ORIGINAL ARTICLE

Significance of diffusion weighted imaging (DWI) as an improving factor in contrast enhanced *magnetic resonance imaging* (MRI) enterography in evaluation of patients with Crohn's disease

Bilal Imširović[1], Enver Zerem[2], Alma Efendić[3], Alma Mekić Abazović[4], Omar Zerem[5], Muhamed Djedović[6]

[1]Department of Radiology, General Hospital "Prim. dr. Abdulah Nakaš", Sarajevo, [2]Department of Gastroenterology, University Clinical Centre Tuzla, Tuzla, [3]Department of Radiology, Cantonal Hospital Zenica, Zenica, [4]Department of Oncology, Cantonal Hospital Zenica, Zenica, [5]School of Medicine, University of Tuzla, Tuzla, [6]Department of Surgery, Clinical Centre, University of Sarajevo, Sarajevo; Bosnia and Herzegovina

ABSTRACT

Aim To determine capabilities and potential of contrast enhanced magnetic resonance imaging (MRI) enterography in order to establish the diagnosis and to evaluate severity and activity of intestinal inflammation.

Methods Fifty-five patients with suspicion for presence of Crohn's disease were evaluated. All patients underwent contrast enhanced MRI enterography and diffusion weighted imaging (DWI), and subsequently endoscopic examination or surgical treatment. Four parameters were analysed: thickening of the bowel wall, and presence of abscess, fistula and lymphadenopathy.

Results Comparing results of DWI and contrast enhanced MRI enterography a significant difference between results given through diffusion and histopathological test was found, e.g. a significant difference between results obtained through diffusion and MRI enterography was found. MRI enterography sensitiveness for bowel wall thickening was 97.7% and specificity 70%, whilst DWI sensitivity for bowel wall thickening was 84% and specificity 100%. The diagnostics of abscess and fistula showed no significant difference between DWI and MRI, while in lymphadenopathy significant difference between contrast enhanced MRI enterography and DWI was found.

Conclusion Contrast enhanced MRI enterography in combination with DWI allows for excellent evaluation of disease activity, but also problems or complications following it. The examination can be repeated, controlled, and it can contribute to monitoring of patients with this disease.

Key words: magnetic resonance imaging, diffusion, inflammatory bowel disease

Corresponding author:
Bilal Imširović
Department of Radiology,
General Hospital "Prim. dr. Abdulah Nakaš"
Kranjčevićeva 12, 71000 Sarajevo,
Bosnia and Herzegovina
Phone: +387 33 285 100;
Fax: +387 33 285 370;
E-mail: bilal_imsirovic@yahoo.com
ORCID ID: http://www.orcid.org/0000-0002-0941-6593

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INTRODUCTION

Due to its length and location, small intestine is challenging both for clinical and radiological evaluation. Crohn's disease is the most common disease of the small intestine (1). Even though the medical problem was defined in the previous century, Crohn's disease patients even today represent a diagnostic challenge, and each attempt of diagnostic progress is both of scientific and practical significance (2).

Beside non-invasive and accurate disease diagnostic in its earliest possible phase, modern radiology also requires a possibility to evaluate activity and seriousness of a disease. This is important because the spread of disease affects medical and surgical approach (3).

Until recently, the main diagnostic modality was a standard radiological examination which could neither show the bowel wall nor the changes located extraluminarly (4). One should also have in mind that these examinations have harmful ionizing radiation. The development of computed tomography (CT) devices and appearance of multi-slice computed tomography (MSCT) devices made a progress in diagnostics, where the CT enterography made a huge step forward in the diagnostic evaluation of intestinal wall changes and thickening, but also it could display extra luminal changes (5).

However, ionizing radiation is still a major problem, especially because patients with the Crohn's disease are mostly young (6). Since the ailment demands constant tracking, there is a question whether constant CT examinations are justified (6).

Even though endoscopic diagnostic methods are the best for diagnosing and tracking digestive tract diseases, they are limited in displaying proximal and distal segments of small intestine (7).

Introducing the imaging radiological techniques, adequate diagnose and valuable information tend to be found, but not to disturb the commodity and security of the patient (8). That is essential, considering that this is a long-term illness which requires constant monitoring (6). The use of magnetic resonance imaging in the evaluation of patients with inflammatory bowel disease was conditioned by the development of devices that had technical predispositions for performing such examinations (9,10). Protocol development for MRI enterography made a huge step forward in the diagnostic treatment of patients with inflammatory bowel disease (11). Problems such as insufficient intestinal distension and intestinal peristalsis are solved with the application of oral contrast media and intravenous spasmolytic application (11). Studies which compared contrasted enhanced MRI enterography with other examination methods have given promising results. The use of magnetic contrast medium with dynamical postcontrast evaluation has improved examination quality (12-15).

The use of diffusion weighted imaging (DWI) sequences represents a new possibility of expanding the ability of MRI, which can give additional information about the changes of the inflammatory bowel disease (16-18). The DWI represents changes in water mobility caused with static membrane interactions, macromolecules and the surrounding (19).

To contribute in the diagnostic treatment of patients with Crohn's disease, based on our previous experience in MRI diagnostics we have decided to conduct this research. Initial hypotheses were that the contrast enhanced MRI enterography provides an excellent assessment of the disease activity as well as the estimation of complications that followed the disease, so that DWI, in comparison with contrast enhanced MRI enterography, provides better sensitivity, and in combination with the apparent diffusion coefficient (ADC) map, it can potentially improve specificity, and that contrasting MRI enterography in combination with DWI has a significantly higher success in detecting the activity and complications of Crohn's disease.

This research was conducted in order to determine a potential for diffusion weighted imaging (DWI) in the evaluation of patients with Crohn's disease, as a new possibility of spreading the ability of magnetic resonance, and the improvement of sensitivity and specificity of the examination. The results of this study will provide indicators that will represent guidelines for setting up new diagnostic criteria in the evaluation of patients with Crohn's disease.

PATIENTS AND METHODS

Patients and study design

The research implied prospective study where patients with Crohn's disease were diagnostically treated with dynamic contrast enhanced MRI

(DCE-MRI), and diffusion weighted imaging (DWI-MRI).

The research included 55 patients with clinical and laboratory suspicion of the Crohn's disease, who were diagnostically evaluated and treated at the Cantonal Hospital Zenica in the period between July 2013 and December 2015.

A research protocol was approved by the Ethics Committee of the Cantonal Hospital Zenica.

After the MRI enterography, which included dynamic contrast sequences and diffusion weighted imaging sequences, all patients underwent endoscopic examinations or they were surgically treated. Surgical and endoscopic findings were taken as reference findings.

This study included patients whose clinical and laboratory tests made them suspicious of having Crohn's disease, which included the patients with earlier diagnosis and PH verification of Crohn's disease (endoscopically and surgically) and who were in the phase of exacerbation (patients who have clinical and laboratory indicators of the disease presence). Patients with suspicion of having Crohn's disease were also taken into consideration. In that case, the disease was located on endoscopically accessible places because of endoscopic imaging confirmation (colon, terminal ileum, the area of ileocolic anastomosis, proximal part of digestive tract available to endoscope). This study also included patients who were surgically treated after imaging.

The study excluded patients who rejected to participate, patients with contraindication for MRI examination (electromagnetic implants, foreign metal objects, claustrophobia), patients with contraindications for appliance of MRI contrast medium (renal insufficiency, high values of urea and creatinine, allergy to the contrast medium, patients who were diagnosed with changes on some parts of the digestive tract, which were not accessible to endoscopic confirmation, but which do not require urgent surgical treatment).

The study implied the analysis of DCE-MRI and DWI for every patient included in the study. Clinical and morphological characteristics were analysed, such as thickening of the bowel wall (more than 3 mm) presence of fistula and abscess. The analysis included both local lymphadenopathies as an indirect sign of inflammation.

Methods

All patients who qualified for participation in the study underwent an MRI examination (SIEMENS Magnetom Avanto 1.5 T, Erlangen, Germany), which included DCE-MRI, and DWI.

Even though there is no consensus about the universal protocol for contrast enhanced MRI enterography, each examination should consist of fast and ultrafast T1W and T2W sequences in transversal and coronary plane. Dynamic postcontrast evaluation implies the use of GE T1W sequences with fat saturation.

After the native examination and intravenous application of the contrast medium, dynamic postcontrast recordings on T1 VIBE sequences biplanary (transversal and coronary) were performed.

The examination was amended with diffusion weighted sequences for abdomen and pelvis area: ADC maps were automatically calculated with computer program workstations of MRI device, and on the basis of the given diffusion sequence. DWI sequence was recorded before intravenous application of the contrast medium. Before the examination the patients drank 1.5 litre of fluid consisting of 10% mannitol and water in proportion 1:2; at the end they drank 100 mL of dilution every 5 minutes. After that the patients were put on the device table where the magnetic coils were applied: 4-channel flex large and 8-channel body matrix tim coil.

Before starting both native and postcontrast scanning, the patients were given intravenous spasmolytic in order to slow down peristalsis and to avoid effects of intestinal twitching.

Statistical analysis

The applied methods of descriptive statistical analysis were used to describe distribution of examined variables. Kolmogorov-Smirnov test was used to test normal distribution of quantitative variables**.** Since these samples are not normally distributed but at the same time they are dependent, in questioning the significance nonparametric Wilcoxon's test (Wilcoxon signed rank test) was used.

A statistical analysis was performed using the "R" program.

In order to establish the diagnostic characteristics, respectively the quality of one method in

relation to the other, we performed receiver operating characteristic curve (ROC) analysis.

The statistical hypotheses were tested at the level of $\alpha < 0.05$, which means that the difference between samples was considered significant if $p < 0.05$.

RESULTS

A total of 55 patients underwent MRI enterography before the endoscopic or surgical treatment. This MRI enterography included DCE-MRI and DWI. The affected bowel segment after the contrast administration increased intensity of the signal and showed signs of the diffusion restriction (Figure 1).

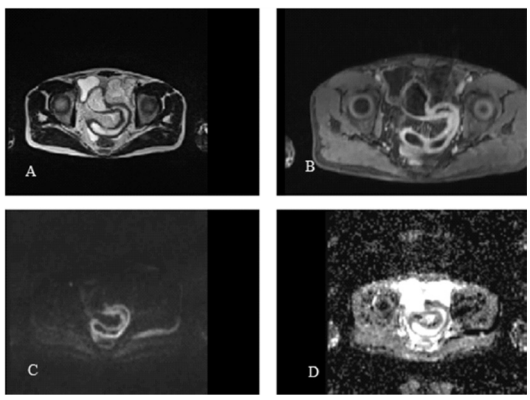

Figure 1. A) T2 BLADE axial multi breath hold (mbh), B) T1 VIBE FS axial mbh postcontrast, C) and D) diffusion weighted imaging (DWI) and ADC map: intestinal wall thickening with signs of diffusion restriction (Department of Radiology, Cantonal Hospital Zenica, 2014)

Out of 55 checked patients, 10 patients were lacking histopathological confirmation of the disease presence. Three of them had positive results on MRI enterography.

Out of 55 patients, there were 22 males aged between 19 and 75 (the average age of 47 years), and 33 females aged between 19 and 72 (the average age of 45.5 years) ($p = 0.21$).

Out of 55 patients who underwent MRI enterography, 47 encountered thickening of the bowel wall: in 44 (80%) patients the result was histopathologically confirmed, while in three (5.45%) patients histopathological confirmation was missing. In seven (12.7%) patients absence of histopathological thickening of the bowel wall on MRI enterography was found.

Diffusion restriction of free water in affected segments was detected in 38 (69%) patients, while it was negative in six (10.9%) patients. There was a finding of pronounced diffusion restriction in 25 (45.5%) patients, while in 13 (23.6%) patients moderate restriction of diffusion of the affected segments was established.

Applying Wilcoxon test with 95% level of significance, the following results were obtained: $V = 0$ and $p = 0.008151$ suggesting that there was statistically significant difference between results obtained through DWI and histopathological results.

A statistically significant difference between results obtained through diffusion and MRI enterography was found ($V=45$; $p=.0027$).

In case of MRI enterography, obtained results for sensitivity showed TPR (the truly positive rate) = 0.9777 and for specificity, FPR (falsely positive rate) = 0.3. In case of DWI, sensitivity for TPR (exact positive rate) of 0.84, and specificity for FPR =0 was found.

Sensitivity for MRI enterography for bowel wall thickening of 97.7%, and specificity of 70% was found, while the sensitivity for DWI for bowel wall thickening was 84%, and specificity 100%.

In order to compare predictive properties of MRI enterography versus DWI, the area under curve (AUC) was used. In majority of cases, higher values of AUC represented a better method, which is a predictive feature of the method. In case of MRI enterography the obtained value for AUC was 0.838, while for DWI value AUC was 0.922. On the basis of sensitivity values, TPR (true positive rate), specificity, FPR (false positive rate), and area under curve (AUC), it can be concluded that the application of DWI improved predictive features of the method, especially specificity; the sensitivity, in the obtained pattern was not improved, which can be seen from the TPR value and cross section of the ROC (Figure 2).

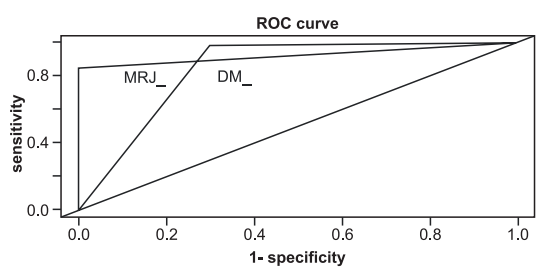

Figure 2. Magnetic resonance imaging (MRI) and diffusion weighted imaging (DWI) correlation depended of wall thickening

Out of 55 checked patients, MRI enterography determined the presence of abscess collection in

four (7.2%) patients, where the abscess collections were located dominantly in perirectal and perianal region. All abscess collections showed free water diffusion restriction.

Applying the Wilcoxon test, since there were identical results, there was no significant difference between results obtained with DWI and MRI results.

MRI enterography confirmed the presence of fistula in 11 (20%) patients: five patients had enteroenteral fistula, one had enterocutaneous fistula, one had enterovesical fistula, and seven patients had perianal fistula; four patients had combined fistulas. All fistulas showed restriction of free water diffusion.

In order to determine significance between results obtained through MRI enterography and DWI there was no significant difference between the results obtained with DWI and MRI.

MRI enterography detected significant lymphadenopathy in 29 (52.7%) patients.

Free water diffusion restriction in case of affected lymph nodes was confirmed in 21 (38.1%) patients, while in eight (14.5%) patients with MRI verified lymphadenopathy the presence of diffusion restriction was not confirmed.

In order to establish significance between results obtained through DWI and results obtained through MRI enterography, V=45 and p=0.0027 were obtained, suggesting a statistically significant difference between results obtained through MRI enterography compared to DWI.

DISCUSSION

Standard tools such as Crohn's Disease Activity Index or the Crohn's Disease Endoscopic Index of Severity, the Simplified Endoscopy Score do not show total bowel damage (20). Because of that it is essential to find new tools for evaluation of functional and structural bowel damage and its progress over time.

Magnetic resonance imaging (MRI) has more and more application in diagnosing and patient monitoring with inflammatory bowel disease. The absence of ionizing radiation, excellent tissue characterization and functional imaging are important characteristics which make the MRI a suitable method for digestive tract recording (21-23).

Results of the presented study have shown no significant difference in approximate age between males and females, which is consistent with previous researches (24).

Results obtained for bowel wall thickening showed no significant difference between results obtained through MRI enterography in comparison with histopathological test. Comparing DWI results and MRI postcontrast enterography, significant difference between DWI and histopathological results was found, e.g. statistically significant difference between DWI and MRI enterography was found. Considering the fact that there was no statistically significant difference between MRI enterography and histopathological results, it can be concluded that DWI as a single method cannot be used as a reliable diagnostic method for confirmation of the wall thickening.

In comparison with earlier studies where the sensitivity for DWI of 100% and specificity up to 92.9% were found (25), our results in terms of DWI specificity were better. Previous studies have shown sensitivity for MRI enterography of 83%-100% which correspond with our results, and specificity of 94-100%, which does not correspond with our (lower) results (25-27).

In case of MRI enterography the results of our study have shown that by applying DWI predictive property method was being improved, especially specificity, while the sensitivity in case of obtained pattern was not improved. Unlike lymphadenopathy, in abscess collection and fistula detection there was no significant difference between the results obtained by diffusion weighted imaging and MRI findings. Recent functional techniques such as DWI and dynamic contrast-enhanced MRI (DCE-MRI) give promising results in evaluation and monitoring of Crohn's disease, but they require additional prospective studies (28-30).

There are numerous studies which dealt with different diagnostic aspects of Crohn's disease.

Different studies were implemented with the aim of comparing MRI enterography with other examination techniques, and they give promising results (31,32). Sato et al. comparing ability to detect lesions in Crohn's disease with MRI enterography and ileocolonoscopy concluded that MRI enterography can be useful, not only for the detection of ulcers, but also for discovering endoscopically verified smaller lesions of Crohn's disease suggesting clinical benefit of MRI ente-

rography for the detection and monitoring of this disease (33). Diffusion weighted imaging (DWI) represents a new possibility of widening ability of magnetic resonance imaging which can give additional information about the bowel tissue structure which is being recorded; thus representing fast and precise tool for detection and evaluation of the inflammation of the small intestine in case of Crohn's disease (25).

DWI-MRI enterography is a reliable tool for evaluation of small intestine inflammation and colon, and with its use it could avoid a need for application of gadolinium based contrast agent (34). Oto et al. concluded that DWI is a reliable technique for the detection of inflammation in patients with Crohn's disease, and that dynamic contrast MRI and DWI give quantitative measures of the small intestine inflammation, which can differentiate actively inflammation segments from normal small intestine in Crohn's disease (16). The DWI allows better sensitivity compared to DCE-MRI, while the combination of ADC and K (trans) parameters for the analysis can potentially improve specificity (16,17).

In a study about the importance of MRI enterography and DWI in Crohn's disease patients, Buisson et al. concluded that DWI-MR enterography is a good and precise tool for detection and evaluation of the small intestine inflammation (25). Tielbeek et al. suggested that quantitative parameters of conventional MRI sequences, dynamic contrast MRI sequences and DWI sequences correlate with histopathology of surgical specimens. In addition, conventional MRI enterography can be used for evaluation of the Crohn's disease activity. Parameters of dynamic contrast MRI and DWI MRI give additional information (35).

In conclusion, contrast enhanced MRI enterography provides an excellent assessment of the disease activity as well as the associated complications.

Applying the DWI, the second-order error is reduced, reducing the possibility of accepting a wrong diagnosis. In some future studies, it would be essential to examine whether the DWI sensitivity would increase or get closer to MRI sensitivity if the number of patients is increased. Considering commodity, and taking into consideration security and simplicity of the treatment, MRI enterography in combination with DWI is suitable for repetition, control treatments, and it can contribute to monitoring of Crohn's disease patients, but also it is an excellent tool for complication evaluation of the basic illness, for fistula detection and especially for perianal fistulas.

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TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

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