Reviewer’s report

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

Version: 4 Date: 26 August 2015

Reviewer: Helene Korvenius Nedergaard

Reviewer’s report:

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 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?

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.

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?

**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