Author's response to reviews

Title: Effect of a high-dose target-controlled naloxone infusion on pain and hyperalgesia in patients following groin hernia repair: study protocol for a randomized controlled trial

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Author's response to reviews: see over
Dear Editors-in-Chief,

Thank you for evaluating our manuscript so positively. We have revised the manuscript according to the reviewers’ suggestions and, as requested, point-by-point responses to the reviewers’ concerns are provided below. The authors’ replies are in italic with blue font color.

Sincerely yours,

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Reviewer's report:

Thank you for reviewing our manuscript so positively and for the suggestions regarding the revision of the manuscript.

In general:

A very well designed trial, and a well written protocol.

The purpose is clear, background well described and the design, a cross-over study, is appropriate. That the wash-out period is appropriate is justified in the discussion. Based on the corresponding authors own submitted data from a previous trial, the authors are confident that their model of generating secondary hyperalgesia with high dose naloxone will work. The chosen timing for the trial (6-8 weeks post-surgery) is accounted for and is relevant.

The safety in giving such a high dose of naloxone is well accounted for. That the risk of developing sustained pain is considered highly unlikely is also accounted for.

Selection of participants is well described, inclusion and exclusion criteria relevant.

Randomization and blinding procedures is well described and thorough, thus minimizing the risk of bias.

The intervention is clearly described, and would enable others to replicate the trial.

Tables and illustrations are fine and illustrative, and help understanding well.

Study management is well described and adequate.

Discretionary Revisions:
Regarding the primary outcome: reading the section, it is not entirely clear to me if the TCI-SPI is based on a summated score of NRS recordings at three different timepoints, ie 9 NRS values? Or the three values at the last timepoint (65-75 min)?

Regarding the primary outcome: the baseline SPI-score (summated NRS score) will be subtracted from the SPI-score (summated NRS score), recorded at the highest obtainable TCI step. This explanation was added to the subsection “Primary Outcome” (page 10) for clarification.

Regarding the secondary outcome Secondary hyperalgesia/Allodynia: It is not entirely clear to me what exactly the outcome is – the difference in the summated areas at all three timepoints versus baseline, naloxone-group versus placebo-group? Same question goes for secondary outcome PPT – what exactly is the outcome?

Regarding the secondary outcome: baseline outcome values (of secondary hyperalgesia area, allodynia area and PPT) will be subtracted from the scores of secondary hyperalgesia, allodynia and PPT, assessed at the highest obtainable TCI-step. An explanation was added to the manuscript for clarification (subsection
Sample size calculation is relevantly based on the primary outcome. The MIREDIF at 3 NRS-units is a relatively high value. I could be worried that this rather large difference will not be found? Significance level and power are fine. The number of participants seems to be sufficient, assuming that the MIREDIF is realistic.

Thank you for your question. In fact, we consider that a MIREDIF of 3 NRS-units (0/10) is not very much in terms of our use of a summated measure (SPI) of three assessments (resting pain, movement-related pain and pressure evoked pain. Baseline SPI is estimated to be 8 [mean per assessment = 2.7] NRS-units: a significant increase would then be ≥ 11 [mean per assessment ≥ 3.7] NRS-units, i.e., ≥ 38% increase from baseline. Further, the patients are required to experience low pain intensity prior to Nx-administration. The MIREDIF is therefore is, in fact, a rather conservative measure.

This explanation was added to the Discussion section (page 17, 2nd paragraph).

Regarding funding: It is stated that no funding has been obtained. I am curious as to how for example the compensation to the patients (20 EUR/h – roughly equal to: 2,5 hours/day x 2 days x 16 participants = 1600 EUR), study-drugs, publication fees, use of randomization software (might be free, I am not familiar with it) is paid?

Costs of the study will include, as mentioned, participants’ compensation, study drug and eventually publication fees. The randomization software (random.org) is free of charge. In the mean time, author MUW was granted funding by the National Institutes of Health (NIH DA37621), which will be used to finance part of this study. The remaining funding will be by departmental resources. This was added to the section Funding (page 20).

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests
I consider that the article could be published without any successive revision.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that i have no competing interest.

**Reviewer 3**

*Thank you for reviewing our manuscript so positively and for the suggestions regarding the revision of the manuscript.*

**Reviewer's report:**
The study design appears adequate to test the hypotheses, which are genuinely formulated according to the problem under study. The statistical analysis is appropriate to do the intended tests, and proper sample size considerations are done. The presentation is sufficient enough to allow replication. Finally, the layout of figures and writing style appears satisfying, the length of the presentation is reasonable, and references are comprehensively provided.

My only minor comment regards the calculation of sample size. This calculation relies on an "estimate(s) of intra-individual standard deviation of mean BL-SPI of 1.2 NRS-units...". I believe that this figure is an assumed standard deviation? If so, this should be explicitly stated, otherwise, the source of the estimate reported. Also, if it is an assumed figure, an indication of the sensitivity to the assumption might conveniently be shortly reported; for example as the increase in sample size under assumption of larger standard deviation(s).

*Since no past studies with similar design and hypothesis have been performed to support our assumptions, we opted for this calculation to use an assumed estimate of intra-individual standard deviation of mean BL-SPI of 1.2 NRS-units. This explanation has been added to the manuscript (subsection “Sample Size Calculation”, page 12).*

*The second part of the questions is very interesting, indeed!! Thank you!! If the assumed estimate of intra-individual standard variation is larger than expected, i.e., 1.7 or 2.5 NRS-units vis-à-vis 1.2 NRS-units, the corresponding sample size would increase from 9, to, 14 or 20, respectively (P < 0.01, power = 0.90). This explanation has been added to the manuscript (subsection “Sample Size Calculation”, page 13).*

Level of interest: An article of importance in its field

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests

Reviewer 4

Thank you for reviewing our manuscript so positively and for the suggestions regarding the revision of the manuscript.

Reviewer's report:

I VERY MUCH CONGRATULATE WITH THE AUTHOR; I FIND THE PROTOCOL REALLY INNOVATIVE.

I DON'T HAVE MAJOR CONCERNS. ENGLISH IS HIGH-QUALITY AND COMPREHENSIBLE. ALL POTENTIAL DOUBTS THAT MAY RISE DURING READING ARE WELL EXPLAINED IN THE DISCUSSION.

Discretionary revision

my suggestion is to reduce a little bit the length of the discussion and avoid repetition of concepts between introduction and discussion.

Thank you very much for this comment. Really appreciated! The first paragraph of the Discussion section, which in fact did repeat some of the ideas, already explored in the introduction, was shortened.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: i HAVO NO COMPETING INTERESTS TO DECLARE