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Peer Review Report for "Short-Term Effects of Flupentixol-Melitracen on Regional Brain Function in Patients with Irritable Bowel Syndrome: An fMRI Study"

Author(s): Jie Li, Ping He, Xingqi Lu, Ying Yang, Yun Guo, Li Li, Yuming Yin, Guoxiong Li, Jianping Ding

Review Timeline:

Submit Date: 27 Mar 2019
Revised Date: 8 Dec 2019
Accepted Date: 12 Feb 2020

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)

13 Jun 2019

Dear AE,
There are some comments which should be addressed by the author:
1- Didn't the control group receive placebo?
2- The study is clinical trial. It is better the trial be registered in a trial registry and authors add a registration number in paper.
3- Please add in paper that the ethics committee have approved the study.
4- What was the randomization method? Block randomization? Please mention in paper.
5- Authors mentioned: "There were no significant differences in age, gender, or IBS duration ($P > 0.05$) between two groups (Table 1)." While these data are mentioned in table 2.
6- The questionnaires HAMD-17, HAMA-14 and GSRS should be validated in native language of the study country. Please add references if there are such validation studies.
7- Please arrange and number tables in text based on their order of presentation.
8- Please the data of SPSS manufacturer completely.
9- The authors mentioned: "we performed a voxel wise two-way analysis of variance (ANOVA) with group and therapy as factors." While the groups are differentiated based on

the therapy, so it is unknown when they mention two way ANOVA. In fact, groups and therapy are the same factor.
10- What os the meaning of * * P < 0.001, * P < 0.05 Pre-treatment vs Post-treatment in table 2 footnote? They are statistically non-significant.
11- Pease corrects the fiure 2 legends. It is unclear somehow. In fact, the parts A-D explanations in legend are not matched with the figures.
12- Is it expectable that the similar findings are seen in anxiety or depression? [patients without IBS] please discuss.
13- Was the analyzer [fMRI data analyzer] blind regarding the treatment group and time session of each data? please describe and add in paper.
Thanks.

REFEREE: Reviewer | **Revision (0)** 3 Aug 2019

Dear AE,
This paper has a potential to be accepted at least as short communication, but some important points have to be clarified or fixed before we can proceed and a positive action can be taken.
1) This paper would benefit from review by a native English speaker.
2) Sample size is small.
3) Although, the authors find statistically significant difference between OG and CG in evaluated variables during 4 weeks, such as most published papers in this field, it was be better to follow the patients for 6 to 12 weeks (about 8 weeks).
4) The authors is better to explain the mechanism of action of the flupentixol-melitracen and its probable mechanism of action in modulating precuneus function.
Thanks.

REFEREE: Associate Editor | **Revision (0)** 19 Aug 2019

Dear EIC,
This article needs minor revision as peer reviewers.
Thanks.

REFEREE: EIC | **Revision (0)** 21 Aug 2019

Dear Author,
The reviewers' comments are mentioned. Please correct the details as mentioned above carefully according to reviewers' request.
Thanks.

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.

Point-by-point responses to the reviewers' comments:

Dear Editor and Reviewers,

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Short-term effects of flupentixol-melitracen on regional brain function in irritable bowel syndrome patients assessed by resting-state functional magnetic resonance imaging". Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Editor

Response: Thank you very much for your comments and suggestions. Certain modifications have been made accordingly.

Reviewer: 1

Comments to the Author

1-didn't the control group receive placebo?

Response: This is a good question. The purpose of our research is to observe the changes of brain function in IBS patients after taking flupentixol-melitracen on the basis of routine treatment. Patients in the control group received routine treatment as a baseline measure. In addition, related literature study has reported that taking placebo can change the brain function of patients, which may have an impact on the research results. In several clinical randomized controlled trials, in order to evaluate the efficacy and safety of combination therapy (PB combined with FM) in patients with IBS, patients were divided into two groups: PB combined with FM and PB alone (Qin L., et al; 2019). For these reasons, the control group in the study did not receive a placebo.

The suggestion you mentioned is very good and really critical. Due to different treatment methods, the results of this study may be influenced by non-therapeutic factors (for example, the treatment behavior itself leads to differences in the scale and fMRI

results). Therefore, the placebo group can be added in future studies to make the results of inter-group differences more rigorous. We have described this problem as a defect in the discussion section of the article. Thanks again for your advice.

2-the study is clinical trial. It is better the trial be registered in a trial registry and authors add a registration number in paper.

Response: Thank you very much for your advice. Our study has been approved by Zhejiang provincial department of health science and technology (2015C33292). The research protocol has been approved the Ethics Committee of the Affiliated Hospital of Hangzhou Normal University (approval no. HZNU20160427) (the Chinese and English versions of the ethical approval and certificate of project are attached to the "other" type of file type). We have already added in the revised draft. (page4， line95-98).

The main purpose of this experiment is to observe the brain function changes of patients with IBS before and after treatment by functional magnetic resonance imaging. All the drugs used in this study have been included in the clinical treatment program of patients with IBS, and their safety and efficacy have been confirmed by a large number of clinical trials (Yan XJ., et al; 2015) (Qin LF., et al; 2019). If necessary, we can upload the experimental data and all materials to pass the verification and make up the registration. Thank you very much for your reminding. In the follow-up further study, we will register the trial in the trial registry in advance.

3-please add in paper that the ethics committee have approved the study.

Response: Thank you very much for your review. We mistakenly thought that the journal required the submission of blind review articles, so we did not add the committee's name in the articles. The experimental study has been approved by the ethics committee and the patient's informed consent, which has been explained in the text. (page4， line97-98)

4-what was the randomization method? Block randomization? Please mention in paper.

Response: Thank you very much for your reminding. We have already added in the revised draft. (page4， line111)

5-authors mentioned: “There were no significant differences in age, gender, or IBS duration (P > 0.05) between two groups (Table 1).” While these data are mentioned in table 2.

Response: The order of the tables in the manuscript is wrong, which is our mistake. Thank you for your careful review, we have made changes accordingly.

6-the questionnaires HAMD-17, HAMA-14 and GSRS should be validated in native language of the study country. Please add references if there are such validation studies.

Response: Thank you very much for your advice. The Chinese version of the questionnaire used in our study has good reliability and validity, which can be used for the mental and psychological state and gastrointestinal symptoms of the local population. Relevant literatures have been added to the corresponding place of revised manuscripts.

7-please arrange and number tables in text based on their order of presentation.

Response: Our text here is not accurate. We are very grateful to you for your careful review, we have arranged and numbered tables in text based on their order of presentation.

8-please the data of SPSS manufacturer completely.

Response: Thank you very much for your advice. We have already added in the revised draft. (page6，line167-168)

9-the authors mentioned: “we performed a voxel wise two-way analysis of variance (ANOVA) with group and therapy as factors.” While the groups are differentiated based on the therapy, so it is unknown when they mention two way ANOVA. In fact, groups and therapy are the same factor.

Response: This is a good question. This passage is indeed misleading. Group and therapy are really the same factor. The two factors in the two-way ANOVA should be within-subject factor (time; pre-treatment and post-treatment) and between-subject factor (therapy; observation group and control group). We are very grateful to the reviewer for careful correction and have made corresponding amendments in the revised draft.

10-what os the meaning of * * $P < 0.001$, * $P < 0.05$ Pre-treatment vs Post-treatment in table 2 footnote? They are statistically non-significant.

Response: I'm sorry we didn't make it clear here.* * $P < 0.001$, * $P < 0.05$ pre-treatment vs post-treatment means that there is a significant statistical significance between the scale scores (GSRS, HAMA, HAMD) before treatment and the scores after treatment in each group. The values of *t* and *P* in the last line refer to the two-sample analysis results between the scale scores measured at the same time between the two groups (OG group and CG group).

11-please correct the fiure 2 legend. It is unclear somehow. In fact, the parts A-D explanations in legend are not matched with the figures.

Response: Thank you for your correction, corresponding changes have been made.

12-is it expectable that the similar findings are seen in anxiety or depression? [patients without IBS] please discuss.

Response: Thank you very much for your question. We have supplemented relevant discussions in the revised draft.

By referring to relevant literature, we expected that patients with anxiety or depression would have the same partial results as this study after anxiolytic/antidepressant treatment. For example, the precuneus showed significant differences in spontaneous activity when treatment and time interaction were the main effects. After combined anti-anxiety and depression treatment, the change of ReHo value was significantly correlated with the change of anxiety and depression symptoms. The brain region responsible for thought-action fusion is the precuneus, which is also altered in the sensory disturbances in panic disorder (PD) (Lai CH., et al; 2013b) and self-referential ruminations in major depressive disorder (MDD) (Jones R., et al; 2014). It suggested that precuneus would play a role in the pathophysiology for depression and anxiety. Therapeutic studies have shown that abnormal activity and recovery of DMN, especially in the precuneus, may be a state indicator for predicting anxiety and depression (Quah-Smith I., et al; 2013, Spies M., et al;

2017, Amen DG., et al; 2018). A large number of fMRI studies showed that abnormal prefrontal-limbic emotional circuits, including the prefrontal cortex, anterior cingulate cortex, hippocampus, basal ganglia, amygdala and insula, are potential neuropathological mechanisms for anxiety and depression. The neural activity of the circuits can predict the efficacy of antidepressants (Kupfer DJ., et al; 2012, Phillips ML., et al; 2015, Fonseka TM., et al; 2017). In the combined anxiolytic/antidepressant treatment group in our study, we also observed changes in neural activity in some brain areas of the prefrontal-limbic system in IBS patients. The results suggest that anxiolytic/antidepressant drugs can significantly improve mood disorders in IBS patients by regulating emotional processing circuits. We speculate that patients with anxiety/depression may have a larger range of brain function changes after treatment.

However, the anxiety and depression symptoms of IBS patients in this study were only concomitant symptoms and did not reach the diagnosis of clinical mental illness. In future studies, anxiety or depression patients can be included for comparison to find out whether there is significant difference in brain activity between IBS patients and anxiety/depression patients, as well as the difference in brain function changes after treatment.

13-was the analyzer [fMRI data analyzer] blind regarding the treatment group and time session of each data? please describe and add in paper.

Response: This is a good question. The fMRI data analyzer was blinded to the treatment protocols and time session of each data. We have already added in the revised draft. (page5，line143)

Reviewer 2:

This paper has a potential to be accepted at least as short communication, but some important points have to be clarified or fixed before we can proceed and a positive action can be taken.

Response: Thank you very much for your review of our article and your valuable

questions. We hope that through careful revision, our article can be accepted as full paper.

1) This paper would benefit from review by a native English speaker.

Response: Thank you very much for your advice. This manuscript has been modified by a professor whose native language was English.

2) Sample size is small.

Response: Thank you very much for your advice. As you mentioned, the sample size of this study is small. Please allow us to explain. First of all, All of subjects were screened by gastroscopy and colonoscopy. Subjects who did not want to be examined were not included in the study. In addition, all the subjects in the experiment have completed the full course of treatment according to the clinical treatment plan, and the patients who have not completed the treatment strictly have not been included. Finally, the question you mentioned is really critical, and we have described this problem as a defect in the discussion section of the article. In the following study, we will further increase the number of experimental subjects and obtain more data to verify. We hope our explanation and modification can make our article more rigorous.

3) Although, the authors find statistically significant difference between OG and CG in evaluated variables during 4 weeks, such as most published papers in this field, it was be better to follow the patients for 6 to 12 weeks (about 8 weeks).

Response: First of all, we agree with the reviewer's point of view. In most published papers in this field, patients were followed for 6 to 12 weeks (about 8 weeks). At the fourth week, we analyzed the evaluation variables (including fMRI data) of the two groups and found statistically significant results. The reasons why we conducted the comparative analysis four weeks later are as follows. Firstly, through the analysis of previous studies, we found that as early as 4 weeks after follow-up, the symptoms of IBS patients in OG group (PB+FM) were significantly better than those in CG group (PB) (see figure below. Qin LF., et al; 2018). Moreover, changes in brain function appear earlier than changes in clinical symptoms. Therefore, we selected 4 weeks as the observation node to detect the

changes in brain function corresponding to the improvement of clinical symptoms as early as possible. Finally, according to your suggestion, we will extend the observation time in future studies to observe the stability of the research results.

Table 1

Characteristics of studies.

Study	Subject	Interventions		Follow-up	Outcomes
	Experimental/Control group	Experimental group	Control group		
Huang[9]	38/35	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	4 weeks	Total symptom relief rate Adverse effects
Huang et al[10]	60/42	PB 50 mg thrice daily FM: one tablet once daily	PB: 50 mg thrice daily	4 weeks	Total symptom relief rate Adverse effects
Yan[11]	120/118	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	12 weeks	Total symptom relief rate Adverse effects
Li and Wang [12]	42/36	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate Adverse effects
Li[13]	77/77	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	4 weeks	Total symptom relief rate HAMA and HAMD scores Adverse effects
Meng[14]	38/38	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	1 month	Total symptom relief rate Adverse effects
Zhang and Cao[15]	40/40	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate
Qin[16]	39/39	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	2 months	Total symptom relief rate Adverse effects
Zhu[17]	43/39	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate Adverse effects
Chen and Zhou[18]	32/32	PB: 50 mg thrice daily FM: one tablet once daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate SAS and SDS scores Adverse effects
Ni and Zheng[19]	72/70	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate HAMA and HAMD scores Adverse effects
Shi[20]	32/32	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	4 weeks	Total symptom relief rate HAMD scores
Deng[21]	25/25	PB: 50 mg thrice daily FM: one tablet once daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate SAS and SDS scores
Lin[22]	43/43	PB: 50 mg thrice daily FM: one tablet once daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate
Peng and Xie[23]	60/60	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate SAS and SDS scores Adverse effects

FM = Flupentixol-melitracen; HAMA = hamilton anxiety scale; HAMD = hamilton depression scale; PB = Pinaverium bromide; SAS = self-rating anxiety scale; SDS = self-rating depression scale.

(Qin LF., et al; 2018)

4) The authors is better to explain the mechanism of action of the flupentixol-melitracen and its probable mechanism of action in modulating precuneus function.

Response: This is a very good opinion. We have added relevant content in the introduction and discussion section of the revised draft.

Flupentixol-melitracen is a combination preparation of has both anxiolytic and antidepressant properties and has been proven to be safe and effective in the treatment of IBS. Flupentixol acts on dopamine receptors in the presynaptic membrane, and increasing the amount of dopamine in the synaptic gap to play an antianxiety and antidepressant role.

Small doses of melitracen can inhibit the reuptake of norepinephrine and serotonin in presynaptic membrane, and increase the content of monoamine transmitters in synaptic space, thereby exerting an antidepressant effect. These two components work synergistically and the side effects cancel each other, so as to effectively and timely improve the neuropsychiatric symptoms, regulate the function of the gastrointestinal autonomic nerves, and reduce visceral hypersensitivity, finally relieve the physical and mental discomfort.

Therapeutic studies have shown that abnormal activity and recovery of default mode network, especially in the left precuneus, may be a state indicator for predicting anxiety and depression. While flupentixol-melitracen could modulate complex interactions of dopamine and serotonin that could also cause upregulation of spontaneous activity in precuneus. Thus, we speculate that increased spontaneous activity in precuneus may be a neuromechanism of selective serotonin reuptake inhibitors.

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) 5 Oct 2019

Dear AE,
The authors have corrected many parts. There are some points that should be addressed in this version.
1- I asked about two-way ANOVA and they mentioned: “we performed a voxel wise two-way analysis of variance (ANOVA) with time (pre-treatment and post-treatment) and therapy (OG and CG) as factors.” The mentioned design consists of two factors that one of them is between group [therapy] and the other is within group [time; because the time is a factor that refers to the comparison of each group with itself before and after the intervention]. So the analysis plan should be [I think] mixed model ANOVA [instead of two-way ANOVA; as in two-way ANOVA, both factors are between group] [it is probable the fMRI designs urge two-way ANOVA analysis plan and I’m not sure about this????]. Please explain and correct if it is necessary. On the other hand, regarding the clinical assessment of depression, anxiety and GI symptoms [HAMD, HAMA and GSRS scores], we could consider such analysis plan. In fact, these variables could be analyzed in mixed model ANOVA design for assessment of main effects of therapy and time. In addition to these main effects, detailed comparisons of groups [as mentioned correctly in table 1] are necessary [of course considering stat. techniques such as bonferroni correction and post hoc tests]. Thus, comparison plan of table 1 is appropriate and should not be deleted and the author is better to furtherly complete and if necessary, correct them. The authors should mention the analysis plan of clinical data in addition to fMRI data in stat methods and follow these points in paper.
2- The authors mentioned regression analysis while there is no data in this regard in the paper. Please mention or complete the data more explicitly in this regard [if it is necessary]
3- The table 1 legend does not reflect the real data presented in this table. I recommend the authors correct this legend to something like this one: “Baseline and Clinical characteristics of observation group and control groups and comparison of depression, anxiety and GI symptoms between groups and before and after the study”
Thanks.

REFEREE: Reviewer | **Revision** (1) 1 Nov 2019

Dear AE,
This paper could be accepted as a short communication.
Thanks.

REFEREE: Associate Editor | **Revision (1)** 27 Nov 2019

Dear EIC
The reviewer(s) have recommended publication, but also suggest some minor revisions to the manuscript. Therefore, I invite the author to respond to the reviewer(s)' comments and revise his manuscript.
Kind regards,

Kavous Firouznia: EIC | **Revision (1)** 27 Nov 2019

Dear authors
Your article needs minor revision in statistical analyses.
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.

Point-by-point responses to the reviewers' comments:

Dear Editor and Reviewers,

On behalf of my co-authors, we thank you very much for giving us a second opportunity to revise and resubmit our manuscript, we appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled "**Short-term effects of flupentixol-melitracen on regional brain function in patients with irritable bowel syndrome： a fMRI study**". Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Attached please find the revised version, which we would like to submit for your kind consideration. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Editor

Response: Thank you very much for your comments and suggestions. Certain modifications have been made accordingly.

Reviewer: 1

Comments to the Author

1-I asked about two-way ANOVA and they mentioned: "we performed a voxel wise two-way analysis of variance (ANOVA) with time (pre-treatment and post-treatment) and therapy (OG and CG) as factors." Mentioned design consists of two factors that one of them is between group [therapy] and the other is within group [time; because the time is a factor that refers to comparison of each group with itself before and after the intervention]. So the analysis plan should be [I think] mixed model ANOVA [instead of two-way ANOVA; as in two-way ANOVA, both factors are between group] [it is probable the fMRI designs urge two way ANOVA analysis plan and I'm not sure about this????]. Please explain and correct if it is necessary. On the other hand, regarding the clinical assessment of depression, anxiety and GI symptoms [HAMD, HAMA and GSRS scores], we could

consider such analysis plan. In fact, these variables could be analyzed in mixed model ANOVA design for assessment of main effects of therapy and time. In addition to these main effects, detailed comparisons of groups [as mentioned correctly in table 1] are necessary [of course considering stat. techniques such as bonferroni correction and post hoc tests]. Thus, comparison plan of table 1 is appropriate and should not be deleted and the author is better to furtherly complete and if necessary, correct them. The authors should mention the analysis plan of clinical data in addition to fMRI data in stat methods and follow these points in paper.

Response: First of all, thank you for your careful review. Through your explanation of statistical methods, we have further consulted relevant materials and found that there are errors in our description here. Our study used a 2(therapy)×2(time) mixed model ANOVA instead of a two-way ANOVA. We have not describe it correctly and have made corresponding amendments in the revised draft.

Secondly, thank you very much for your advice. We further analyzed variables [HAMD, HAMA and GSRS scores] in mixed model ANOVA design for assessment of main effects of therapy and time. Two-sample t-test analysis were used for the comparison between the groups. We added relevant content and divided the demographic data and clinical scale scores into two tables (table 1 and table 3). Detailed comparisons results of groups are shown in table 3. We have made corresponding amendments in the revised draft. We supplemented the analysis method of clinical data in the statistical methods section of the revised draft. Thanks again for your advice.

2-the authors mentioned regression analysis while there is no data in this regard in paper. Please mention or complete the data more explicitly in this regard [if it us necessary]

Response: Thank you very much for your question. We apologize for not explaining it clearly in these parts. The regression model written on page 6, line 166, refers to the statistical analysis of the resting state data (ANCOVA and post-hoc test) that is accomplished through the regression analysis method. Age, gender, course of disease, etc. are used as covariates for analysis in the processing of resting state fMRI data, which is

one step of automatic processing on DPABI software. To avoid being misleading, we have removed the regression model here. In addition, due to the addition of these covariables, the analysis of resting state data was performed by ANCOVA analysis rather than ANOVA analysis. This is our mistake, the corresponding part have been revised.

3-the table 1 legend does not reflect the real data presented in this table. I recommend the authors correct this legend to something like this one: “Baseline and Clinical characteristics of observation group and control groups and comparison of depression, anxiety and GI symptoms between groups and before and after the study”}

Response: Thank you for your correction, corresponding changes have been made.

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.

Madjid Shakiba: Reviewer | **Revision** (2) — 31 Dec 2019

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) — 18 Jan 2020

Dear EIC,
This article was accepted as a short communication, according to peer review.
Thnaks.

Mehranoosh Dolatshahi: Associate Editor | **Revision** (2) — 11 Feb 2020

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

Kavous Firouznia: EIC | **Revision** (2) — 12 Feb 2020

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