OPEN PEER REVIEW

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Peer Review Report for "The Impact of Compression Duration on the RhoA, P75, S100 Expression in Spinal Cord Injury in Rat"

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Review Timeline:

Submit Date: 6 Oct 2020
Revised Date: 9 Dec 2020
Accepted Date: 14 Dec 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) 12 Oct 2020

Dear AE,
The authors of the manuscript tried to evaluate long lasting pressure on SCI vs short one on expression of RhoA, S100, p75. It rise several question for me
1- How did they select 3sec and 10 min? It is a very wide time difference. Why did they did not select 1 min vs 10 or 15 min?
2- Up to 2 weeks we do not expect any recovery in animals. after 3 weeks most studies showed that BBB of injured animal without any intervention begin to rise. Why authors evaluate the BBB before week 3. I suggest to evaluate them after week 3 to see how higher RhoA expression can affect recovery.
Thanks.

REFEREE: Reviewer | **Revision** (0) 21 Nov 2020

Dear AE,
The effect of early spinal cord decompression was assessed in rats, to indicate molecular changes. Expression of RhoA, P75, S100 was increased in late decompression, leading to secondary injuries.

The role of early decompression is well known and studied in clinical series at literature! Moreover, the major pathologic mechanism of spinal cord injury is contusion and liquefactive necrosis. Therefore, a useful regenerative process with favorable outcomes is confirmed to be a myth, through hundreds of well-designed studies.
However, early application of medications to prevent secondary injuries would be applicable in the future.
Thanks.

REFEREE: Associate Editor | **Revision (**0**)** 23 Nov 2020

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,

REFEREE: EIC | **Revision (**0**)** 23 Nov 2020

Dear Author,
Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.
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.

Dear Drs. Hussain Khan and Samii,

We appreciate the reviewers' time, and thank them very much for their comments:

Reviewer 1:

Authors of the manuscript tried to evaluate long lasting pressure on SCI vs short one on expression of RhoA, S100, p75. It rise several question for me

1- How did they select 3sec and 10 min? It is a very wide time difference. Why did they did not select 1 min vs 10 or 15 min?

This is a good question. Our first study examined whether spinal cord decompression improves functional recovery and decreases lesion volume in paraplegic rats and, if so, at what postoperative time it is most efficacious. Rats in this study were randomly assigned to five different treatment groups of 3 sec, 1 hr, 6 hrs, 3 weeks, and 10 weeks (Rahimi-Movaghar et al., 2008). Among the five groups, the mean BBB was significantly higher in the 3 sec group ($P < 0.05$). Comparison of progressive changes in BBB in each group revealed statistically meaningful improvement in the 3 sec group as well. Spared surface area of spinal cord was 81.5% +/- 4.9% in the 3 sec group and 10.8% +/- 1.4% in the delayed groups of decompression ($P = 0.039$). Rats undergoing immediate decompression showed significantly better functional recovery and smaller lesion volumes. Subsequently, our main intent was to select one time point between the effective decompression timeframe of 3 sec and the non-effective decompression timeframe of 1 hr. We selected 10 minutes (10 min). Your suggestion of 15 minutes would be valid as well. The presence of a control group is necessary. Therefore, in the second study, we compared the effective decompression of 3 sec with the 10 min decompression. Our study showed that the 3 sec group is significantly better than the 10 min group (Jazayeri et al., 2013).

Rahimi-Movaghar V, Yazdi A, Karimi M, Mohammadi M, Firouzi M, Zanjani LO, Nabian MH. Effect of decompression on complete spinal cord injury in rats. Int J Neurosci. 2008 Oct;118(10):1359-73.

Jazayeri SB, Firouzi M, Abdollah Zadegan S, Saeedi N, Pirouz E, Nategh M, Jahanzad I, Mohebbi Ashtiani A, Rahimi-Movaghar V. The effect of timing of decompression on

neurologic recovery and histopathologic findings after spinal cord compression in a rat model. Acta Med Iran. 2013 Aug 7;51(7):431-7.

2- up to 2 weeks we do not expect any recovery in animals. after 3 weeks most studies showed that BBB of injured animal without any intervention begin to rise. Why authors evaluate the BBB befor week 3. I suggest to evaluate them after week 3 to see how higher RhoA expression can affect recovery.

Excellent question. We evaluated BBB of rats from the first week to the 11th week. Figure 5 shows that spontaneous improvement in locomotor function has started in the 3-second compression group three days after decompression. On the other hand, the goal of this study was to evaluate the changes in expression of RhoA, p75NTR, S100β in the short and prolonged compression of spinal cord in a compressive model of SCI. Therefore, to select the ideal time-point of the evaluation of these molecules, as we have written in the discussion of the manuscript, literature shows that p75NTR expression starts six hours after SCI and continues to increase at 24 hours and seven days, reducing at 10 days after injury. Alterations in p75NTR expression within the spinal cord may play a key role in apoptotic cell death (Montazeri et al., 2013). It has been shown that the S100β immunoreactive area is significantly increased at 72 hours, 1 week, and 3 weeks after injury in a spinal cord contusion model (Do Carmo Cunha et al., 2007). Finally, increased RhoA expression in neurons and glial cells has an important role in inhibiting neural regeneration in the first week after SCI (Kang et al., 2013).

Reviewer 2:

The effect of early spinal cord decompression was assessed in rats, to indicate molecular changes. Expression of RhoA, P75, S100 was increased in late decompression, leading to secondary injuries.

The role of early decompression is well known and studied in clinical series at literature! Moreover, the major pathologic mechanism of spinal cord injury is contusion and liquefactive necrosis. Therefore, useful regenerative process with favorable outcome is confirmed to be a myth, through hundreds of well designed studies.

However, early application of medications to prevent secondary injuries would be applicable in future.

Thank you. Yes, identification of molecular mechanisms in early and late decompression could lead to the development of novel clinical interventions that may improve function. Although there are several studies discussing the effect of higher expression of p75, RhoA and S100 on cell death after SCI, the extent of overexpression of these molecules after SCI and their association with the severity of injury is not well defined. In this study, we evaluated the effect of these two variables, i.e. time of decompression after SCI, and the extent of expression of p75, RhoA and S100, which are important biomolecules influencing secondary pathophysiological events after traumatic SCI.

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Revision (1)

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

REFEREE: Reviewer | **Revision** (1) 13 Dec 2020

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

REFEREE: Associate Editor | **Revision** (1) 14 Dec 2020

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

REFEREE: EIC | **Revision** (1) 14 Dec 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.