

PAIN

Gradual withdrawal of remifentanyl infusion may prevent opioid-induced hyperalgesia[†]

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Abstract

Background: The aim of this study was to examine if gradual withdrawal of remifentanyl infusion prevented opioid-induced hyperalgesia (OIH) as opposed to abrupt withdrawal. OIH duration was also evaluated.

Methods: Nineteen volunteers were enrolled in this randomized, double-blinded, placebo-controlled, crossover study. All went through three sessions: abrupt or gradual withdrawal of remifentanyl infusion and placebo. Remifentanyl was administered at 2.5 ng ml⁻¹ for 30 min before abrupt withdrawal or gradual withdrawal by 0.6 ng ml⁻¹ every five min. Pain was assessed at baseline, during infusion, 45–50 min and 105–110 min after end of infusions using the heat pain test (HPT) and the cold pressor test (CPT).

Results: The HPT 45 min after infusion indicated OIH development in the abrupt withdrawal session with higher pain scores compared with the gradual withdrawal and placebo sessions (both $P < 0.01$. Marginal mean scores: placebo 2.90; abrupt 3.39; gradual 2.88), but no OIH after gradual withdrawal compared with placebo ($P = 0.93$). In the CPT 50 min after end of infusion there was OIH in both remifentanyl sessions compared with placebo (gradual $P = 0.01$, abrupt $P < 0.01$. Marginal mean scores: placebo 4.56; abrupt 5.25; gradual 5.04). There were no differences between the three sessions 105–110 min after infusion.

Conclusions: We found no development of OIH after gradual withdrawal of remifentanyl infusion in the HPT. After abrupt withdrawal OIH was present in the HPT. In the CPT there was OIH after both gradual and abrupt withdrawal of infusion. The duration of OIH was less than 105 min for both pain modalities.

Clinical trial registration: NCT 01702389. EudraCT number 2011-002734-39.

Key words: analgesia, postoperative; analgesics, opioid; hyperalgesia; pain, postoperative; remifentanyl

Opioids are paramount in the treatment of moderate and severe, acute pain and essential in general anaesthesia. The paradox that opioids may increase pain perception and the need for analgesics after end of administration has been studied in the

last decades.^{1–4} The phenomenon is termed opioid-induced hyperalgesia (OIH).^{4–7} OIH is well documented in rodents,^{8,9} and in experimental studies done with healthy volunteers.^{10–12} It has been difficult to demonstrate OIH in clinical trials as a result of

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Editor's key points

- Opioid induced hyperalgesia (OIH) has been shown to occur in the perioperative period.
- Improved understanding is needed of OIH in the clinical setting, to minimize harm.
- The effect of variable reduction in remifentanyl is studied on sensory responses in volunteers.
- Rapid withdrawal of remifentanyl resulted in higher pain scores to heat than gradual withdrawal.
- Further study is needed to direct prevention and management of OIH.

the lack of good models, which eliminate both the problem of OIH masking by slowly eliminated analgesics necessary for post-operative pain relief, and the problem of differentiating between OIH and acute opioid tolerance. However, there are studies showing increased opioid consumption, higher pain scores and larger areas of pinprick hyperalgesia and allodynia near the wound after high-dose opioid infusion in patients.^{1–3 13} The duration of OIH is also debated and varies between the opioids. Fentanyl has led to hyperalgesia for up to ten days post-injection in rodents,^{8 9} while a meta-analysis on the clinical significance of OIH in surgical patients concluded that increased postoperative pain is present for up to 24 h after high-dose remifentanyl infusion.¹⁴

There are many studies on OIH modulation with different adjuvants such as ketamine,^{3 10} clonidine,¹⁵ NSAID,¹² nitrous oxide,¹⁶ propranolol¹¹ and propofol.¹³ However, adjuvants have the disadvantage of possible unwanted effects. A different approach to prevent OIH, such as modulating the administration of the opioid, is therefore of interest. A study on spinal dorsal horns from rats showed that abrupt withdrawal of remifentanyl induced long-term potentiation (LTP) in synapses, whereas a gradual withdrawal did not induce LTP.¹⁷ This is of relevance because opioid withdrawal LTP shares pharmacology and signal transduction pathways with OIH.¹⁷ The effect of gradual withdrawal of remifentanyl infusion on hyperalgesia has not been studied in humans.¹⁸ The main aim of our study was to evaluate the effect of gradual vs abrupt remifentanyl withdrawal on OIH in humans. As a secondary aim we wanted to evaluate the duration of OIH after short-term and low-dose remifentanyl infusion.

Methods

The protocol of this randomized, double-blinded, placebo-controlled, crossover study was approved by the Regional Committee for Medical Research Ethics in South Eastern Norway and The Norwegian Medicines Agency, and conducted in adherence to the guidelines for Good Clinical Practice.¹⁹ The study was registered in www.clinicaltrials.gov (accessed 14 January 2016) (ID: NCT 01702389) and EudraCT (ref: 2011:002734:39).

We obtained written informed consent from the 19 subjects upon inclusion. The subjects were recruited through posters at the University of Oslo and Oslo University Hospital. Exclusion criteria were use of pain medication and complementary medicine, previous substance abuse, chronic illness, participation in other clinical trials the previous six months, and known allergies or serious side-effects to opioids. The subjects were informed not to drink alcohol 24 h before the sessions. Women were not included in the study because of variations in pain sensitivity during menstrual cycle that potentially could confound our findings.²⁰

The subjects were familiarized with the numeric rating scale (NRS) for rating pain from 0 to 10 (0 = no pain, 10 = worst pain imaginable), the heat pain test (HPT)²¹ and the cold pressor test (CPT)²² before the first session. Each subject went through three sessions: abrupt withdrawal of remifentanyl infusion (session A), gradual withdrawal of remifentanyl infusion (session B) and placebo infusion with saline (NaCl 0.9%) (session C). There was a minimum interval of four days between each session. Computer-generated codes stored in sequentially numbered envelopes secured randomization of the sessions. A nurse anaesthetist not participating in the handling or evaluation of the subjects prepared remifentanyl and saline in 50 ml syringes for infusion according to the randomization, thus blinding the investigators and the subjects.

Figure 1 illustrates the experimental setup. In all three sessions two infusion pumps (Orchestra® Base Primea, Fresenius Vial, 38590 Brezins, France) were running simultaneously to ensure the blinding. Infusion time and remifentanyl dose were chosen based on a previous study done by our research group, demonstrating OIH after 30 min infusion of remifentanyl with a target dose of 2.5 ng ml⁻¹.¹² In session A, pump 1 administered remifentanyl until it was stopped abruptly after 30 min, while

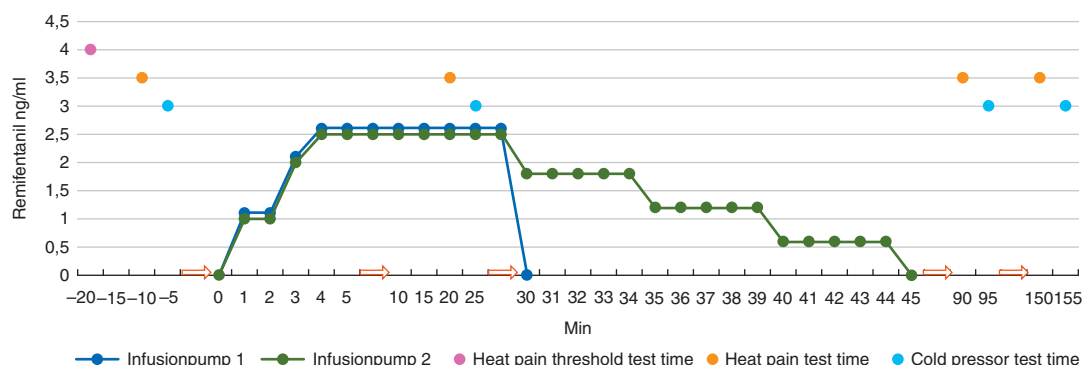


Fig 1 Schematic illustration of the experimental model. A heat pain threshold test was done 20 min before infusions at each session. Baseline pain for cold pressor test (CPT) and heat pain test (HPT) were scored with the numerical rating scale (NRS) 5–10 min before infusions. Pain assessment with HPT and CPT was done 20–25 min into infusion, 45–50 min after end of infusions and 105–110 min after end of infusions. Infusion pump 1 (abrupt withdrawal protocol) and 2 (gradual withdrawal protocol) were started simultaneously. The periods with gradual increase of remifentanyl at start of infusion and the gradual withdrawal period have been accentuated with 1 min intervals.

pump 2 with saline was gradually reduced over an additional 15 min (see detailed explanation under session B). In session B, pump 2 was the active pump administering remifentanyl for 30 min, before gradual withdrawal was done by 0.6 ng ml^{-1} every 5 min for the final 15 min of the infusion. Accordingly, pump 1 contained saline and the infusion was abruptly stopped after 30 min in session B. In session C both pumps contained saline. A saline drip was also connected to make sure no remifentanyl was left in the i.v. set after the pumps were stopped.

The HPT was conducted with heat stimuli applied to the left volar forearm using the computer-controlled Medoc ATS Thermal $3 \times 3 \text{ cm}$ stimulator (Pathway ATS, Medoc LTD, 30095 Ramat Yishay, Israel). Individual heat pain threshold temperatures were determined before each session by a pre-test starting at 32°C , increasing 1°C/s until the subject felt the heat change from heat to pain and pushed a stop button (Fig. 1). A mean threshold temperature for heat pain for the session was calculated from three repeated measurements and the following HPTs started 4°C below this threshold temperature. During the HPTs the phasic heat stimuli ascended with 1°C/s , descended with 8°C/s and time at target temperature was five s. Endpoints were measured as NRS scores after five s exposure to target temperature. To avoid cumulative heat injury a different skin area on the volar forearm was used after a four s rest period between the phasic heat stimuli. Target temperature was increased 1°C for each phasic heat stimuli up to maximum 50°C or stopped if the subject stated a NRS score of seven or higher. The HPTs were applied 10 min before, 20 min into, 45 and 105 min after the infusions (Fig. 1).

The CPT was conducted using a temperature-controlled bath with circulating 3°C water (FP 45-HE Refrigerated/Heating Circulator, Julabo Labortechnik, 77960 Seelback, Germany). The subjects submerged their right hand to the wrist with fingers abducted for up to 90 s. Endpoints were measured as NRS scores every 10 s. The CPTs were applied 5 min after the HPTs (Fig. 1).

During the infusions the subjects were asked about possible opioid adverse effects (nausea, dizziness, pruritus). Non-invasive bp, electrocardiography and pulse oximetry were monitored during the sessions.

Statistical analysis

The sample size was calculated based on results from a previous study conducted by our group,¹² using the sample power program nQuery Advisor 7.0 (Statistical Solutions, Boston MA 02110, USA). A sample size of 16 would have 96% power to detect a difference in means of 0.5 in NRS (e.g. a First condition mean of 6.0 and a Second condition mean of 5.5), assuming a standard deviation of differences of 0.5, using a paired t-test with a 0.05 two-sided significance level.

For heat pain ratings, curve fitting was performed, modelling the stimulus-response function for each subject \times condition \times test, using the power function $\text{NRS} = \alpha(t - 32)^\delta$, where α is a scaling factor, t is the stimulus temperature and δ is the exponent which defines the shape of the stimulus response function. The intercept temperature for which we assume NRS to be zero is 32°C . This function has previously been shown to provide excellent fit for ratings of experimental heat pain, also when responses for individual subjects are analysed.²³ The predicted NRS response for the full temperature range from 36 to 50°C was then computed from the calculated parameters. By this procedure subject responses are directly comparable across the full temperature range, irrespective of whether the full range was completed by all subjects. As an overall index of pain the average

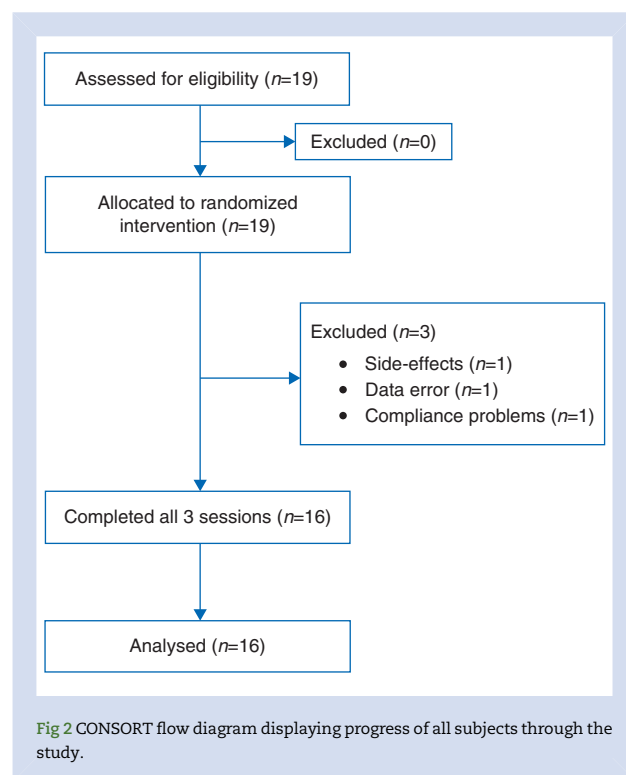
predicted NRS score for the range $36\text{--}50^\circ\text{C}$ was computed for each subject \times condition \times test. These scores formed the basis for further statistical tests. Similarly, curve fitting procedures were carried out for the CPT using the function $\text{NRS} = \alpha(1 - \exp(s^\beta))$. This is a growth to limit function, where parameter α is the asymptote, s is the time in s and β is constrained to be less than zero. As for heat pain, for each subject \times condition \times test the predicted stimulus-response function was computed and the average NRS for the range 0–90 s was calculated as an overall index of pain. All curve fitting was performed with the Levenberg-Marquardt nonlinear least-squares algorithm, implemented in the minpack.lm package for R version 3.0 (www.R-project.org) (accessed 14 January 2016).

The average NRS scores for HPT and CPT were then subjected to separate analyses in linear mixed models with baseline pain, time, condition and the time-condition interaction as fixed effects, and with a random intercept for each study subject in order to incorporate within-subject dependency between observations.²⁴ Statistical comparisons were done using estimated marginal means and unadjusted contrast tests. Robustness analyses were performed for different within-subject covariance structures and residuals were used to check the model assumptions. The statistical analyses were done in Stata v13 and the significance level was set at $P < 0.05$.

Results

We included 19 healthy, male volunteers (Fig. 2 Consort flow diagram). The 16 subjects who completed the study in accordance to protocol had a mean age of 30 (range 18–40 yr), a mean weight of 79 kg (range 54–100 kg), a mean height of 184 cm (range 165–199 cm) and a mean BMI of 23 (range 19.8–31.2 kg m^{-2}).

There were no statistically significant differences between the baseline NRS scores of the sessions during HPT or CPT (data not shown). During infusion the remifentanyl sessions were



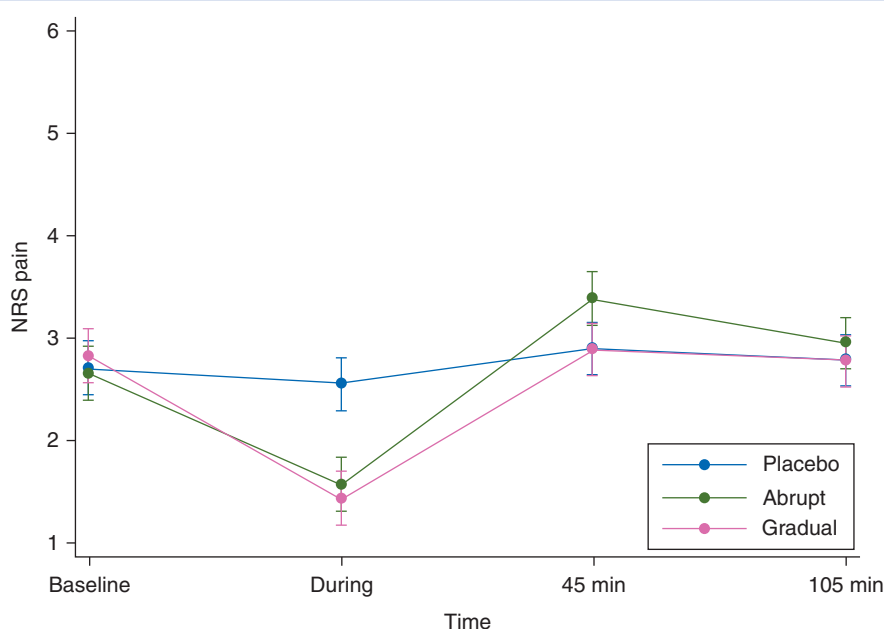


Fig 3 Heat pain test (HPT) pain scores measured 10 min before infusion (Baseline); 20 min into infusion (During); 45 min after end of infusion; 105 min after end of infusion. During infusion no significant difference between gradual and abrupt withdrawal sessions ($P=0.39$), but both remifentanyl sessions were significantly different from the placebo session (both $P<0.01$). Forty-five minutes after end of infusion the abrupt withdrawal session was significantly different from the gradual withdrawal and the placebo sessions (both $P<0.01$), while the gradual withdrawal and placebo session were similar ($P=0.93$). There were no significant differences between the sessions at 105 min after end of infusion (gradual vs placebo $P=0.94$; abrupt vs placebo $P=0.29$; gradual vs abrupt $P=0.26$). CI 95%.

significantly lower in NRS scores compared with the placebo session, indicating analgesic effect of remifentanyl, both when testing with HPT and CPT (Figs 3 and 4). When testing with HPT there was development of OIH 45 min after end of infusion in the abrupt withdrawal session with statistically significant higher NRS scores, compared with both gradual withdrawal and placebo sessions (both $P<0.01$) (Fig. 3). There was no indication of OIH development in the gradual withdrawal session as it was similar to NRS scores in the placebo session ($P=0.93$) (Fig. 3). In the CPT however, we saw evidence of OIH in both remifentanyl sessions, as there were statistically significant higher NRS scores 50 min after end of infusion compared with placebo (gradual vs. placebo $P=0.01$; abrupt vs. placebo $P<0.01$), and there was no significant difference in the OIH effect between the remifentanyl sessions ($P=0.27$) (Fig. 4). At the final assessment with HPT and CPT a 105 and 110 min after end of infusion there were no significant differences in the NRS scores for the remifentanyl sessions compared with the placebo session (Figs 3 and 4).

Discussion

We found that abrupt withdrawal of remifentanyl infusion resulted in OIH 45–50 min after the end of infusion, as assessed by both HPT and CPT. After gradual withdrawal of infusion we found OIH when testing with CPT, but there was no evidence of OIH in the HPT, as the NRS scores were similar to the placebo session at 45–50 min after end of infusion. The duration of OIH from remifentanyl seems to be brief, as we found NRS scores in the remifentanyl sessions to be similar to placebo when testing with HPT and CPT at 105–110 min after end of infusion.

Several possible peripheral and central mechanisms which involve opioid receptors, TRPV1, cytokines, NMDA receptors,

NK-1 receptors, 5-HT₃ receptors and cholecystokinin may take part in the development of primary hyperalgesia after opioid infusion.^{5,7} An interesting cellular model for pain amplification and hyperalgesia after opioid withdrawal is long-term potentiation (LTP) of synaptic strength in nociceptive pathways. Opioid withdrawal LTP is described as: “a brief application of remifentanyl *in vivo* leads to acute depression of synaptic strength in C-fibers. Upon withdrawal synaptic strength not only quickly returns to normal, but becomes potentiated for prolonged periods of time.”²⁵ A study on spinal dorsal horns from rats showed that withdrawal LTP may be prevented by tapering of the remifentanyl infusion instead of abrupt withdrawal.¹⁷ Our HPT findings support this in humans, as we found significant OIH after abrupt withdrawal of remifentanyl infusion, but not after gradual withdrawal of the infusion. We did not find the same result when testing with CPT as the subjects developed OIH in both the abrupt and gradual withdrawal sessions. A possible explanation for this discrepancy between the pain models, is the persisting problem of finding a valid experimental pain model for clinical pain. This problem has been evident in other studies testing OIH with different experimental pain modalities.^{10,11,26} OIH seems to be modality-sensitive, thus the effects from opioids when using one pain modality test cannot be extrapolated to another.²⁷ It should be noted that negative findings in one pain modality does not rule out an effect in another. Experimental pain models are poorly correlated and it is still unclear which experimental models best reflect clinical pain conditions.^{27,28}

As a larger skin surface area of the hand was exposed to cold water than by the 3×3 cm heat thermode, the CPT would lead to greater spatial summation than the HPT. Thus, the CPT may have activated endogenous pain mechanisms stronger than the HPT, and led to increased painfulness of the cold pressor stimuli and

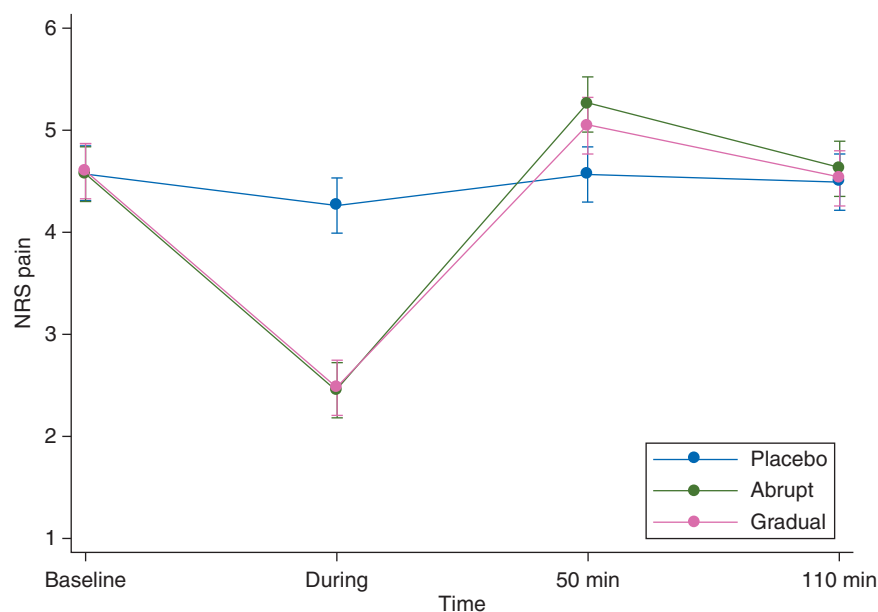


Fig 4 Cold pressor test (CPT) pain scores measured 5 min before infusion (Baseline); 25 min into infusion (During); 50 min after end of infusion; 110 min after end of infusion. During infusion no significant difference between gradual and abrupt withdrawal sessions ($P=0.90$), but both remifentanyl sessions were significantly different from the placebo session (both $P<0.01$). Fifty minutes after end of infusion both the gradual and abrupt withdrawal sessions were significantly different from the placebo session (gradual vs placebo $P=0.01$; abrupt vs placebo $P<0.01$), but similar to each other ($P=0.27$). There were no significant differences between the sessions a 110 min after end of infusion (gradual vs placebo $P=0.83$; abrupt vs placebo $P=0.47$; gradual vs abrupt $P=0.61$). CI 95%.

higher pain ratings.²⁹ Also, suprathreshold cold pain is mainly conveyed by receptors in cutaneous vein walls, which become highly stimulated by the return of cooled venous blood from the fingers, thereby affecting the vasomotor regulation of finger arteries which could influence pain during the CPT.²⁹ One could speculate that endogenous pain modulation mechanisms such as spatial summation and vasomotor reactions led to more negative skewness of pain rating in the CPT, but not in HPT, explaining the divergence between our results.

The investigators were not equally blinded to the sessions as remifentanyl effects were evident in all subjects in both remifentanyl sessions, but not the placebo session. However, it was not possible to distinguish between the remifentanyl sessions as there was no discernible difference in effects, even after the end of infusions.

Exactly how gradual withdrawal of remifentanyl infusion can prevent OIH is not clear. At a cellular level it has been shown that μ -opioid receptors (MOR) internalize into endosomes upon exposure to exogenous receptor agonists,³⁰ and this process takes place rapidly with remifentanyl.³¹ To our knowledge the time course of MOR recycling back to the plasma membrane has only been examined for the synthetic μ -opioid agonist DAMGO.³⁰ As internalization occurs rapidly upon remifentanyl exposure, one could speculate that abrupt withdrawal likewise leads MOR to re-emerge rapidly to the membrane, thus exposing an abundance of receptors simultaneously and resulting in hyperalgesia. As endogenous opioids do not take effect through the same mechanisms, but target MOR at a presynaptic level or via delta-opioid receptors (DOR),³⁰ it is possible the endogenous system has insufficient time to adjust to a rapid release of MOR from cytosol after abrupt remifentanyl withdrawal. With gradual withdrawal of remifentanyl the release of MOR might be slower,

allowing endogenous anti-hyperalgesic systems time to adapt. Another possible explanation is an effect via DOR which is shown to participate in remifentanyl-induced hyperalgesia.³² A gradual withdrawal of remifentanyl may allow some kind of adaptation of membrane DOR that prevents hyperalgesia.

A recent review on remifentanyl and OIH discusses to what extent the phenomenon occurs clinically, as OIH is found in some clinical studies, while other studies fail to find any significant effects in a clinical setting.³³ Another recent meta-analysis could not test if mode of withdrawal was a predictive factor for remifentanyl-induced hyperalgesia because of insufficient data.¹⁴ Thus, with the findings in our present study we pose the question if different practices in remifentanyl withdrawal have contributed to the variable expression of OIH in previous studies.

In our study it is noteworthy that the total dose of remifentanyl and administration time in session A and B were not identical, because gradual withdrawal required 15 min longer infusion time. However, as the gradual withdrawal session received the larger total dose, one could expect an even stronger impact of OIH in this session, which was not the case. It could also be questioned if a residual effect of a very low dose remifentanyl influenced the post-infusion measurements in the gradual withdrawal session, as the infusion in the gradual withdrawal session ended 15 min later than the infusion in the abrupt withdrawal session. We consider this unlikely as remifentanyl elimination half-life is three to five min,³⁴ thus the plasma concentration would have been reduced by more than 99% 30 min after the end of administration and our first post-infusion measurement was done 45–60 min after the end of active drug infusion (gradual and abrupt withdrawal respectively).

Our results on the duration of OIH add further support to previous studies in humans.¹⁴ Our subjects returned to baseline

NRS 105–110 min after the end of this short-lasting, low-dose infusion in both pain modalities. This indicates that remifentanyl-induced hyperalgesia may be relevant for the first postoperative hours in a clinical setting. However, the duration and magnitude may be different with longer administration periods, higher infusion rates or larger total doses of remifentanyl, which should be investigated further.¹⁴

The effect of gradual withdrawal of remifentanyl infusion remains to be studied in a clinical setting. If confirmed, gradual remifentanyl withdrawal is easy to implement and an inexpensive way to prevent postoperative OIH, while also avoiding side-effects from adjuvants and other OIH associated complications, such as need for increased rescue analgesics.

In conclusion we found no development of OIH after gradual withdrawal of remifentanyl infusion as opposed to abrupt withdrawal when we used HPT as a pain model. We did not find the same results when testing with CPT. The duration of OIH from a short-lasting, low-dose infusion of remifentanyl was less than 105 min after the end of infusion. We regard our findings as an incentive to study the effect of gradual remifentanyl withdrawal on OIH in a clinical setting with postoperative patients.

Authors' contributions

Study design/planning: M.C., J.R., A.S., T.D., H.L.

Study conduct: M.C., J.R., T.D., H.L.

Data analysis: M.C., H.L., C.S.N.

Writing paper: M.C.

Revising paper: all authors

Declaration of interest

None declared.

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