Author's response to reviews

Title: Subanesthetic ketamine for the treatment of children and adolescents with chronic pain: a longitudinal study

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Author's response to reviews: see over
Response to Reviewer’s

Reviewer 1.

1. Interesting manuscript. Text sometimes unclear. Some correction is needed. Major revisions Page 7, line 16: other therapies are associated? what? it's unclear. It's better to specify in the text
Response: We thank the reviewer for his kind words. The text was revised for clarity we now specify therapies and indications for therapy (Page 9, lines 4-8)

2. Page 7, lines 19-20: the ketamine treatment is unclear. It's necessary to better explain Therapies intravenously were well accepted to patients? Such expedients have been used to make them acceptable?
Response: The description of the ketamine treatment was revised page 6 lines 22-23 and page 7 lines 1-2

Page 10, line 11: "...non tolerated side effects...". What? It's better to specify in the text
Response: The text was revised (Page 9, lines 4-8)

Page 11, lines 7-8: onset time of ketamine effects? It's better to specify.
Response: We did not determine the time when the onset time of ketamine effect. However, we now clearly indicate that “The primary outcome was change in pain scores measured with a numeric rating scale. Pain scores were measured both before and after each ketamine infusion”

Reviewer 2

This is a further study reporting positive effects of low dose ketamine for treatment of chronic pain including CRPS. Unfortunately this is a retrospective analysis with a small number und vast heterogeneity of patients, which makes it difficult to draw any sound conclusion. Furthermore effects on long term pain relief are missing.
Response: We agree with the reviewer and list these limitations on the discussion of the manuscript

INTRODUCTION: a brief explanation of the role of NMDA receptors and NMDA receptor antagonists for chronic pain should be added.
Response: We revised the introduction and give a brief explanation of the role of NMDA receptors antagonists for chronic pain and added a few references. Page 4 lines 22-23 and
METHODS: there can only be one primary outcome. All other measures are secondary outcomes (adverse effects included).
Response: We revised the methods as suggested by the reviewer. Page 7 lines 10-14

Regarding adverse effects of ketamine – have any ‘non psychotropic’ effects been assessed, such as hypertension, nausea, anorexia, insomnia, hepatic enzyme profile?
Response: We revised the text to indicate that those side effects except for hepatic enzyme profile were assessed. Page 7, lines 12-14

How was the percentage of pain relief calculated?
Response: We now indicate in the statistical methods section that “For the analysis of percent changes in pain scores and opioid intake, we calculated these changes by subtracting post infusion from pre-infusion values and dividing the difference by pre-infusion values of respective outcomes”. Page 8, lines 16-18

Was NRS measured after each infusion or only after completion of the entire treatment?
Response: NRS was measure after each infusion. Page 7, line 11.

Was there a cumulative effect of pain relief?
Response: We postulate that that might be the case as when we examined the effect of ketamine after each treatment the effect size appeared greater than that after each infusion.

How was the percentage of reduction in morphine consumption calculated?
Response: We now indicate in the statistical methods section that “For the analysis of percent changes in pain scores and opioid intake, we calculated these changes by subtracting post infusion from pre-infusion values and dividing the difference by pre-infusion values of respective outcomes”. Page 8, lines 16-18

Definition of inclusion / exclusion criteria is missing
Response: We thank the reviewer for pointing out this oversight. We revised the text and now cite inclusion and exclusion criteria on page 6 lines 11-13

RESULTS: should be presented in order: primary outcome followed by secondary outcomes.
Response: We thank the reviewer for the suggestion. We revised the text accordingly – page 9, lines 22-23, page 10 lines 1-23, and page 11, lines 1-8.
Was morphine the only previous treatment that failed or were there other treatments? If so, which ones?

Response: No. We now indicated on page 9 lines 4-8 that “Indications for ketamine administration included 1) requirement of escalating doses of opioid associated with non-tolerated side effects (excessive sedation or constipation) or 2) lack of improvement in pain intensity and/or disabilities with other standard treatment modalities (anticonvulsants and/or antidepressants”).

DISCUSSION: too long. Could be shortened by one third.

Response: While we shortened the discussion, we could not do so by one third as in order to address the issues raised below, we needed to add a few paragraphs.

Please consider previous studies on low dose ketamine for chronic pain/CRPS in adults and see Dutch/UK guidelines for CPRS which rate the evidence for treatment with ketamine as ‘moderate’ or ‘level 3’. There is still insufficient evidence to suggest ketamine as part of routine clinical treatment for CRPS in adults (see Pickering et al Br J Clin Pharmacol 2013: 77:2: 233-238. Prolonged ketamine infusion as a therapy for CRPS: synergism with antagonism)

Response: We thank the reviewer for the suggestions and added these comments to the discussion and added a few references to support the points raised by the reviewer. Page 13, lines 7-10

Please discuss mechanism of action / role of ketamine in the treatment of chronic pain /CRPS.

Response: We thank the reviewer for the suggestion and added a paragraph to the discussion. Page 13, lines 1-7

How do the authors explain a reduction in pain scores, but at the same time no reduction in morphine consumption?

Response: We added a paragraph to the discussion addressing these contradictory findings. We consider two possibilities to explain this apparent inconsistency 1) the study lacked power to determine the effect of ketamine in opioid use given that in only 77 of the 277 infusions, patients were taking opioid and 2) the use of opioid was measured by the prescribed doses during follow up appointments at varying intervals. Page 15, lines 21-23 and page 16, lines 1-2.

How do the authors explain that they did not observe any psychotropic effect? This is in contrast with previous studies with a similar design (see reference 25)

Response: We added a paragraph to the discussion to address this discrepancy. We postulate that these discrepant results could be related to differences in doses used on a per kg/h basis, duration of infusions, or differences in pharmacokinetics comparing children
and adults. For example, pharmacokinetic and pharmacodynamic studies indicate that children have a shorter context-sensitive half-time and lower sensitivity to ketamine compared to adults. Page 16, lines 2-10