OPEN PEER REVIEW

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As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

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- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:

Peer Review

Anesthesiology and Pain Medicine
Article DOI: https://doi.org/10.5812/aapm.110531
Published in: Anesthesiology and Pain Medicine: 12(1) ; e110531

Peer Review Report for "Pulsed Radiofrequency Increases Nestin and Matrix Metalloproteinase-2 Expression in Porcine Lumbar Dorsal Root Ganglion"

Author(s): Mihails Arons, Mara Pilmane, Arun Bhaskar, David J Kopsky, Vladimir Romanenko, Olav Rohof

Review Timeline:

Submit Date:	7 Mar 2021
Revised Date:	27 Dec 2021
Accepted Date:	7 Jan 2022

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

20 Mar 2021

This is an original research article that complains with the requirements of the peer review form. That was a great pleasure to review this original work and well written article and the implications of the authors discoveries may have huge implications in the clinical settings, since it opens a new avenue in the possible use of PRF for tissue regeneration proposes.

The study design is innovative and in line with the previous work of the authors group, in reference 3. In the Methods section the analysis of the results was performed in a very elegant way and in the discussion they correctly made a call of

attention for the possible benefits but also for the possible risks and the need for future inquiries and scientific work.

That said I have some questions to the authors and to refer minor aspects that I would like to be corrected and a limitation of the study.

I consider a limitation the lack of a shame control. The contralateral side could have been subjected to the insertion of the RF cannulas without passing the current. That was the protocol used by Marteen Van Kleef and al in goats in with thermal RF

“The morphological effects of a radio frequency lesion adjacent to the dorsal root ganglion (RF-DRG)—an experimental study in the goat. European Journal Pain, Vol 5, issue 2, 2001, pages 169-174”

The authors used 45 volts not allowing a raise in temperature above 42C, that means that there was adjustments in the voltage and current intensity if the temperature raised above the stipulated limit value. I would like the authors to describe the range of values of voltage and current used and the respective means.

The title is correct but too much comprehensive, in my view it could be more focused as they say in the results line 129: PRF to the DRG increases the expression of biomarkers Nestin and MM-2, identifying the biomarkers.

Nestin is an acronym for neuroectodermal stem cell intermediary filament. To refer this could help doctors not acquainted with this molecule to grasp immediately one of its main functions as a regenerative agent. This is obviously just a suggestion.

Regarding References

a) Reference 3 refers to a Russian article by the authors and is not accessible for most people. The article is easily accessible at this place and must be included:

Pulsed Radiofrequency Effects on Lumbar Dorsal Root Ganglion of Domestic Porcine: Pilot Study. Acta Chirurgica Latviensis, 2012 (12);51-60.

b) In introduction line 14 the reference 47 is misplaced only ref. 14 should be there.

c) Regarding the synaptic effects of PRF the Cahana article should be referred:

Cahana et al. Acute differential modulation of synaptic transmission and cell survival during exposure to pulsed and continuous radiofrequency energy. J Pain, 2003 May;4(4):197-202.

d) Reference 20 concerns the transcutaneous application of pulsed Electromagnetic energy with a frequency of 22,4 MHz, different duty load an parameters as pulses in the microsecond range. As a consequence, it is displaced and should be removed.

e) The first two publications where PRF is referred as a possible agent for the treatment of non-painful conditions, namely systemic diseases with immunodepression and allostatic load was this Journal. These articles are in line with the innovation spirit of this article, and I think the authors should consider their inclusion in the references.

Sluijter ME, Imani F. Evolution and Mode of Action of Pulsed Radiofrequency. Anesth Pain Med. 2013;2(4):139-41.

Teixeira A, Sluijter ME. Intravenous Application of Pulsed Radiofrequency–4 Case Reports, Anesth Pain Med. 2013;3(1):e93350

In my opinion it is an excellent article that needs minor corrections

Reza Aminnejad : Reviewer

27 Mar 2021

I read the article with great interest and I want to add some points to it;
1- In the introduction, you must first introduce the problem that you are trying to find a solution for it. So, it is better to write briefly about back pain and management options first.
2- Nestin is the acronym for neuroectodermal stem cell marker. Adding this sentence to the introduction will help to a better understanding of the following text.
3- Please explain all abbreviations at the first time use, for example, as a pain physician, I don't know what ATF3 and NS are!
4-In line 30, is 1-85% true?
5- In line 242, what is "oy"?!
6- Recently, the role of reactive astrocytes in controlling chronic pain has been suggested.(1) Can this role be analyzed with the findings of your study? Could nestin and MMP2 play a role in the role of reactive astrocytes? Did you study the effect of PRF on astrocytes?
7- English grammatical revision is strongly recommended.
8- Please consider and add Six below articles to the reference list:
Imani F, Gharaei H, Rezvani M. Pulsed Radiofrequency of Lumbar Dorsal Root Ganglion for Chronic Postamputation Phantom Pain. Anesth Pain Med. 2012;1(3): 194-7.
Imani F. Using Pulsed Radiofrequency for Chronic Pain. Anesth Pain Med. 2012;1(3):155-6
Shofwan S, Liem L, Janitra G, Basuki N, Rhatomy S. Discitis Following Radiofrequency Nucleoplasty: A Case Report, Anesth Pain Med. 2020;10(6):e110322.
Arvaniti C, Madi AI, Kostopanagiotou G, Batistaki C. Can Pulsed Radiofrequency of the Occipital Nerves Cause Sedation? A New Perspective of Existing Knowledge. Anesth Pain Med. 2020;1(2):e96418.
Brasil L J, Marroni N, Schemitt E, Colares J. Effects of Pulsed Radiofrequency on a Standard Model of Muscle Injury in Rats, Anesth Pain Med. 2020;10(1):e97372.
Marliana A, Setyopranoto I, Setyaningsih I, Rhatomy S. Effectiveness of Pulsed Radiofrequency on Radicular Pain in Lumbar Herniated Nucleus Pulposus: Systematic Review and Meta-analysis. Anesth Pain Med. 2021;11(2):e111420.

REFEREE : Reviewer

28 Mar 2021

Dear
1. The structure of essay writing has not been observed by the authors and needs to revision major.
2. Please delete old references.

REFEREE : Associate Editor

10 Apr 2021

Dear Editor in Chief
Based on the reviewers' comments, this article needs to be amended
Final decision: Minor revision

Regards
AE

REFEREE : EIC

10 Apr 2021

Minor Revision

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.

A letter to the Reviewer 1

Manuscript ID: 110531

Manuscript title: Pulsed Radiofrequency Increase Nestin and Matrix Metalloproteinase-2 Expression in Porcine Lumbar Dorsal Root Ganglion

New manuscript title: Pulsed Radiofrequency to the DRG increases the expression of biomarkers Nestin and Matrix Metalloproteinase-2

Dear Reviewer,

We would like to thank You for the valuable criticism and suggestions upon our submitted manuscript. We are firmly convinced that the careful revision of our work regarding your suggestions has significantly improved the quality and readability of our paper and hope that these major revisions will meet the criteria of the Anesthesiology and Pain Medicine journal to be published. Once again, thank You for the motivating review.

Responses to reviewers' comments:

1. *The structure of essay writing has not been observed by the authors and needs to revision major.*

   Response: Thank You, we changed the Introduction. We have tried introduce the problem first and find solution for it. We hope that the structure of manuscript is better now.

2. *Please delete old references.*

   Response: Thank You very much, we have deleted old references, excluding some very important, basic science articles dedicated to the Matrix Metalloproteinases and Nestin.

A letter to the Reviewer 2

Manuscript ID: 110531

Manuscript title: Pulsed Radiofrequency Increase Nestin and Matrix Metalloproteinase-2 Expression in Porcine Lumbar Dorsal Root Ganglion

New manuscript title: Pulsed Radiofrequency to the DRG increases the expression of biomarkers Nestin and Matrix Metalloproteinase-2

Dear Reviewer,

We would like to thank You for the evaluation of our work and suggestions upon our submitted manuscript. We are firmly convinced that the careful revision of our work regarding your suggestions has significantly improved the quality and readability of our paper and hope that these minor revisions will meet the criteria of the Anesthesiology and Pain Medicine journal to be published. Once again, thank You for the motivating review.

Remark: I consider a limitation the lack of a shame control. The contralateral side could have been subjected to the insertion of the RF cannulas without passing the current. That was the protocol used by Marteen Van Kleef and al in goats in with thermal RF "The morphological effects of a radio frequency lesion adjacent to the dorsal root ganglion (RF-DRG)—an experimental study in the goat. European Journal Pain, Vol 5, issue 2, 2001, pages 169-174"

Response: Thank You for the great remark, we take on board the comments regarding the lack of sham control. The van Kleef study was looking at morphological changes due to a radiofrequency lesioning adjacent to the DRG. The sham would snable to identify the diffreence between the thermal lesion and possible mechanical trauma. In our study with PRF we were looking at microscopic evaluation of immunohistochemistry and decided to avoid physical trauma to the control site as trauma could potentially cause expression of the markers which could lead to erroneous interpretation of the immunohistochemical studies. We would be certainly interested in performing an another study with sham electrodes inserted as control as suggested by the reviewer.

Remark: The authors used 45 volts not allowing a raise in temperature above 42C, that means that there was adjustments in the voltage and current intensity if the temperature raised above the stipulated limit value. I would like the authors to describe the range of values of voltage and current used and the respective means.

Response: Thank You, we did not make any manual changes to adjust the voltage or current intensity. We performed using the preset protocol of the Neurotherm RF pulse generator delivering PRF at 5Hz 45V and to maintain the temperature of the active tip at or up to 42 C and not above it.

Remark: The title is correct, but too much comprehensive, in my view it could be more focused as they say in the results line 129: PRF to the DRG increases the expression of biomarkers Nestin and MM-2, identifying the biomarkers.

Response: Thank You, we changed the title as You recommended, hope it is more appropriate now.

Remark: Nestin is an acronym for neuroectodermal stem cell intermediary filament. To refer this could help doctors not acquainted with this molecule to grasp immediately one of its main functions as a regenerative agent. This is obviously just a suggestion.

Response: Thank You very much for valuable remark, we added this sentence to the introduction.

Additional Remarks
- regarding References:
a) Reference 3 refers to a Russian article by the authors and is not accessible for most people. The article is easily accessible at this place and must be included:
Pulsed Radiofrequency Effects on Lumbar Dorsal Root Ganglion of Domestic Porcine: Pilot Study. Acta Chirurgica Latviensis, 2012 (12);51-60.

Response: Thank You very much, we removed from references article in Russian language and included Your recommended manuscript: Pulsed Radiofrequency Effects on Lumbar Dorsal Root Ganglion of Domestic Porcine: Pilot Study. Acta Chirurgica Latviensis, 2012 (12);51-60.

b) In introduction line 14 the reference 47 is misplaced only ref. 14 should be there.

Response: Thanks You for the remark, it was just mistake.

c) Regarding the synaptic effects of PRF the Cahana article should be referred:
Cahana et al. Acute differential modulation of synaptic transmission and cell survival during exposure to pulsed and continuous radiofrequency energy. J Pain, 2003 May;4(4):197-202.

Response: Thank You very much, we included recommended article in the references.

d) Reference 20 concerns the transcutaneous application of pulsed Electromagnetic energy with a frequency of 22,4 MHz, different duty load an parameters as pulses in the microsecond range. As a consequence, it is displaced and should be removed.

Response: Please accept our apologies and thank You for great remark. Reference 20 concerns the transcutaneous application of pulsed electromagnetic energy and is removed.

e) The first two publications where PRF is referred as a possible agent for the treatment of non-painful conditions, namely systemic diseases with immunodepression and allostatic load was this Journal. These articles are in line with the innovation spirit of this article, and I think the authors should consider their inclusion in the references.
Sluijter ME, Imani F. Evolution and Mode of Action of Pulsed Radiofrequency. Anesth Pain Med. 2013;2(4):139-41.
Teixeira A, Sluijter ME. Intravenous Application of Pulsed Radiofrequency–4 Case Reports, Anesth Pain Med. 2013;3(1):e93350

Response: Thank You very much, we included both Your recommended articles in the references.

A letter to the Reviewer 3

Manuscript ID: 110531

Manuscript title: Pulsed Radiofrequency Increase Nestin and Matrix Metalloproteinase-2 Expression in Porcine Lumbar Dorsal Root Ganglion

New manuscript title: Pulsed Radiofrequency to the DRG increases the expression of biomarkers Nestin and Matrix Metalloproteinase-2

Dear Reviewer,

We would like to thank You for the evaluation of our work and suggestions upon our submitted manuscript. We are firmly convinced that the careful revision of our work regarding your suggestions has significantly improved the quality and readability of our paper and hope that these minor revisions will meet the criteria of the Anesthesiology and Pain Medicine journal to be published. Once again, thank You for the motivating review.

Point 1: In the introduction, you must first introduce the problem that you are trying to find a solution for it. So, it is better to write briefly about back pain and management options first.

Response: Thank You for the great remark, we changed introduction. We have tried introduce the problem first and find solution for it. We hope that the structure of introduction is better now.

Point 2: Nestin is the acronym for neuroectodermal stem cell marker. Adding this sentence to the introduction will help to a better understanding of the following text.

Response: Thank You very much, we added this sentence to the introduction.

Point 3: Please explain all abbreviations at the first time use, for example, as a pain physician, I don't know what ATF3 and NS are!

Response: Please accept our apologies and thank You for the great remark, we explained both abbreviations: ATF3: Activating Transcription Factor 3; NS: NF neurofilaments.

Point 4: 4-In line 30, is 1-85% true?

Response: Thank You, we have removed this sentence together with the mentioned reference.

Point 5: In line 242, what is "oy"?!

Response: Thank You very much, it was printing error.

Point 6: Recently, the role of reactive astrocytes in controlling chronic pain has been suggested. Can this role be analyzed with the findings of your study? Could nestin and MMP2 play a role in the role of reactive astrocytes? Did you study the effect of PRF on astrocytes?

Response: Yes, indeed, the astrocytes are very important for the events into the CNS, but their effects is rather common/non-specific than specific, because they usually react with the similar reactions to many irritants (trauma, diseases, etc), and we suppose that their reaction is non-specific also in case of PRF irritation. Thus, we excluded selective astrocyte reaction description from the analyses. However, thank you for great idea, - the research only about the astroglia in relation with tissue degradation/regeneration/growth factors and defence/inflammatory cytokines plus neural tissue quality markers really seems to be sense-full and interesting research topic for the future.

Point 7: English grammatical revision is strongly recommended.

Response: Thank You very much for the very important suggestion. Native English speaker (anesthesiologist and pain specialist) has developed English grammatical revision.

Point 8: Please consider and add Six below articles to the reference list:
Imani F, Gharaei H, Rezvani M. Pulsed Radiofrequency of Lumbar Dorsal Root Ganglion for Chronic Postamputation Phantom Pain. Anesth Pain Med. 2012;1(3): 194-7.
Imani F. Using Pulsed Radiofrequency for Chronic Pain. Anesth Pain Med. 2012;1(3):155-6
Shofwan S, Liem L, Janitra G, Basuki N, Rhatomy S. Discitis Following Radiofrequency Nucleoplasty: A Case Report, Anesth Pain Med. 2020;10(6):e110322.
Arvaniti C, Madi AI, Kostopanagiotou G, Batistaki C. Can Pulsed Radiofrequency of the Occipital Nerves Cause Sedation? A New Perspective of Existing Knowledge. Anesth Pain Med. 2020;1(2):e96418.
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Marliana A, Setyopranoto I, Setyaningsih I, Rhatomy S. Effectiveness of Pulsed Radiofrequency on Radicular Pain in Lumbar Herniated Nucleus Pulposus: Systematic Review and Meta-analysis. Anesth Pain Med. 2021;11(2):e111420.

Response: Thank You very much, we included as You recommended following 4 from 6 articles in our reference list.

Imani F, Gharaei H, Rezvani M. Pulsed Radiofrequency of Lumbar Dorsal Root Ganglion for Chronic Postamputation Phantom Pain. Anesth Pain Med. 2012;1(3): 194-7.
Imani F. Using Pulsed Radiofrequency for Chronic Pain. Anesth Pain Med. 2012;1(3):155-

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OPEN PEER REVIEW

Revision (1)

REFEREE : Reviewer

21 Nov 2021

Dear Editor in Chief
Thank you for inviting me again to review this revised article.
I read with interest this manuscript. Although author tried to correct previous comments, due to high rate of article submission, this topic can be accepted only as brief report. There for my suggestion are as below:
Change the article style to Brief Report
Summarize the whole text
Reduce the Word Count to 2000
Reduce the references to 20
Regards

REFEREE : Associate Editor

21 Nov 2021

Dear Editorial
Based on reviewers' comments this revised manuscript need to change to brief report
Final decision: Major revision
Sincerely
AE

REFEREE : EIC

21 Nov 2021

Major Revision

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.

A letter to the Reviewers

Manuscript ID: 110531

Brief report title: Pulsed Radiofrequency to the DRG increases the expression of biomarkers Nestin and Matrix Metalloproteinase-2

Dear Reviewers,

We would like to thank You for your latest comment and recommendations. We correct our article according to your suggestions and hope that these major revisions will meet the criteria of the Anesthesiology and Pain Medicine journal to be published. Once again, thank You for the motivating review.

Responses to reviewers' comments:

1. *Change the article style to Brief Report.*

   Response: Thank You, we changed the article style to Brief Report.

2. *Summarize the whole text.*

   Response: Thank You very much, we had summarize the whole text.

3. *Reduce the Word Count to 2000.*

   Response: Thank You very much, we reduced the Word Count to 2000.

4. *Reduce the references to 20.*

   Response: Thank You very much, we reduced the refernces to 20.

OPEN PEER REVIEW

Revision (2)

Farnad Imani : EIC

7 Jan 2022

Dear Authors,

We are pleased to inform you that your manuscript has been accepted for publication. The reviewers found your work to be valuable, scientifically sound, and a meaningful contribution to the field. We appreciate the effort and dedication you invested in this study, and we thank you for choosing our journal to share your research. Congratulations on this achievement, and we look forward to your future submissions.