OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-19-00462
Title: Neuroprotective effects of ketogenic diet in combination with exogenous ketone salts following acute spinal cord injury
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COMMENTS TO AUTHORS

Therapeutic ketosis and ketogenic diet (KD) have attract large attention by its therapeutic potential including neuroprotection in the fields of nutrology and biochemistry. It is known that one of the shortages of KD is the slow blood ketone induction to be applied for spinal cord injury (SCI) patients, for whom fast raise within 12 hour after the injury may be needed. Beta-hydroxybutyrate ketone salt supplementation (KS) is a combinative agent to immediately raise blood ketone level. On this ground, the authors investigated the effects of combination of KD and KS in the treatment of spinal cord cervical hemisection model rats. The authors demonstrated the neuroprotective effect of KD+KS treatment including better upper-limb motor recovery than the control animals. The main topic of this study is the combination of KS. Because the effect of KD is already repeatedly reported (2013 Steijger, 2017 Wang, 2018 Lu), the comparison between groups of KS+KD vs KD alone is indispensable

Major concerns;

- Please introduce previous studies regarding KD for SCI in the introduction section. Although the authors seems only shorty mentioned Steijger's study, I found additional preclinical studies investigating the mechanism and a pilot RCT for human subjects.
- Figure 2, Why the authors assessed blood ketone in different ways between B,C and D? Especially for the difference in the duration (1 or 4), explanation is needed. Besides, why the numbers are different among these assessments? Please provide the rationale how those sample sizes are decided; I am wondering whether the small number (N=8 or 9) in Figure 2 (b) and (c) is affecting the statistical significance.
- The reason why KS via oral gavage did not appear to elicit a prolonged further increase in ketone levels in the acute phase after SCI must be discussed.
- Strictly speaking, the authors failed to show therapeutic potential of KS in SCI animals, because KS administration did not induce a raise of blood ketone level within 12-16 hours and some effect of KD is already reported. This point must be fairly discussed in the discussion section.
- As I mentioned above, the main topic of this study was combination of KS. Now the authors failed to show immediate increase in blood ketone level with this treatment. But there might be a possibility that intermittent ketone increase might have some beneficial effect. On this ground, additional experiment to compare KD vs KD+KS must be needed.

Minor concerns;

- In Introduction, explanation about KS is insufficient.
- (Page3, Line 13) βHB: please spell out at the first appearance.
- (Page3, Line 22-27) the number of animals applied for the feasibility study is unclear.
- Result section: Please describe the number of animals that are applied for each assessments.
- (Page5, Line 25-27) the order of control and KS+KD is not consistent with the followings
- (Page6, Line 22-23) Which side rostral or caudal of the lesion the axonal numbers were assessed?
- (Page 7, Line 45-47) "The tract plays a role in skilled hand movement" needing citation.