OPEN PEER REVIEW

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Iranian Journal of Radiology
Article DOI: 10.5812/iranjradiol.107887
Published in: Iranian Journal of Radiology: 18(2); e107887

Peer Review Report for "Comparison of Blood Perfusion Parameters in the Ipsilateral and Contralateral Sides of the Brain in Known Cases of Mesial Temporal Lobe Epilepsy"

Author(s): Amin Farzadniya, Jafar Mehvari, Reza Basiratnia, Farzad Mehrabi

Review Timeline:

Submit Date: 2 Aug 2020
Revised Date: 15 May 2021
Accepted Date: 19 May 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | Revision (0) — 22 Aug 2020

Dear AE,
In the last sentence in the part of “Results”, the authors should mention which parameters (rCBV, rCBF) instead of both parameters.
Thanks

Madjid Shakiba: Reviewer | Revision (0) — 23 Oct 2020

Dear AE,
Ponts for the authors:
1-Please add objective part for paper before the method section, according to journal format.
2-Please represent more details about ROI drawing. What was the size of ROI? Did the authors assess intra-rater reliability of the author drew ROI?
3-Did the author assess visually the involved side compared to the lateral side [in rel CBF map and rel CBV map?] [for detecting deceased perfusion in the involved side] please add the results and compare two sides if you gathered the data.

4-Please add in paper that the ethics committee of the university approved the study.
5-The author should mention in the method that all the TLEs were unilateral.
6-The authors compared the values between two sides in left side and right side epilepsies separately. This is good but at the first step, I think they should compare the values of CBV and CBF among epileptic side and normal side. In fact, they should compare the mean CBV of 22 involved side [including 9 involved left side and 13 involved right side] with the corresponding values of 22 intact side [including 9 intact left side and 13 intact right side]. They should add this analysis to the table 2. [please don't delete current data of table 2. They are informative]. They should implement this analysis for CBF too.
7-Please add the statistical analysis method of the study to the paper. Which statistical tests has been used?
8-Please add a brief of clinical data including drug therapy and if the patient is intractable to drug therapy? If some of patients are intractable, it would be interesting if the authors implement the analyses in terms of two subgroups of intractable and non-intractable.
9-All patients of the study are TLE but the authors did not mention if they are MTLE or LTLE or both? Please add the relevant data in this regard. I think the ROI placement on hippocampus is logic only for MTLE and in the LTLE, the ROI should be placed on other places; while the authors placed ROI in hippocampus area for all patients. If some of the patients are LTLE, then the authors should rationalize the ROI on hippocampus. In addition, if both MTLE and LTLE are among the patients, the authors should implement the analyses in two subgroups of MTLE and LTLE separately.
10-if all patients are MTLE, it would be interesting we know if all patients show sclerosis in routine MRI? And if some of patients show sclerosis and some do not show sclerosis, implementing the analyses in these two subgroups would be interesting.
11-Please discuss if we can use current method for differentiating MTLE from LTLE in discussion.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 31 Oct 2020

Dear EIC,
This article has major problem in methodology and after solving these defects, will be accepted.
Thanks.

REFEREE: EIC | **Revision** (0) 31 Oct 2020

Dear authors,
Your article needs Major Revision.
Regards

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Answers to editors:

Editor no.1:

The authors should express their special thanks to you for your constructive comments and apologize for the delay as the paper's writer is serving his military service.

1-Please add objective part for paper before method section, according to journal format

We added this part.

2-Please represent more details about ROI drawing. What was the size of ROI? Did the authors assess intra-rater reliability of the author drew ROI?

We added some information about ROI placement. We used single 15 years experienced neuroradiologist. Unfortunately we didn't assessed reliability.

3-Did the author assess visually the involved side compared to the lateral side [in rel CBF map and rel CBV map?] [for detecting deceased perfusion in the involved side] please add the results and compare two sides if you gathered the data.

As the perfusion differences are in range of lower than 10 percent, and practically the hippocampus could be visualized in 2 or 3 axial slices hence we used only quantitative comparison.

4-Please add in paper that the ethics committee of the university approved the study.

We added this part.

5-The author should mention in the method that all the TLEs were unilateral.

We added this part

6-The authors compared the values between two sides in left side and right side epilepsies separately. This is good but at the first step, I think they should compare the values of CBV and CBF among epileptic side and normal side. In fact, they should compare the mean CBV of 22 involved side [including 9 involved left side and 13 involved right side] with the corresponding values of 22 intact side [including 9 intact left side and 13 intact right side]. They should add this analysis to the table 2. [please don't delete current data of table 2. They are informative]. They should implement this analysis for CBF too.

We added this part by mean of a new table (Table 3) and discussed the results.

	Affected side	**P-value**	**Non-affected side**	**P-value**
CBV [mean ± SD]	1.55 ± 0.24	P<0.0001	1.99 ± 0.26	P<0.0001
CBF [mean ± SD]	70.09 ± 12.59	P<0.0001	99.10 ± 13.57	P<0.0001

7-Please add the statistical analysis method of the study to the paper. Which statistical tests has been used*?*

We added this part

8-Please add a brief of clinical data including drug therapy and if the patient is intractable to drug therapy? If some of patients are intractable, it would be interesting if the authors implement the analyses in terms of two subgroups of intractable and non-intractable*.*

Only four of patients were intractable and we found it not valuable to include this parameter with this size of sample. Another study with more patients should be conducted for assessing this parameter.

9-All patients of the study are TLE but the authors did not mention if they are MTLE or LTLE or both? Please add the relevant data in this regard. I think the ROI placement on hippocampus is logic only for MTLE and in the LTLE, the ROI should be placed on other places; while the authors placed ROI in hippocampus area for all patients. If some of the patients are LTLE, then the authors should rationalize the ROI on hippocampus. In addition, if both MTLE and LTLE are among the patients, the authors should implement the analyses in two subgroups of MTLE and LTLE separately.

The MTLE and presence of unilateral sclerosis were mentioned as inclusion criteria. We suggest another study for assessing LTLE without any MTLE patients.

10-if all patients are MTLE, it would be interesting we know if all patients show sclerosis in routine MRI? And if some of patients show sclerosis and some do not show sclerosis, implementing the analyses in these two subgroups would be interesting.

We chose our study sample from patients with sclerosis in order to be sure about unilaterality of seizure site.

11-Please discuss if we can use current method for differentiating MTLE from LTLE in discussion.

As mentioned before.

Editor no.2:

In the last sentence in the part of "Results", please mention which parameters (rCBV, rCBF) instead of both parameters.

It corrected. Thanks in advance

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Madjid Shakiba: Reviewer | **Revision (1)** 2 Feb 2021

Dear AE,
Many of questions have been replied and corrected. There are some other corrections as:
1-The authors mentioned: “Coronal reconstruction of Rel CBV map of one of the patients illustrated. (figure 1)”. This sentence is in the middle of text and does not have verb and is unclear. please co5rect.
2-please add in statistical method section that the normality of data were checked by appropriate stst. Tests and if the data was not normally distributed, the nonparametric tests were used.
3-those sentence is unclear: “It means in patients with left side epilepsy, both parameters in a single patient was significantly lower in the left side comparing to the other side ($p<0.0001$).” please crarify.
4-in table 3 that the authors have added in the revised version, we are comparing the CBV between affected and non-affected sides. This needs a single test and I don’t know why they have mentioned two P values in each comparison. In fact, we nned only two P values in this table [not four p values]. Please explain and correct.
5-the authors have replied to this part: “As the perfusion, differences are in the range of lower than 10 percent, and practically the hippocampus could be visualized in 2 or 3 axial slices hence we used only quantitative comparison.” It is better to be added to the paper.
6-please explain more the statistical method part.
7-some of the sentences in the result section do not have the scientific format; such as: “The results of this study found that the mean (SD) of right side rCBV for all patients was 1.66 (0.29) range of 1.24 to 2.21. Also, the mean (SD) of left side rCBV for all patients was 1.88 (0.34) range of 1.05 to 2.35.” that should be written as: “The mean (SD) of right side rCBV for all patients was 1.66 (0.29) (range: 1.24-2.21). Also, the mean (SD) of left side rCBV for all patients was 1.88 (0.34) (range: 1.05-2.35)” please follow this format in all papers. [such part seems unnecessary: The results of this study found that ….]
8-the authors wrote: “the mean for right side parameters in patients with right side epilepsy were lower than the mean for the left side parameters. also, we did the same analyzes for the patients with left side epilepsy and the result was similar. (Table 2)” it is better the authors add p-values for such analyses at the end of each sentence.
Thanks.

REFEREE: Associate Editor | **Revision (1)** 13 Feb 2021

Dear EIC,

This article is accepted for IJR after minor revision.

Thanks.

REFEREE: EIC | **Revision (1)**

13 Feb 2021

Dear authors,

Your article needs Minor Revision.

Regards

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Answers to editors:

Editor no.1:

The authors should express their special thanks to you for your constructive comments

1--The authors mentioned: “Coronal reconstruction of Rel CBV map of one of patients illustrated. (figure 1)”. This sentence is in the middle of text and does not have verb and is unclear. please co5rect.

The sentence rephrased in order to get more informative.

2-please add in statistical method section that the normality of data were checked by appropriate stst. Tests and if the data was not normally distributed, the non parametric tests were used.

The data added : The DSC MRI-derived perfusion _parameters have been statistically analyzed have been statistically analyzed using SPSS (Version 20.0, The SPSS, Inc., Chicago, IL, USA). Normal distribution of parameters in DSC-MRI was assessed with the Kolmogorov-Smirnov test. The obtained rCBV and rCBF were processed with Paired two-sample t-tests were used to determine differences in perfusion (significance threshold $p < 0.05$).

3-thos sentence is unclear: “It means in patients with left side epilepsy, both parameters in a single patient was significantly lower in the left side comparing to the other side (p<0.0001).” please crarify.

The sentence is rephrased in term of affected side and contralateral one.

“The mean for both rCBV and rCBF were significantly lower in the affected side comparing to the other side. (Table 3)”

4-in table 3 that the authors have added them in revised version, we are comparing the CBV between affected and non affected sides. This needs a single test and I don't know why they have mentioned two P values in each comparison. In fact we nned only two P value in this table [not four p values]. Pleas explain and correct.

The table has been edited

5-the authors have replied this part: "As the perfusion differences are in range of lower than 10 percent, and practically the hippocampus could be visualized in 2 or 3 axial slices hence we used only quantitative comparison." It is better to be added to the paper.

We added this part

6-please explain more the statistical method part.

We added some information, we wish it would be comprehensive.

7-some of sentences in result section do not have the scientific format; such as: "The results of this study found that the mean (SD) of right side rCBV for all patients was 1.66 (0.29) range of 1.24 to 2.21. Also, the mean (SD) of left side rCBV for all patients was 1.88 (0.34) range of 1.05 to 2.35." that should be written as: "The mean (SD) of right side rCBV for all patients was 1.66 (0.29) (range: 1.24-2.21). Also, the mean (SD) of left side rCBV for all patients was 1.88 (0.34) (range: 1.05-2.35)" please follow this format in all paper. [such part seems unnecessary: The results of this study found that ….]

we changed that.

8-the authors wrote: "the mean for right side parameters in patients with right side epilepsy were lower than the mean for the left side parameters. also, we did the same analyzes for the patients with left side epilepsy and the result was similar. (Table 2)" it is better the authors add p-values for such analyses at the end of each sentence.

We added p- values

OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (2) — 31 Mar 2021

Dear AE,
The study is reviewed carefully. According to comments and revisions by the author, this manuscript is accepted.
Thanks

Hassan Hashemi: Associate Editor | **Revision** (2) — 7 Apr 2021

Dear EIC,
This article is accepted by peer review and after a second revision.
Thanks.

Madjid Shakiba: Associate Editor | **Revision** (2) — 7 May 2021

Dear EIC,
Comments for the authors:
1-it is better to mention full term [instead of abbreviation] in title [MTLE is not good in the title, please add a full term of it]
2-please consider these corrections in the paper:
2.1-in abstract: …. different types of neuroimaging methods are used.
2.2-in abstract: ….. to evaluate cerebral hemodynamic conditions and …..
2.3-in abstract: ….. can be used to diagnose and localize the epileptic side. [changing site to side; here and in other similar parts]
2.4-in abstract: ……. the brain was significantly lower than the contralateral side ($p<0.0001$) and the mean …..
2.5-in abstract: …… to localize the epileptic side …….
2.6-please delete this part: “The results of this study showed that”
2.7-in In the main paper, background: …. different types of neuroimaging methods can be used.
2.8-in main paper: These methods include structural MRI to show the temporal lobe anatomy and presence of tissue sclerosis, Diffusion-weighted imaging and Diffusion tensor imaging, Magnetoencephalography, functional MRI (fMRI), positron emission tomography, and single-photon emission computed tomography that all can be helpful and may improve the results of surgery (10,11).
2.9-in main paper: … there is no study on this topic in Iranian patients.

2.10-in objectives: ….. parameters including rCBV and rCBF …..
2.11-in objective: ….. and novel method of ….
2.12-in method section: …. quantative analysis should be quantitative analysis.
2.13-figure 1 legend could be written as: Decreased rCBV on right side hippocampus in case no 10 with right side TLE
2.14-there are two “have been statistically analyzed” sequentially. please correct.
2.15-in result: “with ranged of” should be “with a range of”
2.16-in result: please delete “The results of this study found that”, “The results of this study showed that”
2.17- in result: please delete “As well in all patients.”
2.18-at the beginning of discussion: “amounts of relative cerebral blood volume (RCBV) and relative cerebral blood flow (RCBf)” should be: “amounts of rCBV and rCBF”
3-please change Rel CBV and Rel CBF to rCBV and rCBF; as you have noted these forms earlier in the abstract.
4-please delete patients names and hospital names on the image
5-equation 1 seems wrong and should be written correctly. It is unclear. [the last parenthesis on the right side has not corresponding left sided beginning parenthesis]
6-please check the manufacturer data of SPSS ver 20. I think it is PASW by IBM.
7-please add abbreviations in the full term in the tables as a footnote.
8-the authors mentioned in the discussion: “These data emphasize on the effect of low blood perfusion on TLE” I think the sentence should be: “These data emphasize on the association between blood perfusion and TLE” because the first sentence tells the low blood perfusion effect TLE while we can not make such conclusion based on current study design. Please consider and revise if it is needed.
9-what are LTLE and SPECT in discussion?
10-this sentence in the discussion is wrong. The second part does not have a verb: “Subtracted ictal SPECT co-registered to MRI images were obtained from patients which indicated that hypoperfusion in affected areas in patients with MTE” it seems we should delete “that”.
Thanks.

REFEREE: EIC | **Revision (2)** 8 May 2021

Dear authors,
Your article needs Minor Revision.
Regards

OPEN PEER REVIEW

Revision (3)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Revise letter (revision 3)

Authors strongly appreciate editor's comments and integrated those in text.

1-it is better to mention full term [instead of abbreviation] in title [MTLE is not good in title, please add full term of it] : title has been changed
2-please consider these corrections in paper:
2.1-in abstract: …. different types of neuroimaging methods are used.
2.2-in abstract: ….. to evaluate cerebral hemodynamic conditions and …..
2.3-in abstract: ….. can be used to diagnose and localize the epileptic side. [changing site to side; here and in other similar parts]
2.4-in abstract: ……. the brain were significantly lower than the contralateral side (p<0.0001) and the mean …..
2.5-in abstract: …… to localize the epileptic side …….
2.6-please delete this part: "The results of this study showed that"
2.7-in main paper, background: …. different types of neuroimaging methods can be used.
2.8-in main paper: These methods include structural MRI to show the temporal lobe anatomy and presence of tissue sclerosis, Diffusion-weighted imaging and Diffusion tensor imaging, Magnetoencephalography, functional MRI (fMRI), positron emission tomography and single photon emission computed tomography that all can be helpful and may improve the results of surgery (10,11).
2.9-in main paper: … there is no study on this topic in Iranian patients.
2.10-in objectives: ….. parameters including rCBV and rCBF …..
2.11-in objective: ….. and novel method of ….
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2.16-in result: please delete "The results of this study found that", "The results of this study showed that"
2.17- in result: please delete "As well in all patients."
2.18-at the beginning of discussion: "amounts of relative cerebral blood volume (RCBV) and relative cerebral blood flow (RCBf)" should be: "amounts of rCBV and rCBF"

all of the modifications have been applied and have been highlighted by yellow color.

3-please change Rel CBV and Rel CBF to rCBV and rCBF; as you have noted these forms earlier in abstract.
4-please delete patients name and hospital name on image
5-equation 1 seems wrong and should be written correctly. It is unclear. [last parenthesis in the right side has not corresponding left sided beginning parenthesis]
6-please check the manufacturer data of SPSS ver 20. I think it is PASW by IBM.
7-please add abbreviations in full term in the tables as footnote.
8-the authors mentioned in discussion: "These data emphasize on the effect of low blood perfusion on TLE" I think the sentence should be: "These data emphasize on association between blood perfusion and

TLE" because the first sentence tell the low blood perfusion affect TLE while we can not make such conclusion based on current study design. Please consider and revise if it is needed.
all of modifications have been applied as stated by editor

9-what are LTLE and SPECT in discussion?

Full term of acronyms have been stated in text previously but without acronym mentioned hence we corrected it

Magnetoencephalography, functional MRI (fMRI), Positron emission tomography and single photon emission computed tomography (SPECT) that all can be helpful and may improve the results of surgery (10,11). Perfusion MRI is also one of the

temporal (amygdalohippocampal) and lateral temporal or neocortical (LTLE) (5)

10-this sentence in discussion is wrong. The second part does not have verb: "Subtracted ictal SPECT co registered to MRI images were obtained from patients which indicated that hypoperfusion in affected areas in patients with MTE" it seems we should delete "that".

The authors would like to thank again for constructive and precise comments and also ask for faster review process if possible as the first author needs paper's acceptance to achieve his certification.

OPEN PEER REVIEW

Revision (3)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (3) 19 May 2021

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

REFEREE: EIC | **Revision** (3) 19 May 2021

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