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REVIEW

Remifentanil-induced postoperative hyperalgesia: current perspectives on mechanisms and therapeutic strategies

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Abstract: The use of remifentanil in clinical practice offers several advantages and it is used for a wide range of procedures, ranging from day-surgery anesthesia to more complex procedures. Nonetheless, remifentanil has been consistently linked with development of opioid-induced hyperalgesia (OIH), which is described as a paradoxical increase in sensitivity to painful stimuli that develops after exposure to opioid treatment. The development of OIH may cause several issues, delaying recovery after surgery and preventing timely patient's discharge. Moreover, it causes patient's discomfort with higher pain scores, greater use of analgesics, and associated side effects. Remifentanil is the opioid most convincingly associated with OIH, and hereby we provide a review of remifentanil-induced hyperalgesia, describing both the underlying mechanisms involved and the available studies investigating experimental and clinical pharmacologic approaches aiming at reducing its incidence and degree.

Keywords: opioid-induced hyperalgesia, pain, opioid consumption, opioid tolerance

Introduction

The aim of this review is to provide an updated knowledge on the relationship between the use of remifentanil in clinical practice and the development of opioid-induced hyperalgesia (OIH). Although remifentanil offers several advantages from clinical perspectives during both the intraoperative and the immediate postoperative period, its pharmacokinetic and pharmacodynamic unique characteristics have been linked with the development of OIH. The occurrence of hyperalgesia may slower patient's recovery after surgery, preventing a timely discharge and also causing discomfort not only through higher pain scores, but also with greater amount of analgesics and side effects related to their administration. A recent meta-analysis including 27 studies and almost 1500 patients found that high intraoperative doses of remifentanil are associated with small but significant increases in acute pain at 4 and 24 hours after surgery, and also with higher morphine requirements after the first postoperative day.[1]

OIH is described as a phenomenon occurring in patients treated with opioids, causing a subsequent paradoxical increase in sensitivity to painful stimuli. Such occurrence could be described as hyperalgesia, allodynia, or both. A dilemma faced by clinician is to distinguish OIH from other phenomena such as acute opioid tolerance (AOT) or opioid withdrawal. More importantly, research has often investigated surrogate markers of OIH such as increased pain intensity scores and opioid consumption at variable time-points, rather than clearly distinguishing OIH from the other phenomena linked to need for opioids. This has also contributed to difficulties in comparing available data and in a heterogeneous literature.

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We provide a review of OIH focusing mainly on remifentanil, summarizing the evidence on the mechanisms involved in OIH and of the available studies investigating specific therapies aimed at reducing the incidence and degree of OIH.

Remifentanil: an opioid with unique properties

Remifentanil is a very potent and ultra-short-acting opioid drug widely used for general anesthesia and also for sedation in the intensive care unit. Indeed, remifentanil has structurally unique pharmacokinetic properties, allowing for a fast onset of action and a predictable rapid recovery, which, importantly, is independent of the duration of its infusion. Remifentanil is ~100–200 times more potent than morphine, and its half-life remains in the range of few minutes, without accumulation even after prolonged infusion.[2] For these characteristics, its use is recommended only as continuous infusion. The drug is metabolized through ester linkage susceptible to hydrolysis by nonspecific plasma and tissue esterases, and it is not affected by pseudocholinesterase deficiency. Therefore, remifentanil can be safely used in patients with renal and/or hepatic disease. Apart from the rapid metabolism in patients that may present issues with opioid clearance, there are several clinical advantages of conducting anesthesia with continuous opioid (remifentanil) infusion. In fact the avoidance of opioid boluses allows to decrease the fluctuations of both hemodynamic conditions and of anesthesia/analgesia depth. However, among the clinically available opioids, only remifentanil does not accumulate with prolonged intravenous infusion, while such accumulation develops in various degrees for all the other opioids (ie, morphine, fentanyl, sufentanil). Therefore, remifentanil offers the best profile for continuous infusion, allowing the rapid modulation of anesthesia/analgesia depth according to surgical stimulation and decreasing hemodynamic fluctuations consequent to opioid boluses. The rapid offset of remifentanil allows a faster recovery from anesthesia with quick regaining of consciousness and shorter time to extubation,[3,4] translating into a more efficient operating theater use and reduced length of stay in the recovery room.[5] Thus, remifentanil seems ideal for intervention of short duration and indeed it is highly used during "day-surgery" procedures. For instance, anesthesia for outpatients ("day surgery") requires high-quality sedative-analgesic effects, together with a rapid recovery or maintenance of protective airway reflexes, and a fast restoration of cognitive and psychomotor functions after the procedure. Moreover, several brief procedures (ie, electroconvulsive therapy) require intraoperative analgesia, but they do not ordinarily result in postoperative pain.[6] In all these settings, anesthesia conducted with remifentanil infusion may offer extraordinary clinical advantages and we describe few examples. During elective septorhinoplasty, remifentanil has shown quicker emergence from anesthesia as compared to fentanyl,[7] and similarly during dental[8] or endoscopic[9] procedures. Remifentanil administration by target-controlled infusion is effective and safe in the reduction of pain intensity during ambulatory procedure (ie, extracorporeal lithotripsy).[10] Sedation with remifentanil has shown some advantages over dexmedetomidine during flexible bronchoscopy, resulting in a shorter time to recovery.[11] In a population of children undergoing bone marrow aspiration, remifentanil offered analgesic advantages over alfentanil during the procedure.[12]

Currently, remifentanil is also largely used in more complex procedures and patients. In a systematic review in critically ill patients including 23 randomized controlled studies, remifentanil as compared with other opioids was associated with decreased duration of mechanical ventilation, time to extubation, and intensive care length of stay. Nonetheless, the authors reported no significant differences with regard to hospital stay, costs, mortality, or agitation.[13] Another challenging setting where remifentanil has shown a safe profile is in patients undergoing cardiac surgery, where remifentanil offers stable operating conditions and facilitates rapid tracheal extubation, representing a valid option for fast-track cardiac anesthesia protocols.[14] Remifentanil is a valid option during neurosurgery too. In elective surgery of supratentorial lesions, it appears as a reasonable alternative to fentanyl, providing faster recovery and decreasing the need for intraoperative propofol, with similar incidence of postoperative nausea and vomiting.[15] Interestingly, the use of remifentanil has been studied also in morbidly obese patients undergoing laparoscopic gastric banding, with the aim of investigating its effects on postoperative analgesia, recovery, and pulmonary function tests, as compared with sufentanil.[16] Despite better hemodynamic stability offered by remifentanil, the recovery from anesthesia and the spirometry values showed no significant between-group differences. Indeed, not all the studies are in concordance with the advantages of remifentanil anesthesia, and occurrence of greater postoperative pain is a commonly reported concern, which is under serious investigation. A multicenter study showed that neurosurgical patients receiving sufentanil–propofol anesthesia had reduced analgesic requirements and a better postoperative cognitive function than those who received remifentanil–propofol combination.[17] The abovementioned

study on bariatric patients demonstrated a higher early (first two postoperative hours) cumulative morphine consumption in the remifentanil group as compared to sufentanil, although this difference disappeared afterwards.[16] A recent study in cardiac surgery patients compared patients treated with remifentanil infusion with those receiving fentanyl boluses. The authors found not only higher morphine consumption at 24 and 48 hours in the remifentanil group, but also increased thoracic pain and analgesic requirements until 3 months after surgery, although such difference was not detectable at 1 year after surgery. Interestingly, this effect was more pronounced in younger patients and in those receiving a higher dose of remifentanil.[18] Another observational study showed worse patient-reported outcomes (higher "worst pain" and lower satisfaction with pain control) after thyroidectomy when they received remifentanil as compared with patients receiving fentanyl as intraoperative opioid.[19] Such and other studies highlight the importance of adopting strategies to decrease the risk of remifentanil-induced hyperalgesia (RIH), from the avoidance of high doses of remifentanil to the implementation of drugs specifically targeting the mechanisms of OIH/RIH.

Mechanisms of OIH

Before describing the current knowledge on experimental and clinical studies aiming at blunting the occurrence of OIH, it is worth to summarize the available evidence on the mechanisms of OIH.

First of all, it is important to distinguish hyperalgesia from allodynia. These two are different concepts with different definitions and mechanisms: allodynia is the pain evoked by a stimulus that does not usually provoke pain, whereas hyperalgesia represents an increased pain response from stimuli that usually provoke pain.[20] Such symptoms are prominent in patients with neuropathic pain, and both are seen in various peripheral neuropathies and central pain disorders, affecting 15%–50% of patients with neuropathic pain.[20] Allodynia and hyperalgesia can be classified according to the sensory modality (touch, pressure, pinprick, cold, and heat) used to elicit sensation. Peripheral sensitization and maladaptive central changes contribute to the generation and the maintenance of these reactions, with separate mechanisms in different subtypes of allodynia and hyperalgesia. Three types of mechanical allodynia and hyperalgesia are usually described: dynamic mechanical allodynia evoked by light touch; punctate allodynia and hyperalgesia evoked by punctate skin stimulation with a pin; and static allodynia and hyperalgesia provoked by pressure to skin or deep tissue.[20]

With regard to the postoperative period, hyperalgesia results in higher opioid consumption and increased pain sensibility, causing discomfort in patients and exposing him/her to side effects and also to longer-than-expected hospital stay. Although opioids are among the strongest drugs for pain relief and are widely used both for acute and chronic pain, there is clear evidence that these molecules may enhance pain sensation at later stage, especially when administered acutely and in high doses.[21] Hyperalgesia is distinguished as primary and secondary. Primary hyperalgesia occurs as a response to a noxious stimulation, such as trauma or surgical incision, and arises from peripheral nociceptor sensitization. Primary hyperalgesia is limited to the area of the insult. On the other side, secondary hyperalgesia usually manifests far from the damaged area and is thought to derive from central sensitization to pain.[22] Hyperalgesia caused by opioid treatment represents a form of secondary hyperalgesia, and it is associated with diffused nociceptive sensitization induced by the exposure to the drug.[23] Following a sensitization of opioid-signaling pathways,[24] OIH results in generalized hypersensitivity to pain stimuli, which is not necessarily located at the source of insult or disease,[25] but it can involve distant sites. Allodynia and/or hyperalgesia are both symptoms of OIH, but one should keep in mind that such symptoms are also present in case of AOT or acute opioid withdrawal (AOW). It is clinically difficult to distinguish these three phenomena.[25] Indeed, OIH, AOT, and AOW describe distinct phenomena sharing several common symptoms. AOT represents the desensitization of pain-signaling pathways to opioids so that exposure to the drug gradually produces less receptor activation and thus lower pain relief.[24] Both phenomena, OIH and AOT, can result from acute and long-term exposure to opioids and they clinically translate into an increased opioid requirement.[26] However, quantitatively measured pain sensitivity remains unaltered with AOT, whereas OIH is characterized by gradual hypersensitivity and reduction of pain thresholds.[27] The other condition that should be distinguished from OIH is AOW. In both cases there is a need for higher opioid doses. The abrupt discontinuation of opioids can result in AOW and its symptoms are typically seen in the inpatient setting. The initial withdrawal symptoms are not limited to pain but include also neurovegetative manifestations, such as agitation, anxiety, dysphoria, insomnia, and also temperature instability; such acute manifestations make more easy the differential diagnosis with OIH. On the other side, symptoms of chronic AOW may be more similar to OIH because neurovegetative response is more blunted. In

truth, the distinction between AOT, OIH, and AOW is more theoretical than practical and it remains very difficult, if not impossible, in clinical practice.

Even though several mechanisms participating in the development of secondary hyperalgesia – and thus OIH – have been described, their single quantitative contribution to the phenomenon of OIH/RIH remains still unclear.[28] Central sensitization of nociceptive pathways results in reduced pain thresholds, which is characteristic of OIH.[29] One mechanism causing central sensitization is the suppressed reuptake or the increased release of excitatory neurotransmitters (glutamate and aspartate). The N-methyl-D-aspartate (NMDA) receptor and its ligands glutamate and aspartate are critical for neuroplasticity, long-term potentiation, learning, and memory, and are also thought to play an important role in the development of OIH.[26] In particular, NMDA receptors in the spinal dorsal horn and rostroventral medulla have been linked to OIH.[30,31] In addition to central sensitization at spinal level, pain can also be potentiated by the descending pain modulatory system. This system includes the periaqueductal gray matter, the nucleus raphe magnus, and also adjacent structures to the rostral ventromedial medulla, all projecting to the spinal dorsal horn along the dorsolateral funiculus. Such projections can produce either inhibitory or facilitating nociceptive effects.[32] Recently, it has been found that remifentanil infusion downregulates μ-opioid receptors in the periaqueductal gray; this effect seems preventable by blocking the "neuron-restrictive silencer factor" (a regulator of μ-receptor expression), which could become a potential target in the prevention/treatment of OIH in future studies.[33]

Also, neuro-immune mechanisms (microglial activation) seem involved in OIH. Microglia and astrocytes are certainly activated by chronic opioid use and, on the other hand, their inhibition seems to reduce OIH and AOT.[34,35] It seems that OIH, but not AOT, is dependent on microglial activation at the spinal dorsal horn level,[36] and in a rat model of microglial cell culture, Mika et al showed that μ- and κ-receptors are responsible of this process.[37] Other studies have suggested that morphine can play a role in activating microglia through Toll-like receptor 4,[35,38] and antagonizing this receptor activity may be another target for blunting the development of hyperalgesia, although other authors found that microglial activation is independent of Toll-like receptor 4.[39] Finally, one study suggested a crucial role for peripheral μ-receptor on primary afferent nociceptors for the development and maintenance of both OIH and AOT.[40]

Strategies for prevention of opioid (remifentanil)-induced hyperalgesia

As highlighted before, there are several mechanisms contributing to OIH/RIH, and the balance between such mechanisms is not completely understood. Among them, modulation of NMDA receptor, cyclooxygenase (COX) enzyme, voltage-dependent calcium channel, and adenosine and adrenergic receptors are the most studied pathways, and we discuss them briefly in this paragraph, summarizing experimental and clinical evidence and the strategies with regard to the modulation of OIH, specifically focusing on remifentanil.

There are evidences that glutamate release and NMDA receptors activation may be one of the more important key players in the development of OIH. Animal experiments suggest that antagonists of the NMDA receptors inhibit the development of OIH.[41,42] For instance, the role of the NMDA receptor in the development of opioids tolerance and hyperalgesia has been demonstrated by Shimoyama et al in a rat model. The authors showed that the administration of 18-mer phosphodiester antisense oligo-deoxy-nucleotide interrupts the upregulation of NMDA receptor with consequent anti-hyperalgesic effect.[43] However, whether the administration of NMDA receptor antagonists is effective in preventing OIH/RIH in the postoperative period and in reducing opioid tolerance remains controversial, because results from human clinical study are grossly inconsistent. For instance, Joly et al demonstrated that a small dose of ketamine led to reduced postoperative opioid consumption and hyperalgesia in patients undergoing major abdominal surgery.[44] Conversely, Engelhardt et al found no differences in pain scores or in postoperative opioid consumption when low-dose ketamine was used intraoperatively in the setting of scoliosis surgery.[45] A more recent prospective randomized double-blind clinical study conducted by Leal et al studied the addition of ketamine (5 μg/kg/min) to remifentanil in patients undergoing laparoscopic cholecystectomy and found no changes in OIH at incisional level nor differences in opioid consumption or cytokine concentrations, although there were differences in pain intensity at distant site from surgical insult.[46]

Another drug tested in clinical studies is buprenorphine, a partial opioid receptor agonist with peculiar characteristics (partial μ-receptor agonist and k- and δ-receptor antagonist). Buprenorphine has shown to reduce RIH in human pain model of electrically induced pain,[47] and possible explanations for its antihyperalgesia effects are both k-receptors antagonism and downregulation of δ-receptors.[48] A recent study demonstrated that perioperative low-dose buprenorphine infusion decreases postoperative hyperalgesia and

reduces the hyperalgesic area following major thoracic surgery,[22] thus highlighting the need for further research.

Magnesium sulfate has been investigated as a possible intervention to decrease OIH/RIH. Indeed, the prevention of phosphorylation of the NMDA receptor subunit NR1 as well as the blockade of NR2B subunit by magnesium may offer theoretical therapeutic opportunities. From clinical perspectives, Lee et al reported that a high-dose (80 mg/kg) magnesium infiltration at the incisional wound reduced OIH after laparoscopic prostatectomy;[49] similar results have been shown with a lower (30 mg/kg) magnesium bolus followed by infusion at 10 mg/kg/hour in patients undergoing thyroidectomy.[50] However, it should be noted that the latter study showed benefits of magnesium treatment only when used in patients receiving high doses of remifentanil, whereas no differences were found in the group receiving lower remifentanil doses.

Prostaglandins stimulate glutamate secretions from the dorsal horns of the spinal cord with activation of NMDA receptors, and antagonism at this level can be achieved with COX inhibition. Both COX-1 and -2 enzymes are present in the spinal cord and both seem to play a role in the development of hyperalgesia, although the effects of COX-2 enzyme may be prominent. An experiment of electrically induced and cold-pressor pain conducted on healthy volunteers showed the development of hyperalgesia after remifentanil infusion.[51] In this crossover study, pretreatment with both parecoxib and ketorolac reduced the postinfusion area of hyperalgesia, but selective COX-2 inhibition (parecoxib) had greater effects than COX-1 inhibition (ketorolac) in reducing the area of hyperalgesia. Thus, it is possible that systemic administration of COX inhibitors reduces RIH by a direct action at spinal cord level. Notwithstanding, in a pain model of capsaicin-induced hyperalgesia after a moderate dose of remifentanil, Eisenach et al tested the effects of intrathecal ketorolac on 30 healthy volunteers; in contrast with their hypothesis, prostaglandin levels were not increased during OIH and nonselective intrathecal COX inhibition did not reduce hyperalgesia.[52]

Gabapentin is a γ-aminobutyric acid (GABA) analog commonly used both as an anticonvulsant drug and for the treatment of neuropathic pain.[53] However, its mechanism of action does not involve binding to GABA receptors nor direct GABAergic actions.[54] Indeed, gabapentin regulates neurotransmitter release binding the *α2δ* subunit of the voltage-dependent calcium channel,[55] inhibiting Ca^{2+} influx and decreasing noradrenaline release in rat neocortex.[56] There are reports of gabapentin's role in the reduction of hyperalgesia,[57,58] and a recent review concluded that gabapentin diminishes the propagation of pain signals along afferent neurons, also stimulating an anti-inflammatory activity at spinal neuron level.[59] Pregabalin, another GABA analog, has a more rapid onset and a more linear pharmacokinetics as compared with gabapentin.[60] A preoperative pregabalin dose of 300 mg given to patients undergoing laparoendoscopic urologic surgery showed a reduction in hyperalgesia around the incisional area.[61] Nonetheless, Gustorff et al failed to demonstrate antihyperalgesic effects of gabapentin in a pain model at skin level (sunburn) in healthy volunteers.[62]

Adenosine is an endogenous purine nucleoside that modulates neuronal and non-neural cellular functions. Cellular signaling by adenosine occurs through four known receptor subtypes (A1, A2A, A2B, A3), and adenosine is mainly used as an antiarrhythmic agent.[63] However, adenosine also modulates central and peripheral nociception, activating the A1 receptor with antinociceptive effects in a mice model of inflammatory and neuropathic pain.[64] Analgesic properties and opioid-sparing effects of adenosine in the perioperative period have been described in humans too.[65,66] Lee et al compared an intraoperative infusion of adenosine (80 μg/kg/min) versus placebo, as adjunct to anesthesia conducted with sevoflurane and remifentanil, demonstrating a reduction of AOT and OIH in the adenosine group.[67] However, a recent meta-analysis including over 750 patients from nine studies concluded that the overall postoperative pain score and opioid requirements are not reduced by adenosine. The group of patients treated with adenosine had significantly reduced systolic blood pressure, warranting some cautions in regard to its cardiovascular effects. Nonetheless, a small subgroup analysis including patients receiving remifentanil showed that adenosine may reduce postoperative pain at 4 hours after surgery, although this result warrants lots of caution because it comes from just two small studies.[68]

Dexmedetomidine is a highly selective α_2-adrenergic receptor agonist primarily used for sedation in the intensive care setting, but it use is spreading to anesthesia too. This drug determines sedation with no respiratory depression and also has mild analgesic properties.[69] Systemic administration of dexmedetomidine enhances analgesic effects of opioids and reduces opioid requirements in the perioperative period.[70,71] An antihyperalgesic effect of dexmedetomidine, linked to the reduction in NMDA-mediated synaptic transmission at spinal level, has been suggested.[72] In an animal model, Zheng et al demonstrated that dexmedetomidine attenuates RIH, reducing the phosphorylation of NMDA receptor NR2B subunit in spinal cord,[72] and similar results have been

reported in another animal experiment.[73] Therefore, it seems that dexmedetomidine may be an option to improve pain control for OIH patients, as suggested in a small case series describing the clinical utility of dexmedetomidine in 11 patients who have developed OIH.[74] Lee et al conducted the only clinical study on humans published so far evaluating the antihyperalgesia effects of dexmedetomidine, randomizing patients into three groups: placebo with low-dose remifentanil (0.05 μg/kg/min) and placebo or dexmedetomidine combined with high-dose remifentanil (0.3 μg/kg/min). The authors concluded that dexmedetomidine infusion efficiently alleviated RIH symptoms and increased the hyperalgesia threshold around the surgical incision 24 hours after surgery.[75] A similar effect on the reduction of RIH has been reported for clonidine, another less selective α2-agonist.[76] Not only α-receptor, but also β-signaling seems involved in OIH. In particular, genetic investigation suggests that β-adrenergic receptors are associated with OIH. Collard et al reported that intraoperative esmolol infusion (5–15 μg/kg/min) is effective in postoperative opioid sparing.[77] Chu et al also found that nonselective β-adrenergic receptor antagonist like propranolol modulates RIH in humans, in particular reducing the hyperalgesic skin area.[78]

Propofol is the most commonly used intravenous anesthetic drug and inhibits NMDA receptor; for such reason, it is theoretically possible that propofol infusion attenuates RIH. Clinically relevant interactions of propofol and remifentanil in humans have been described,[79] at the same time with pro- and antinociceptive effects. Indeed, propofol, although attenuating the intensity of remifentanil-induced antianalgesia in humans, led also to enlarged areas of secondary hyperalgesia. Another anesthetic agent, nitrous oxide (N_2O), has shown NMDA antagonist effects,[80] and animal experiments hypothesized that exposure to N_2O may reduce OIH.[81] A randomized human study demonstrated that 70% N_2O gas mixture during propofol–remifentanil anesthesia reduced postoperative RIH as determined by touch sensitivity test (von Frey filaments).[82]

Withdrawal

As previously reported, there are many trials on OIH modulation with different adjuvants, but each of them have the disadvantage of possible side effects (adenosine, beta-blockers, ketamine, and so on), and not for all of them is available an intravenous formulation (gabapentin, pregabalin). A slice preparation from rat spinal dorsal horn showed that abrupt withdrawal of remifentanil induced long-term synaptic potentiation, whereas a gradual withdrawal did not. Recently, Camelon and coworkers studied the effect of withdrawal of remifentanil infusion on RIH in humans, and they found no RIH after gradual withdrawal of remifentanil infusion as opposed to abrupt withdrawal, when a heat pain test was administered. Furthermore, the onset of OIH started after 45 min after the infusion was stopped, with a duration that lasted <110 min.[83] This may indicate that in some cases RIH might be relevant just for the first postoperative hours. On the other hand, there are reports of increased pain sensitivity even up to 3 months after remifentanil-based anesthesia. It is likely that these results may be directly correlated to the dose and length of administration as well as with the approach for remifentanil withdrawal. If confirmed in larger clinical trials, tapering of remifentanil infusion could be an easy and inexpensive way to prevent postoperative OIH.

In summary, remifentanil is a unique opioid drug, offering several clinically relevant advantages over other opioids. Nonetheless, the development of OIH is a well-established risk of remifentanil infusion especially when the drug is used for long periods and at a high dosage. In this context, it seems highly desirable to perform large-scale prospective randomized trials in order to find the best alternatives for attenuating OIH/RIH. It is the authors' opinion that it would be ideal to use a standardized clinical approach for diagnosing and measuring OIH, and to conduct such studies with a multicenter strategy. Indeed, small single-center studies are often biased by local protocols and practice, and more importantly by lower sample sizes that increase the risk of both alpha and beta statistical error (falsely rejecting or accepting the null hypothesis, respectively). While more research is needed to establish the usefulness of the abovementioned strategies during remifentanil anesthesia in order to reduce occurrence, duration, and intensity of RIH, the most reasonable anesthesiologic approach seems to limit the intraoperative doses of remifentanil, especially in the case of prolonged infusions, and to perform gradual withdrawal with superimposed multimodal analgesia.

Summary

- Remifentanil has unique pharmacologic properties as compared with other opioids, offering several clinical advantages.
- Remifentanil is the opioid with the highest reported incidence of OIH.
- The development of hyperalgesia slowed recovery after surgery, preventing the patient's discharge and causing discomfort.

- Several drugs have been proposed in order to reduce hyperalgesia, but the evidence is still inconsistent and mostly arising from small single-center studies.
- More research is needed, possibly performing large-scale randomized trials with a standardized clinical approach for diagnosis and measurement of hyperalgesia.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth.* 2014;112(6):991–1004.
2. Remifentanil (FDA Approved Labeling Text). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/20630se5-005_ultiva_lbl.pdf. Accessed January 20, 2018.
3. Dahaba AA, Grabner T, Rehak PH, List WF, Metzler H. Remifentanil versus morphine analgesia and sedation for mechanically ventilated critically ill patients: a randomized double blind study. *Anesthesiology.* 2004;101(3):640–646.
4. Davis PJ, Finkel JC, Orr RJ, et al. A randomized, double-blinded study of remifentanil versus fentanyl for tonsillectomy and adenoidectomy surgery in pediatric ambulatory surgical patients. *Anesth Analg.* 2000;90(4):863–871.
5. Philip BK, Scuderi PE, Chung F, et al. Remifentanil compared with alfentanil for ambulatory surgery using total intravenous anesthesia. The Remifentanil/Alfentanil Outpatient TIVA Group. *Anesth Analg.* 1997;84(3):515–521.
6. Takekita Y, Suwa T, Sunada N, et al. Remifentanil in electroconvulsive therapy: a systematic review and meta-analysis of randomized controlled trials. *Eur Arch Psychiatry Clin Neurosci.* 2016;266(8):703–717.
7. Coskun D, Celebi H, Karaca G, Karabiyik L. Remifentanil versus fentanyl compared in a target-controlled infusion of propofol anesthesia: quality of anesthesia and recovery profile. *J Anesth.* 2010;24(3):373–379.
8. Lacombe GF, Leake JL, Clokie CM, Haas DA. Comparison of remifentanil with fentanyl for deep sedation in oral surgery. *J Oral Maxillofac Surg.* 2006;64(2):215–222.
9. Sultan SS. Patient-controlled sedation with propofol/remifentanil versus propofol/alfentanil for patients undergoing outpatient colonoscopy: a randomized, controlled double-blind study. *Saudi J Anaesth.* 2014;8(Suppl 1):S36–S40.
10. Fouladi A, Soleimani A. Comparison of different analgesic techniques for pain relief during extracorporeal shock wave lithotripsy: a double-blind, randomized clinical trial. *Acta Inform Med.* 2017;25(2):94–98.
11. Ryu JH, Lee SW, Lee JH, Lee EH, Do SH, Kim CS. Randomized double-blind study of remifentanil and dexmedetomidine for flexible bronchoscopy. *Br J Anaesth.* 2012;108(3):503–511.
12. Antmen B, Sasmaz I, Birbicer H, et al. Safe and effective sedation and analgesia for bone marrow aspiration procedures in children with alfentanil, remifentanil and combinations with midazolam. *Paediatr Anaesth.* 2005;15(3):214–219.
13. Zhu Y, Wang Y, Du B, Xi X. Could remifentanil reduce duration of mechanical ventilation in comparison with other opioids for mechanically ventilated patients? A systematic review and meta-analysis. *Crit Care.* 2017;21(1):206.
14. Lison S, Schill M, Conzen P. Fast-track cardiac anesthesia: efficacy and safety of remifentanil versus sufentanil. *J Cardiothorac Vasc Anesth.* 2007;21(1):35–40.
15. Del Gaudio A, Ciritella P, Perrotta F, et al. Remifentanil vs fentanyl with a target controlled propofol infusion in patients undergoing craniotomy for supratentorial lesions. *Minerva Anestesiol.* 2006;72(5):309–319. [Italian]
16. De Baerdemaeker LE, Jacobs S, Pattyn P, Mortier EP, Struys MM. Influence of intraoperative opioid on postoperative pain and pulmonary function after laparoscopic gastric banding: remifentanil TCI vs sufentanil TCI in morbid obesity. *Br J Anaesth.* 2007;99(3):404–411.
17. Martorano PP, Aloj F, Baietta S, et al. Sufentanil-propofol vs remifentanil-propofol during total intravenous anesthesia for neurosurgery. A multicentre study. *Minerva Anestesiol.* 2008;74(6):233–243.
18. de Hoogd S, Ahlers S, van Dongen EPA, et al. Randomized controlled trial on the influence of intraoperative remifentanil versus fentanyl on acute and chronic pain after cardiac surgery. *Pain Pract.* 2017.
19. Sanfilippo F, Conticello C, Santonocito C, et al. Remifentanil and worse patient-reported outcomes regarding postoperative pain management after thyroidectomy. *J Clin Anesth.* 2016;31:27–33.
20. Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. *Lancet neurol.* 2014;13(9):924–935.
21. Weber L, Yeomans DC, Tzabazis A. Opioid-induced hyperalgesia in clinical anesthesia practice: what has remained from theoretical concepts and experimental studies? *Curr Opin Anaesthesiol.* 2017;30(4):458–465.
22. Mercieri M, Palmisani S, De Blasi RA, et al. Low-dose buprenorphine infusion to prevent postoperative hyperalgesia in patients undergoing major lung surgery and remifentanil infusion: a double-blind, randomized, active-controlled trial. *Br J Anaesth.* 2017;119(4):792–802.
23. Celerier E, Rivat C, Jun Y, et al. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. *Anesthesiology.* 2000;92(2):465–472.
24. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology.* 2006;104(3):570–587.
25. Yi P, Pryzbylkowski P. Opioid induced hyperalgesia. *Pain Med.* 2015;16(Suppl 1):S32–S36.
26. Arout CA, Edens E, Petrakis IL, Sofuoglu M. Targeting opioid-induced hyperalgesia in clinical treatment: neurobiological considerations. *CNS Drugs.* 2015;29(6):465–486.
27. Angst MS. Intraoperative use of remifentanil for TIVA: postoperative pain, acute tolerance, and opioid-induced hyperalgesia. *J Cardiothorac Vasc Anesth.* 2015;29(Suppl 1):S16–S22.
28. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain physician.* 2011;14(2):145–161.
29. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain.* 2009;10(9):895–926.
30. Mao J, Sung B, Ji RR, Lim G. Chronic morphine induces downregulation of spinal glutamate transporters: implications in morphine tolerance and abnormal pain sensitivity. *J Neurosci.* 2002;22(18):8312–8323.
31. Gladding CM, Raymond LA. Mechanisms underlying NMDA receptor synaptic/extrasynaptic distribution and function. *Mol Cell Neurosci.* 2011;48(4):308–320.
32. Vanegas H, Schaible HG. Descending control of persistent pain: inhibitory or facilitatory? *Brain Res Brain Res Rev.* 2004;46(3):295–309.
33. Lu C, Shi L, Zhang J, et al. Neuron-restrictive silencer factor in periaqueductal gray contributes to remifentanil-induced postoperative hyperalgesia via repression of the mu-opioid receptor. *J Neurol Sci.* 2015;352(1–2):48–52.
34. Raghavendra V, Tanga FY, DeLeo JA. Attenuation of morphine tolerance, withdrawal-induced hyperalgesia, and associated spinal inflammatory immune responses by propentofylline in rats. *Neuropsychopharmacology.* 2004;29(2):327–334.
35. Watkins LR, Hutchinson MR, Rice KC, Maier SF. The "toll" of opioid-induced glial activation: improving the clinical efficacy of opioids by targeting glia. *Trends Pharmacol Sci.* 2009;30(11):581–591.
36. Ferrini F, Trang T, Mattioli TA, et al. Morphine hyperalgesia gated through microglia-mediated disruption of neuronal Cl^- homeostasis. *Nat Neurosci.* 2013;16(2):183–192.
37. Mika J, Popiolek-Barczyk K, Rojewska E, Makuch W, Starowicz K, Przewlocka B. Delta-opioid receptor analgesia is independent of microglial activation in a rat model of neuropathic pain. *PloS One.* 2014;9(8):e104420.

38. Hutchinson MR, Zhang Y, Shridhar M, et al. Evidence that opioids may have toll-like receptor 4 and MD-2 effects. *Brain Behav Immun.* 2010;24(1):83–95.
39. Fukagawa H, Koyama T, Kakuyama M, Fukuda K. Microglial activation involved in morphine tolerance is not mediated by toll-like receptor 4. *J Anesth.* 2013;27(1):93–97.
40. Corder G, Tawfik VL, Wang D, et al. Loss of μ opioid receptor signaling in nociceptors, but not microglia, abrogates morphine tolerance without disrupting analgesia. *Nat Med.* 2017;23(2):164–173.
41. Gu X, Wu X, Liu Y, Cui S, Ma Z. Tyrosine phosphorylation of the N-Methyl-D-Aspartate receptor 2B subunit in spinal cord contributes to remifentanil-induced postoperative hyperalgesia: the preventive effect of ketamine. *Mol Pain.* 2009;5:76.
42. Koppert W, Schmelz M. The impact of opioid-induced hyperalgesia for postoperative pain. *Best Pract Res Clin Anaesthesiol.* 2007;21(1):65–83.
43. Shimoyama N, Shimoyama M, Davis AM, Monaghan DT, Inturrisi CE. An antisense oligonucleotide to the N-methyl-D-aspartate (NMDA) subunit NMDAR1 attenuates NMDA-induced nociception, hyperalgesia, and morphine tolerance. *Minerva Anestesiol.* 2005;312(2):834–840.
44. Joly V, Richebe P, Guignard B, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology.* 2005;103(1):147–155.
45. Engelhardt T, Zaarour C, Naser B, et al. Intraoperative low-dose ketamine does not prevent a remifentanil-induced increase in morphine requirement after pediatric scoliosis surgery. *Anesth Analg.* 2008;107(4):1170–1175.
46. Leal PC, Salomao R, Brunialti MK, Sakata RK. Evaluation of the effect of ketamine on remifentanil-induced hyperalgesia: a double-blind, randomized study. *J Clin Anesth.* 2015;27(4):331–337.
47. Koppert W, Ihmsen H, Korber N, et al. Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. *Pain.* 2005;118(1–2):15–22.
48. Cabanero D, Celerier E, Garcia-Nogales P, et al. The pro-nociceptive effects of remifentanil or surgical injury in mice are associated with a decrease in delta-opioid receptor mRNA levels: prevention of the nociceptive response by on-site delivery of enkephalins. *Pain.* 2009;141(1–2):88–96.
49. Lee C, Song YK, Jeong HM, Park SN. The effects of magnesium sulfate infiltration on perioperative opioid consumption and opioid-induced hyperalgesia in patients undergoing robot-assisted laparoscopic prostatectomy with remifentanil-based anesthesia. *Korean J Anesthesiol.* 2011;61(3):244–250.
50. Song JW, Lee YW, Yoon KB, Park SJ, Shim YH. Magnesium sulfate prevents remifentanil-induced postoperative hyperalgesia in patients undergoing thyroidectomy. *Anesth Analg.* 2011;113(2):390–397.
51. Lenz H, Raeder J, Draegni T, Heyerdahl F, Schmelz M, Stubhaug A. Effects of COX inhibition on experimental pain and hyperalgesia during and after remifentanil infusion in humans. *Pain.* 2011;152(6):1289–1297.
52. Eisenach JC, Tong C, Curry RS. Failure of intrathecal ketorolac to reduce remifentanil-induced postinfusion hyperalgesia in humans. *Pain.* 2015;156(1):81–87.
53. Neurontin (Gabapentin - FDA Approved Labeling Text). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020235s036,020882s022,021129s022lbl.pdf. Accessed January 20, 2018.
54. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. *Anaesthesia.* 2002;57(5):451–462.
55. Fink K, Meder W, Dooley DJ, Gothert M. Inhibition of neuronal Ca(2+) influx by gabapentin and subsequent reduction of neurotransmitter release from rat neocortical slices. *Br J Pharmacol.* 2000;130(4):900–906.
56. Malmberg AB, Yaksh TL. Voltage-sensitive calcium channels in spinal nociceptive processing: blockade of N- and P-type channels inhibits formalin-induced nociception. *J Neurosci.* 1994;14(8):4882–4890.
57. Compton P, Kehoe P, Sinha K, Torrington MA, Ling W. Gabapentin improves cold-pressor pain responses in methadone-maintained patients. *Drug Alcohol Depend.* 2010;109(1–3):213–219.
58. Cuignet O, Pirson J, Soudon O, Zizi M. Effects of gabapentin on morphine consumption and pain in severely burned patients. *Burns.* 2007;33(1):81–86.
59. Stoicea N, Russell D, Weidner G, et al. Opioid-induced hyperalgesia in chronic pain patients and the mitigating effects of gabapentin. *Front Pharmacol.* 2015;6:104.
60. Engelman E, Cateloy F. Efficacy and safety of perioperative pregabalin for post-operative pain: a meta-analysis of randomized-controlled trials. *Acta Anaesthesiol Scand.* 2011;55(8):927–943.
61. Lee C, Lee HW, Kim JN. Effect of oral pregabalin on opioid-induced hyperalgesia in patients undergoing laparo-endoscopic single-site urologic surgery. *Korean J Anesthesiol.* 2013;64(1):19–24.
62. Gustorff B, Hoechtl K, Sycha T, Felouzis E, Lehr S, Kress HG. The effects of remifentanil and gabapentin on hyperalgesia in a new extended inflammatory skin pain model in healthy volunteers. *Anesth Analg.* 2004;98(2):401–407.
63. Adenosine (FDA Approved Labeling Text).
64. Katz NK, Ryals JM, Wright DE. Central or peripheral delivery of an adenosine A1 receptor agonist improves mechanical allodynia in a mouse model of painful diabetic neuropathy. *Neuroscience.* 2015;285:312–323.
65. Gan TJ, Habib AS. Adenosine as a non-opioid analgesic in the perioperative setting. *Anesth Analg.* 2007;105(2):487–494.
66. Segerdahl M, Ekblom A, Sandelin K, Wickman M, Sollevi A. Preoperative adenosine infusion reduces the requirements for isoflurane and postoperative analgesics. *Anesth Analg.* 1995;80(6):1145–1149.
67. Lee C, Song YK, Lee JH, Ha SM. The effects of intraoperative adenosine infusion on acute opioid tolerance and opioid induced hyperalgesia induced by remifentanil in adult patients undergoing tonsillectomy. *Korean J Pain.* 2011;24(1):7–12.
68. Jin X, Mi W. Adenosine for postoperative analgesia: a systematic review and meta-analysis. *PloS One.* 2017;12(3):e0173518.
69. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology.* 2000;93(2):382–394.
70. Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. *Can J Anaesth.* 2006;53(7):646–652.
71. Lin TF, Yeh YC, Lin FS, et al. Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. *Br J Anaesth.* 2009;102(1):117–122.
72. Zheng Y, Cui S, Liu Y, et al. Dexmedetomidine prevents remifentanil-induced postoperative hyperalgesia and decreases spinal tyrosine phosphorylation of N-methyl-d-aspartate receptor 2B subunit. *Brain Res Bull.* 2012;87(4–5):427–431.
73. Yuan Y, Sun Z, Chen Y, et al. Prevention of remifentanil induced postoperative hyperalgesia by dexmedetomidine via regulating the trafficking and function of spinal NMDA receptors as well as PKC and CaMKII level in vivo and in vitro. *PloS One.* 2017;12(2):e0171348.
74. Belgrade M, Hall S. Dexmedetomidine infusion for the management of opioid-induced hyperalgesia. *Pain Med.* 2010;11(12):1819–1826.
75. Lee C, Kim YD, Kim JN. Antihyperalgesic effects of dexmedetomidine on high-dose remifentanil-induced hyperalgesia. *Korean J Anesthesiol.* 2013;64(4):301–307.
76. Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schuttler J. Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. *Anesthesiology.* 2003;99(1):152–159.
77. Collard V, Mistraletti G, Taqi A, et al. Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy. *Anesth Analg.* 2007;105(5):1255–1262.
78. Chu LF, Cun T, Ngai LK, et al. Modulation of remifentanil-induced postinfusion hyperalgesia by the beta-blocker propranolol in humans. *Pain.* 2012;153(5):974–981.
79. Singler B, Troster A, Manering N, Schuttler J, Koppert W. Modulation of remifentanil-induced postinfusion hyperalgesia by propofol. *Anesth Analg.* 2007;104(6):1397–1403.

80. Jevtovic-Todorovic V, Todorovic SM, Mennerick S, et al. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. *Nat Med.* 1998;4(4):460–463.
81. Richebe P, Rivat C, Creton C, et al. Nitrous oxide revisited: evidence for potent antihyperalgesic properties. *Anesthesiology.* 2005;103(4): 845–854.
82. Echevarria G, Elgueta F, Fierro C, et al. Nitrous oxide (N_2O) reduces postoperative opioid-induced hyperalgesia after remifentanil-propofol anaesthesia in humans. *Br J Anaesth.* 2011;107(6):959–965.
83. Comelon M, Raeder J, Stubhaug A, Nielsen CS, Draegni T, Lenz H. Gradual withdrawal of remifentanil infusion may prevent opioid-induced hyperalgesia. *Br J Anaesth.* 2016;116(4):524–530.