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

Authors:

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Version: 2
Date: 15 May 2015

Author's response to reviews: see over
Reviewer's report

Title: Effect of a high-dose naloxone infusion on pain and hyperalgesia after recovery from inguinal herniotomy: A randomized, placebo-controlled, double-blind, cross-over study

Version: 1
Date: 28 October 2014

Reviewer: Roman Rukwied

Reviewer's report:

The study protocol is clearly described and the number of patients carefully calculated by the authors.

Major concerns:

1. The rational for using high-dose naloxone (2 mg/kg) is not quite clear, as it is based primarily on a personal communication and showed a latent sensitization in one third of subjects only thus not as robust as in rodents. Therefore, a titration study with ascending naloxone-doses is recommended.

Taking the concerns of the reviewer into account, we have included in our protocol a naloxone titration study using a target-controlled infusion with ascending doses up to 3.25 mg/kg. This way we aim to show dose-dependent reinstatement of pain and hyperalgesia following recovery from an open groin hernia repair procedure, providing thus evidence of opioid mediated latent sensitization in humans.

2. Please explain the mechanism by which a naloxone-infusion causes central sensitization in pain-free patients, i.e. 6-8 weeks after herniotomy? What about healthy volunteers, do they develop secondary hyperalgesia upon high-dose naloxone?

The mechanism by which administration of a high-dose naloxone infusion causes reinstatement of pain in patients recently operated, i.e. by blocking the endogenous opioid system, is explained in more detail in the introduction section of our manuscript. In the absence of an injury it is unlikely that naloxone causes pain, since studies in healthy volunteers using naloxone doses in the mg/kg range reported behavioral adverse effects as nausea or tiredness but, except for epigastralgia, pain has not been described (see introduction section).

3. Acute skin nociceptor sensitization by brief thermal stimulation (BTS) of the thigh will be investigated for systemic effects of naloxone-evoked central sensitization. What implication will be drawn from these experiments considering the authors assumption of inguinal herniotomy being a model of deep tissue inflammation?

We decided to remove the assessment of secondary hyperalgesia generated by brief thermal stimulation (BTS), which was stated as a secondary outcome in the previous
version of the manuscript, since this outcome was only of exploratory nature and not directly related to the primary aim of the study.

4. Correlation analyses of pain (at rest, during exercise) with QST-parameters, pressure pain and secondary hyperalgesia, along with “high-sensitizers” and “low-sensitizers” as co-variance, should be included as outcome measure.

A mixed model analysis with random effect for subject and fixed-effects for the factors, target-controlled-infusion (step 1/step 2/step 3), secondary hyperalgesia areas, pressure pain thresholds, HADS-scores and PCS-scores, will be used for the primary outcome.

**Level of interest:** An article of limited interest

We consider this study of pivotal importance in the investigation of mechanisms involved in the transition from acute to chronic pain. The protective endogenous opioid system may play a relevant role in the development of persistent post-surgical or post-traumatic pain. Further knowledge on this matter may lead to better pain management strategies.

**Quality of written English:** Needs some language corrections before being published

Language corrections have been performed throughout the manuscript.

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

**Declaration of competing interests:**
There are no competing interests
Dear Editor-in-Chief,

After carefully addressing the comments by peer-review on our study protocol entitled: “Effect of High-dose Naloxone Infusion on Pain and Hyperalgesia in Inguinal Post-herniotomy Patients: A Randomized, Placebo-controlled, Double-blind, Cross-over Study.” (Pereira MP, Werner MU, Dahl JB; ID: 2327252831394013), we hereby wish to resubmit our manuscript for your consideration.

Our study aims to show latent pain sensitization mediated by the endogenous opioid system in humans in a post-operative setting, a phenomenon previously shown in animal studies [1,2]. In a previous study in healthy volunteers, after recovery from a superficial burn, administration of a high-dose naloxone infusion (2 mg/kg) led to substantial reinstatement of secondary hyperalgesia areas in 4 out of 12 volunteers, suggesting that latent sensitization is present in humans [Pereira MP and Donahue RR et al: unpublished observations]. A more invasive model, inducing deep tissue inflammation, as performed in animal studies, may be necessary to consistently show latent sensitization in humans. Therefore, we suggest a study aiming to show latent sensitization using a post-surgical model. We hypothesize that blocking the endogenous opioid system with a high-dose naloxone infusion will reinstate pain and hyperalgesia 6 to 8 weeks after surgery, a time-point at which patients are expected to be pain free.

Taking the concerns of the reviewer into account, we have included in our protocol a naloxone titration study using a target-controlled infusion with ascending doses up to 3.25 mg/kg. This way we aim to show dose-dependent reinstatement of pain and hyperalgesia following recovery from an open groin hernia repair procedure, providing thus evidence of opioid mediated latent sensitization in humans.

Furthermore, as requested by the reviewer, the mechanism by which administration of a high-dose naloxone infusion causes reinstatement of pain in patients recently operated, i.e. by blocking the endogenous opioid system, is explained in more detail in the introduction section of our manuscript. Regarding additional outcomes, we decided to remove the assessment of secondary hyperalgesia generated by brief
thermal sensitization, which was stated as a secondary outcome in the previous version of the manuscript, since this outcome was only of exploratory nature and not directly related to the primary aim of the study. Additionally, a mixed model analysis with random effect for subject and fixed-effects for the factors, target-controlled-infusion (step 1/step 2/step 3), secondary hyperalgesia areas, pressure pain thresholds, HADS-scores and PCS-scores, is used for the primary outcome.

We consider this study of pivotal importance in the investigation of mechanisms involved in the transition from acute to chronic pain. The protective endogenous opioid system may play a relevant role in the development of persistent post-surgical or post-traumatic pain. Further knowledge on this matter may lead to better pain management strategies.

Sincerely yours,

\[signature\]

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