Effect of High-dose Target-controlled Naloxone Infusion on Pain and Hyperalgesia in Patients Following Recovery from Impacted Mandibular Third Molar Extraction. A Randomized, Placebo-controlled, Double-blind Crossover Study.

Preliminary author list:
Anders H. Springborg M.D.,[1] Lars Pallesen D.D.S.[2] Elisabeth Kjær Jensen M.D., Ph.D.,[1] Linda Panbachi D.D.S.,[2] Troels Riis R.N.,[3] Mads U. Werner M.D., Ph.D.,[1] Bradley K. Taylor, Ph.D.[4]

[1] Department of Anesthesia, Pain and Respiratory Support, Neuroscience Center, Copenhagen University Hospital–Rigshospitalet, DENMARK
[2] Copenhagen Clinic for Oral Surgery, Orthodontics & Implants, Copenhagen, DENMARK
[3] DanTrials, Zelo Phase 1 Unit, Copenhagen University Hospitals-Bispebjerg Hospital, Copenhagen, DENMARK.
[4] Department of Anesthesiology, Pittsburgh Center for Pain Research, and the Pittsburgh Project to End Opioid Misuse, University of Pittsburgh, PA, U.S.A.

Background and aim

It has been hypothesized that endogenous opioids may play an important role in the transition from acute to chronic pain in humans [1-3]. Naloxone, an μ-opioid-receptor (MOR) inverse agonist, has been used in research to study the role of the endogenous opioid system (EOS) in the central processing of pain [4]. In previous studies, administration of high-dose naloxone to rodents has demonstrated a reinstatement of hypersensitivity to noxious stimuli following the resolution of an injury, indicating latent sensitization [1, 2, 5]. The current study investigated whether high-dose naloxone would reinstate clinical pain and hyperalgesia three to four weeks after the resolution of a unilateral, impacted mandibular third molar extraction procedure (TME).

Methods

The *main* study was a randomized, placebo-controlled, double-blind crossover study in healthy male participants with unilateral, primary, uncomplicated TME. Participants were assigned to receive intravenous high-dose naloxone 3.25 mg/kg or inactive placebo (normal saline) by a target-controlled infusion in a randomized order during two separate study days (Days 1 and 2). Day 1 was held 28 days (± 72hrs) after the TME surgery. Day 1 and Day 2 were separated by exactly 7 days. Primary outcomes were pain intensity scores (NRS 0-10) during rest, masticatory activity, and pressure algometry (100 kPa) applied at the skin overlying the surgical area. Secondary outcomes were area of secondary hyperalgesia/allodynia, online reaction time, and ratings by the Clinical Opiate Withdrawal Scale. Outcomes were analyzed by two-way repeated-measures ANOVAs.

A separate post-hoc *validity* study was performed to confirm adequate sensitivity of the assessment methods of the primary outcomes. The validity study was performed immediately before and 24 hrs after a TME procedure. Statistical analyses were done by paired-sample t-tests.

Results

Fourteen participants were included in the *main* study between 15-OCT-2017 and 23-APR-2018. None of the participants reported an area of secondary hyperalgesia/allodynia nor pain at rest at any of the measurement time points at any of the study days. High-dose naloxone administration did not affect any of the outcomes significantly ($P > 0.2$).

Eight participants were included in the *validity* study performed on 26- and 27-NOV-2023. Highly significant increases in pain intensities during resting and dynamic conditions were observed 24 hrs after the TME ($P < 0.001$), indicating adequate sensitivity of the pain assessment methods.

Conclusion

Administration of high-dose naloxone following complete recovery from a TME procedure was not associated with reinstatement of pain clearly contrasting with rodent studies documenting an unmasking effect on latent sensitization after high-dose MOR inverse agonists. While two experimental studies have suggested the presence of latent sensitization in humans [6, 7], the current surgical study does not signal its presence. The findings may indicate that the human dental extraction model involves a level of tissue injury and inflammation insufficient to trigger latent sensitization, or that fundamental differences exist between humans and rodents in the mechanisms underlying the pathophysiologic resolution of tissue injury.

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