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OPEN PEER REVIEW

Evaluation of the Effect of Multiple Linear Gadolinium-Based Contrast Agent Exposures on the Signal Intensity of the Dentate Nucleus in Multiple Sclerosis Patients

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

2 comments · 6 Apr 2021 – 7 Apr 2021

Referee 1 Reviewer

ACCEPT 6 Apr 2021

From a methodological point of view, it can be said that this study was properly designed and implemented and was very well and comprehensively written; therefore, it is approved for publication in the IJR.

Editor-in-Chief

MINOR REVISION 7 Apr 2021

Dear authors,
Your article needs Minor Revision.
Regards

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewers' Comments:

Reviewer 1:
From a methodological point of view, it can be said that this study was properly designed and implemented, very well and comprehensively written; therefore it is approved for publication in the IJR.

Response: Thanks for accepting our article.

Reviewer 2:
I suggest that the authors add one or two short paragraphs explaining the differences between macrocyclic and linear contrast agents and define examples of each kind of them.

Response: Thanks for valuable comment. As alluded earlier, chemical properties of the agent shown to be a key factor in the degree of deposition.This This paragraph below inserted in the discussion of paper and highlighted (sentences number 214-224).

The chemical bonds in GBCAs are made of a gadolinium ion and a carrier molecule. A carrier molecule is called a chelating agent, which modifies the distribution of gadolinium within the body to overcome its toxicity while maintaining its contrast properties. Structurally, GBCAs can be divided into two groups based on the type of ligand. Linear agents have an elongated organic molecular ligand that wraps around the ion (such as gadodiamide [Omniscan] and gadopentetate [Magnevist]). Cyclic agents form a cage-like ligand structure with the ion enclosed in the cavity of the complex (such as gadobutrol [Gadavist]and gadoterate [Dotarem]). The cyclic agents tend to have lower dissociation constants and are therefore thought to be more stable than the linear agents. Both linear and cyclic agents can either be ionic or non-ionic, nonspecific extracellular and tissue-specific.

2 Revision 1

2 comments · 14 Apr 2021 – 19 May 2021

sofia Sabouri Reviewer

MINOR REVISION 14 Apr 2021

1- Were all of those MRI examinations performed in your department? Were all of them performed with a single protocol, or did the parameters vary from the first to the last MR imaging exam?
2- How are you confident that the contrast agent was the same from the first to the last exam, especially in patients who underwent MRI more than five times (according to fig4, some patients underwent MRI up to 30 times)? How did you exclude the use of macrocyclic agents in these patients?
3- The number of injections per patient ranges widely, from 5 to 30. This range may affect the results. Can you categorize the patients into narrower ranges of injections, e.g., 5-10 injections, 10-15 injections, …?
4- What was the interval between the first and the last exam in each patient? Based on the literature, is an increase in the SI of DN associated with the number of injections and the intervals between them, and have you considered this?
5- Two different numbers of injections for each patient have been mentioned in the study: more than four and more than five. Which one is correct?
6- What is new in this study compared with similar published articles?

Editor-in-Chief

MINOR REVISION 19 May 2021

Dear authors,
Your article needs Minor Revision.
Regards

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewers' Comments:

Reviewer 1:
Accept

Response: Thank you for your acceptance

Reviewer 2:
1- Were all of those MRI performed in your department? Were all of them with single protocol or they had varying parameters from the first to the last MR imaging exam?

Response: Thank you for your valuable comment. *Most of the patients underwent all their imaging in the MRI part of Sina Hospital. The protocols were all the same and the last T1W image was all taken with the same parameters and machine MRI.*

2- How are you confident that the contrast agent was the same from the first to the last exam? Especially in patients who performed MRI more than five times (according to fig4, some patients did up to 30 times). How did you exclude use of Macrocyclic agents in these patients?

Response: Thank you for your valuable comment. The study data have been taken from a time period in which we know the main contrast agent of the hospital pharmacy was linear contrast agent, so we think the gadolinium contrast agent used for our patients has been mainly the linear gadolinium contrast agent.

3- Number of the injections for the patients has a wide range of 5 to 30 times. This range may affect the results. Can you categorize the patients with smaller range of injection, e.g. 5-10 injections, 10-15 injections,…

Response: Thank you for your valuable comment. This range was chosen based on previous articles. in addition, we implement one analysis according to your comment: In fig. 4, we assessed the correlation of GAD injection time with dentate to pons signal intensity ratio. As we can see, with increase of GAD injection number, this ratio has been increased in a relatively linear pattern.

4- What was the interval between the first and the last exam in each patient? Referring to articles is there any association between the number of injections and intervals in increasing the SI of DN and have you considered it?

Response: Thank you for your valuable comment. Really this data was not evident in our patients but as the MS subtype in all of patients was RR, we expect a relatively

homogeneous population in our study data [regarding the point that you have been mentioned in the question]

5- Two different number of injections for each patient has been mentioned in the study, more than four and more than five. Which one is correct?

Response: Thank you for your valuable comments. More than four is correct. In manuscript is corrected.

6- What is new in this study comparing to the similar published articles?

Response: Thank you for your good point. However, the topic has been discussed earlier, our study has been implemented on a relatively large sample size and this is the point that we considered the data to be published. Gad deposition could be dependent to different factors such as ethnic and genetic factors, management protocols etc. So we decided to report our experience in this topic. In addition, as we mentioned, our sample size was considerable and we could show a higher DN SI in patients with more Gad injection compared to the patients with less Gad injection EVEN in subgroup of patients without any visual hyperintensity in DN. This means even one Gad injection could be important in this regard.

3 Revision 2

1 comment · 5 Jul 2021

Editor-in-Chief

MINOR REVISION 5 Jul 2021

1-The background of the abstract is in fact the objective. Please add a background section to the abstract according to the journal format and change background to objective.
2-line 10: Last standard GAD enhanced exam
3-lines 13-16: “Patients were divided into two subgroups based on the total number of MRI exam (more than 4 times versus others) and subgroups were compared in terms of mean SIR and visual hyperintensity”
4-line 17: “Results: Sixty eight percent (n:83)”
5-line 19: “…. and also healthy controls.”
6-lines 20 and 21: Please delete the following sentence [it has been repeated]: “Mean SIR in patients and controls was 1.10±0.07 and 1.04±0.02 respectively[P<0.001]”
7-lines 25 and 26: “SIR and visual DN hyperintensity are increased when the number of GAD injections are more. This could be due to tissue deposition of GAD.”
8-line 35: “…..… remitting pattern that is more common in women and happens more likely in the age of 15-45 years.”
9-Line 41 is meaningless.
10-lines 47 and 48: “…. would increase the detection ability of lesions especially in patients with active lesions which could be enhanced after contrast injection [15]”
11-lines 51-3: This sentence is unclear: “The concerns about Gadolinium-based contrast media are not limited to the neural tissues, but long-term adverse effects in all human tissues are not far from creating that concern [17]”
12-When you abbreviate a term, please use the abbreviated form thereafter [line 69, dentate nucleus].
13-Please change Methods and Study design to patients and methods. Please add sequential numbers to the titles.
14-lines 85, 103, 118 and 119: T1-W
15-This is unclear: “first time implement MRI with contrast injection”
16-line 89: Delete “present”.
17-line 90: Please change “completed” to “signed”.
18-The Kidney and liver function section could be summarized as follows: Renal and kidney functions were evaluated in all patients and were normal in all patients prior to each GAD injection.
19-line 130: “(classified based on the total number of MRI scans as more than 4 times versus others)”
20-The SPSS manufacturer is wrong. Please correct it. In addition, SPSS stands for statistical package for social sciences.
21-line 141: “were used for statistical analyses”
22-line 143-4: “statistical significance”
23-lines 169 and 174: Change time to number.
24-line 171: “with visual DN hyperintensity”
25-line 185: SIR
26-line 188: retrospective
27-line 19: Change repetition to assessment.
28-line 192: DN
29-line 200: SIR
30-line 203: showed
31-line 243: control

32-line 247: femor, not femora
33-line 252: Change linear gadolinium-based contrast to GBCA.
34-line 274: Change signal intensity ratio (SIR) to SIR.
35-line 276: SIR
36-The figure 5 legend is incomplete.
37-table 1: control group

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Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

1-background of abstract is in fact objective. please add background part in abstract according to journal format and change background to objective. *Response:* In manuscript is corrected.

2-line 10: Last standard GAD enhanced exam *Response:* In manuscript is corrected.

3-lines 13-16: “Patients were divided into two subgroups based on the total number of MRI exam (more than 4 times versus others) and subgroups were compared in terms of mean SIR and visual hyperintensity” *Response:* In manuscript is corrected.lines 16-19

4-line 17: “Results: Sixty eight percent (n:83)” *Response:* In manuscript is corrected.

5-line 19: “….. and also healthy controls.” *Response:* In manuscript is corrected.

6-lines 20 and 21: please delete following sentence [it has been repeated]: “Mean SIR in patients and controls was 1.10±0.07 and 1.04±0.02 respectively[P<0.001]” *Response:* In manuscript is corrected.lines 22-23

7-lines 25 and 26: “SIR and visual DN hyperintensity are increased when the number of GAD injections are more. This could be due to tissue deposition of GAD.” *Response:* In manuscript is corrected.lines 28-29

8-line 35: “……. remitting pattern that is more common in women and happens more likely in the age of 15-45 years.” *Response:* In manuscript is corrected.lines 38-39

9-line 41 is meaningless. *Response:* In manuscript is corrected.lines 44

10-lines 47 and 48: “…. would increase the detection ability of lesions especially in patients with active lesions which could be enhanced after contrast injection [15]” *Response:* In manuscript is corrected.lines 51-53

11-lines 51-3: this sentence is unclear: “The concerns about Gadolinium-based contrast media are not limited to the neural tissues, but long-term adverse effects in all human tissues are not far from creating that concern [17]” *Response:* In manuscript is corrected.lines 56-58

12-when you abbreviate a term, lease use abbreviate form in next times. [line 69, dentate nucleus]. *Response:* In manuscript is corrected.

13-Please change Methods and Study design to patients and methods. Please add sequential numbers to titles. *Response:* In manuscript is corrected.

14-lines 85, 103, 118 and 119: T1-W *Response:* In manuscript is corrected.

15-this is unclear: “first time implement MRI with contrast injection” *Response:* In manuscript is corrected.

16-line 89: delete “present” *Response:* In manuscript is corrected.

17-line 90: pls change “completed” to “signed” *Response:* In manuscript is corrected.

18-part Kidney and liver function could be summarized as: the renal and kidney functions were evaluated in all patients and they were normal in all patients prior to each GAD injection. *Response:* In manuscript is corrected.lines 100-102

19-line 130: “(classified based on the total number of MRI scans as more than 4 times versus others)” *Response:* In manuscript is corrected.lines 132

20-SPSS manufacturer is wrong. Please correct. In addition, it is statistical package for social sciences. *Response:* In manuscript is corrected.lines 140

21-line 141: “were used for statistical analyses” *Response:* In manuscript is corrected.

22-line 143-4: “statistical significance” *Response:* In manuscript is corrected.

23-line 169 and 174, time should be number *Response:* In manuscript is corrected.

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31-line 243: control *Response:* In manuscript is corrected.

32-line 247: femor not femora *Response:* In manuscript is corrected.

33-line 252: linear gadolinium-based contrast to GBCA *Response:* In manuscript is corrected.

34-line 274: signal intensity ratio (SIR) to SIR *Response:* In manuscript is corrected.

35-line 276: SIR *Response:* In manuscript is corrected.

36-figure 5 legend is incomplete *Response:* In manuscript is corrected.

37-table 1: control group *Response:* In manuscript is corrected.

4 Revision 3

1 comment · 10 Jul 2021

Editor-in-Chief

ACCEPT 10 Jul 2021

Dear authors,
Your article is acceptable for publication in IJR.
Regards