnevist.

The mean plaque number in successive time sessions in Gadovist is presented in Table 1. As

Table 1. Mean Brain Plaque Number in Successive Time Sessions for Gadovist and Magnevist and their Statistical Comparisons (Comparison of each contrast with itself in successive time sessions)

		Time Sessions				
		30s	**5 min.**	**10 min.**	**15 min.**	**30 min.**
Gadovist	Mean No. of Plaques±SD	3.7±6.9	4.8±8.3	5.2±8.4	5.5±8.8	5.6±8.5
Magnevist	Mean No. of Plaques±SD	3.5±4.7	4.3±6.1	4.9±7.3	5.2±8.1	5.3±8.2
		Statistical Comparisons				
		30s vs. 5 min	**5 min vs. 10 min**	**10 min vs. 15 min.**	**15 min. vs 30 min.**	
Gadovist	P-Values	<0.001	0.006	0.007	0.28	
Magnevist	P-Values	<0.001	0.001	0.055	0.82	

Abbreviations: s, second; min, minute; SD, standard deviation

demonstrated in this table, the mean number of plaques increased from 3.7±6.9 to 5.5±8.8 and 5.6±8.5 at 30 sec, 15 min, and 30m, respectively. All pairwise comparisons among different time periods were statistically significant, except for 15m and 30m (P=0.28). Thus, the mean number of plaques increased gradually from 30 sec-15 min. Nonetheless, the slight increase from 15m-30m was not clinically and statistically significant.

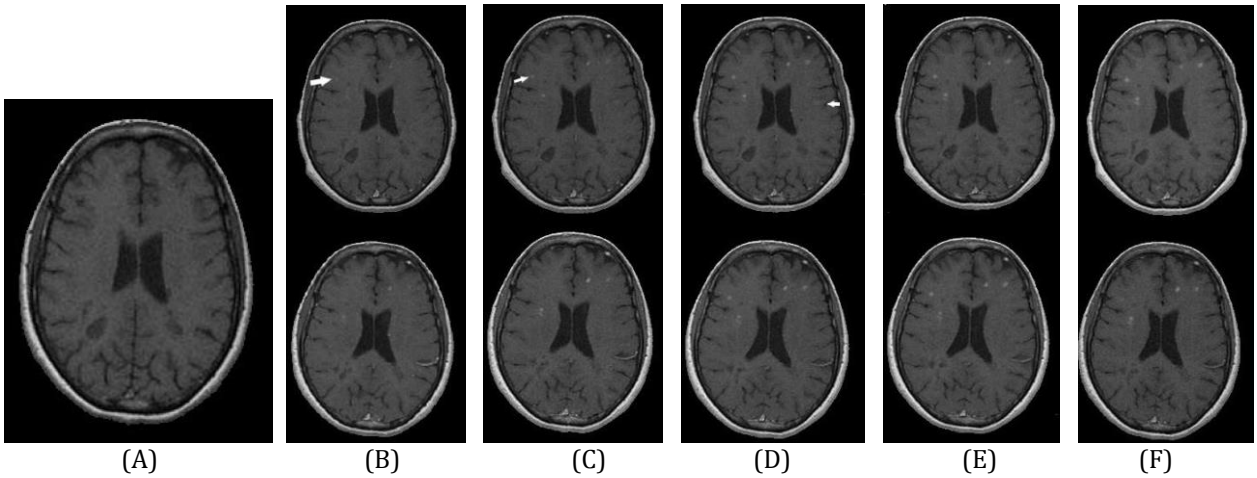
The mean plaque number in the successive time sessions in Magnevist is presented in Table 1. As displayed in this table, the mean number of plaques has increased from 3.5±4.7 in 30 sec to 5.2±8.1 and 5.3±8.2 in 15 and 30 min, respectively. All pairwise comparisons among different time periods were statistically significant, except for 15 and 30 min (P=0.82). It is worth noting that the difference of 10 and 15 min was borderline(P=0.055). Therefore, the mean number of plaques has gradually increased from 30 sec-5 min; subsequently, a slight increase was observed from 15-30 min which was not statistically and clinically significant.

For the comparison of Gadovist and Magnevist, the mean plaque number demonstrated in MRIs was compared between these two agents in similar time sessions. This comparison denoted that the mean number of plaques was higher in all sessions in Gadovist, compared to Magnevist (Table 2; Figure 1). This difference was not statistically significant at 30 sec, 5 min, and 10 min. Nevertheless, the comparison of mean plaque number between the two agents at 15 and 30 min showed borderline P-values (both P-Values were 0.07) in which Gadovist outperformed Magnevist.

Table 2. Comparison of Mean Plaque number in Different Time Sessions between Gadovist and Magnevist

		Mean±SD	**P-Value**
Pair 1	30s G	3.7±6.9	0.64
	30s M	3.5±4.7	
Pair 2	5m G	4.8±8.3	0.41
	5m M	4.3±6.1	
Pair 3	10m G	5.2±8.4	0.39
	10m M	4.9±7.3	
Pair 4	15m G	5.5±8.8	0.07
	15m M	5.2±8.1	
Pair 5	30m G	5.6±8.5	0.07
	30m M	5.3±8.2	

Abbreviations: G: Gadovist, M: Magnevist, s: second, min: minute, SD: standard deviation



(A) (B) (C) (D) (E) (F)

Figure 1. Axial T1-weighted MR imaging in a 35-year-old woman with an acute attack of MS. A T1W image without contrast. B-F, T1W images with contrast (upper row images are enhanced with Gadovist and lower row images are enhanced with Magnevist). Contrast-enhanced images show multiple demyelinating plaques in successive time sessions in both contrast agents (B, C, D, E, and F images are taken in 30 sec, 5 min, 10 min, 15 min, and 30 min after contrast injection, respectively). The images indicate that the number of small enhanced plaques has been relatively higher in Gadovist (arrows), compared to Magnevist. In addition, enhanced plaques are more prominent in later times.

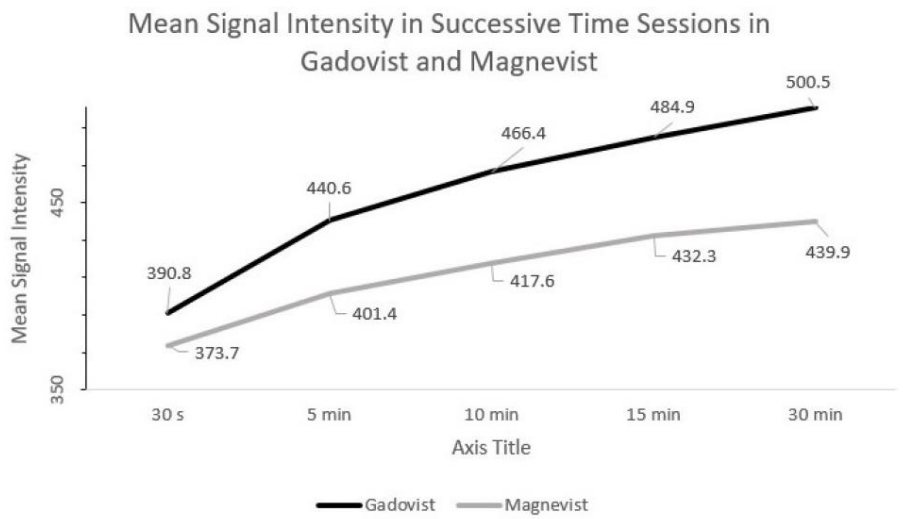


Figure 2. Increase of mean signal intensity in successive time sessions in Gadovist and Magnevist

The comparison of the number of plaques in Gadovist and Magnevist indicated that at 15 min images, 10 (16.4%) patients showed more plaques in Magnevist, 18 (29.5%) subjects demonstrated more plaques in Gadovist, and 33 (54.1%) cases showed a similar number of plaques in 15 min (P=0.18). Among all patients, 15 cases did not show any plaque at all in Gadovist and Magnevist at 15 min. When we deleted these patients (and only considered the patients with at least one plaque in their MRI), 10 (21.7%) patients showed more plaques with Magnevist, 18 (39.1%) cases demonstrated more plaques in Gadovist, and 18 (39.1%) subjects showed a similar number of plaques in 15 min(P=0.18). At 30 m, 8(13.1%) and 19(31.1%) patients had more plaques with Magnevist and Gadovist, respectively. Moreover, 34(55.7%) cases showed no plaque in either contrast or had an equal number of plaques with each (P=0.052).

Regarding the SI, the trend of SI change for both Magnevist and Gadovist was increasing from 30 sec to 30 min, and all successive increases were statistically significant. For Gadovist, the mean SI was 390.8±205.8 in 30 sec which increased to 500.5±267 in 30m (P<0.001). The SI gradually increased in consecutive time sessions (Figure 2). All p-values for the comparison of different pairwise time sessions were obtained at <0.001, except for 15m and 30m that yielded a p-value of 0.002. For Magnevist, the mean SI was reported as 373.7±190.8 in 30 sec which increased to 439.9±208.2 in 30 min (P<0.001). The SI gradually increased in successive time sessions (Figure 2). All p-values for the comparison of different pairwise time sessions were calculated at <0.001, except for a comparison of 30 sec and 5 min that yielded a p-value of 0.065, as well as a comparison of 15 and 30 min that yielded a p-value of 0.23. Finally, we compared the mean SI of similar time sessions between the two contrast agents. In all sessions, the mean SI of Gadovist was statistically higher than Magnevist (Table 3).

Table 3. Comparison of Mean SI between Gadovist and Magnevist in Similar Time Sessions

		Mean±SD	P-Value
30s	G	388.7±206.2	0.15
	M	370.2±190.7	
5m	G	436.0±235.8	0.003
	M	396.6±186.9	
10m	G	462.2±252.0	0.001
	M	413.5±197.6	
15m	G	481.7±267.6	<0.001
	M	426.6±208.3	
30m	G	498.2±268.4	<0.001
	M	437.6±208.2	

Abbreviations: G: Gadovist, M: Magnevist, s: second, min: minute, SD: standard deviation

5. Discussion

Gadolinium-enhanced brain MRI is a sensitive and standard imaging method for the diagnosis of MS, determination of disease severity in the acute and chronic phases, identification of disease progression, and monitoring treatment response in MS patients (MAGNIMS 2016), (1-3, 5). A suitable contrast agent, an appropriate dose, and an efficient scan time can increase imaging value for the detection of acute phase lesions (4-7). Numerous MS lesions could be detected in contrast-enhanced brain MRI without significant corresponding clinical symptoms. Active lesions are associated with blood-brain barrier damage and are enhanced by gadolinium injections in most cases. The integration of delayed scanning and magnetization transfer pulse can lead to increased sensitivity of MRI in the detection of lesions (7).

The optimization of imaging sequence and contrast agent type, dosage, and imaging timing is of

utmost importance. Among the gadolinium contrast agents, Gadovist is a hydrophilic, electrically neutral macrocyclic contrast agent used in contrast-enhanced MRI. The T1 relaxivity of Gadovist is 5.6 L/mmol per sec in plasma at 39°C and 20 MHz. Magnevist, a standard extracellular linear paramagnetic MR contrast agent, has a T1 relaxivity of 4.8 L/mmol per sec in plasma at 39°C and 20 Hz (7). Since Gadovist is prepared in a double concentration of GD^{3+}, in comparison with Magnevist, it has special advantages over Magnevist, including sufficiency in lower volumes and better patient's compliance while maintaining optimal diagnostic value (21).

Therefore, since Gadovist has a higher relaxation rate and a twice GD^{3+} concentration, it produces more T1 shortening than Magnevist and increases signal intensity in T1W-enhanced images, especially in lesions of subtle contrast agent uptake, such as MS plaques. Moreover, it seems that such complications as nephrogenic systemic fibrosis (NSF) are less frequent with cyclic contrast agents, such as Gadovist. In fact, it has higher chelate stability than linear contrast agents, such as Magnevist; therefore, it could be very beneficial, especially for patients with renal impairment (21).

In the present study, a comparison was made between Gadovist and Magnevist in brain MR imaging of acute attack MS patients. A direct relationship was detected between imaging time and signal intensity of MS lesions, increasing from 30 sec-30 min, and the mean SI gradually increased among the enhanced plaques. Mean SI for both Gadovist and Magnevist has increased continuously during 30 minutes and this increase was statistically significant from 30 sec to 15 and 30 min for both contrast agents. In addition, except for 30 sec, the mean SI was statistically higher for Gadovist, compared to Magnevist.

On the other hand, more enhanced lesions were found in later time sessions for both contrasts, and this increase was statistically significant up to 15 min. Nonetheless, the slight increase in the number of plaques in 30 min was not statistically significant in both agents. The comparison of lesion numbers in similar time sessions revealed that the mean number of plaques in Gadovist-enhanced images was higher in 15 and 30 min (Table 2). This increase was statistically borderline and clinically important. In our patients, Gadovist displayed a better profile, compared to Magnevist. In addition, it seems that the best time of imaging is 15m for both agents. Although the mean SI is higher, the number of plaques is not statistically significant, and it is cost-effective to stop imaging in 15 m instead of 30 m.

In a similar vein, Uysal et al. (2007) studied 30 MS patients with immediate and delayed MRI (5 min, 10 min) after Gadovist and Magnevist injection. They reported that Gadovist in contrast-enhanced T1W MR images increased the number of enhancing lesions, as well as the number of lesions in delayed images, and they displayed a delay time of 5 min for the best imaging (7). In line with the mentioned study, the results of the present research suggested that Gadovist is a better contrast agent in these patients. Nonetheless, they showed that the best delay time for imaging is 15 min after the injection. This discrepancy can be ascribed to this point that they continued imaging only up to 10 min. In addition, they did not calculate and compare SI between two contrasts. Furthermore, the patients evaluated in the present outnumbered those who participated in the stated study.

In their study, Bagheri et al. (2008) assessed the diagnostic value of FLAIR and CE-T1W MRI in 46 MS patients. They reported that more lesions were detected in delayed T1W images, compared to the early images (60 min vs. 5 min after the contrast injection) (4). Consistent with the mentioned research, Philippe et al. implemented a study on the use of delayed imaging (30 min versus 5 min) and indicated that the number of plaques was higher in delayed images (23). In a previous study performed by Hashemi et al., it was concluded that 15 min after the injection is the best time for the assessment of MR images in MS patients (regarding plaque detection, and determining the size and signal intensity of the lesions) (1).

The difference in the diagnostic power of contrast agents depends on the evaluated anatomical studied location and the inherent characteristics of the lesion and does not always follow a constant rule. For instance, Esposito et al. compared single dose 1M gadobutrol (Gadovist) with double-dose 0.5M gadolinium-DTPA (Magnevist) in the detection of late enhancement (LE) in the diagnosis of acute myocarditis. The results of the aforementioned study demonstrated no significant difference in LE images (performed 10, 15, and 20 min after contrast injection) between the two contrasts (24).

According to previously conducted studies, it is better to use Gadovist for brain disease, and this better performance of Gadovist in brain pathologies has been approved in experiences. For example, in their study, Anzalone et al. compared the effectiveness of a standard dose of 1.0 M gadobutrol with a standard dose of gadopentetate dimeglumine for MR detection of brain metastases. In the stated study, 27 patients with cerebral metastasis were examined twice with contrast-enhanced MR imaging. The authors reported that gadobutrol improved the conspicuity of detected lesions over gadopentetate dimeglumine for the visualization of brain metastases (25).

A review article conducted by Essig et al. used gadobutrol for the evaluation of neoplastic central nervous system lesions. The results of the referred study demonstrated superior lesion enhancement and diagnostic information, compared to gadopentetate and gadoterate (26). Along the same lines, Frederik

et al. compared gadobutrol and gadopentetate dimeglumine for MR perfusion in normal brain and intracranial tumors at 3T. They observed significantly higher demonstration between parenchymal and demarcation of highly vascularized tumor tissue on the brain using gadobutrol, compared to gadopentetate dimeglumine (27).

Pintaske et al. determined the accurate relaxation rates of Magnevist, Gadovist, and Multihance at 0.2, 1.5, and 3 Tesla in human blood plasma. Multihance demonstrates the highest relaxation rates at all field strengths, compared to other contrast agents. Gadovist showed higher relaxation rates in blood plasma, in comparison with Magnevist (28). The sensitivity of delayed gadolinium-enhanced MRI for the detection of more MS lesions has been reported to be higher than early enhanced MRI. It may be ascribed to increased leakage of contrast material in the blood-brain barrier spaces after delayed scanning (29-31). In a study carried out by Alizade et al., it was reported that the number of enhancing plaques was significantly higher in delayed images, and the best time to observe these plaques was 20-30 min after contrast injection (32).

The elongation of imaging time from 15-30 min may result in the enhancement of plaques and a slim chance of their detection. However, it is time-consuming and more expensive for both patients and health systems and decreases patients' tolerance. It was observed that sufficient details for efficient diagnosis and imaging could be yielded within 15 min for both contrasts, compared to 30 min imaging. It is preferred to lower the imaging time and cost as much as possible, while imaging details are preserved in an acceptable quality.

Regarding study limitations, one can refer to the lack of lesion burden assessment. If we had assessed lesion burden among all patients, a more comprehensive comparison could have been made between Gadovist and Magnevist.

6. Conclusion

Gadovist outperforms Magnevist in brain MRI in MS patients (in the detection of more lesions and better enhancement of lesions|). In both Gadovist and Magnevist, it is sufficient and cost-effective to take the imaging 15 min after contrast injection, and longer imaging is not necessary.

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Footnotes

Authors' Contribution: Hassan Hashemi: assessment, interpretation and acquisition of imaging data, critical revising of the paper for important intellectual content, final approval of the version to be published.

Hossein Ghanaati: conception and idea development, assessment, interpretation and acquisition of imaging data, critical revising of the paper for important intellectual content, final approval of the version to be published.

Somayyeh Behzadi: assessment, interpretation and acquisition of imaging data, critical revising of the paper for important intellectual content, final approval of the version to be published.

Mohammad Hossein Harirchian: acquisition of data, critical revising of the paper for important intellectual content, final approval of the version to be published.

Ghazaleh Amjad: assessment, interpretation and acquisition of imaging data, critical revising of the paper for important intellectual content, final approval of the version to be published.

Madjid Shakiba: study design, statistical data analysis, drafting the paper and critical revising of the paper for important intellectual content, final approval of the version to be published.

Nafiseh Ghavami: acquisition of data, critical revising of the paper for important intellectual content, final approval of the version to be published.

Hamed Naghibi: acquisition of data, drafting the paper and critical revising of the paper for important intellectual content, final approval of the version to be published.

Kavous Firouznia: conception and idea development, study design, assessment, interpretation and acquisition of imaging data, critical revising of the paper for important intellectual content, final approval of the version to be published.

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