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Prevention of Opioid-Induced Hyperalgesia Following Remifentanil Infusion: A Case Report

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Abstract

Remifentanil, a potent mu-opioid agonist, is useful in anesthesia because of its rapid onset and short duration of action. However, the same traits that make remifentanil useful can also lead to increased pain sensation when remifentanil is discontinued. Nociceptive sensitization following opioids is termed opioid-induced hyperalgesia (OIH). Proposed preventive treatments for remifentanil-induced OIH run the spectrum of cost and feasibility. This case report will discuss the use of and rationale for readily available techniques aimed at preventing OIH. These techniques include intravenous ketamine, inhaled nitrous oxide, oral pregabalin, and gradual cessation of remifentanil infusion.

INTRODUCTION

Increases in postoperative pain occur after intraoperative remifentanil infusions. A 2014 systematic review and meta-analysis including 1494 patients found an association between high doses of intraoperative remifentanil and small but significant increases in postoperative pain intensity.[1] Pain in the postoperative period can lead to activation of the stress response, activation of the sympathetic nervous system, and activation of harmful spinal reflex arcs. These processes caused by poorly controlled postoperative pain contribute to increased morbidity and mortality resulting from hypercoagulability, immunosuppression, poor wound healing, myocardial ischemia, delayed return of gastrointestinal function, and decreased pulmonary function.[2] Therefore, if remifentanil is part of the anesthetic plan, preventive analgesia becomes an important component of that plan. The purpose of this case report was to evaluate methods for preventing opioid-induced hyperalgesia (OIH) after remifentanil infusion.

CASE SUMMARY

A 70-year-old, 99-kg, 172-cm man presented with degenerative disc disease and was scheduled for a laminectomy with fusion from lumbar segment 2 to 5. The patient's medical history included coronary artery disease, hypertension, high cholesterol, type 2 diabetes mellitus, neuropathy, obstructive sleep apnea, prostate cancer, and low back pain. His surgical history included cardiac stenting, prostate removal, bladder stone removal, and right shoulder arthroscopy with rotator cuff repair. The patient denied having any previous anesthesia complications. His current medication treatment included metformin, metoprolol, potassium chloride, and nitroglycerine. The patient was noted to have medication allergy to levofloxacin (rash, hives). Laboratory results and electrocardiography and chest radiography findings were unremarkable. No other diagnostic testing was ordered. During the preanesthetic assessment, the patient stated he was not having current back pain. He described having a history of intermittent back pain usually coinciding with activity ranging from 2 to 7 on a 10-cm visual analogue scale (VAS). Midazolam 2 mg was administered intravenously after the standard preprocedural time out.

The patient was taken to the operating room. Intraoperative monitors included pulse oximetry, electrocardiography, noninvasive blood pressure monitoring, carbon dioxide capnography, esophageal temperature, bispectral index (Coviden Ltd, Dublin, Ireland), and somatosensory evoked potentials. Pre-induction vital signs were as follows: pulse, 53; blood pressure, 149/65 mm Hg; oxygen saturation, 97%; respirations, 16; and temperature, 36.3°C. Oxygen was administered via face mask at 10 L/min. After 5 minutes of pre-oxygenation, general anesthesia was induced with 100 mg lidocaine, 100 mcg fentanyl, 180 mg propofol, and 100 mg succinylcholine intravenously. Direct laryngoscopy with a Macintosh #3 blade was performed and the airway was secured with a 7.5 endotracheal tube. Correct endotracheal tube placement was confirmed with visible chest rise, capnography, and auscultation of bilateral breath sounds. After induction of anesthesia, the patient was transferred to a prone surgical bed. Total intravenous anesthesia was utilized because of the need to monitor somatosensory evoked potentials. Anesthesia was maintained by using an intravenous infusion of 100 mcg/kg/min propofol and 0.5 mcg/kg/min remifentanil. The propofol infusion was titrated to maintain a bispectral index between 40 and 60. The patient showed no physiologic indicators of nociception during the procedure, and the remifentanil infusion was not titrated. Physiologic indicators of pain were considered increases in heart rate or blood pressure above baseline. Medical air 1 L/min and oxygen 1 L/min were used together for gas flow. Prophylactic antibiotics included 1.5 g cefuroxime and 1 g vancomycin administered intravenously. The propofol infusion was discontinued at the time of surgical wound closure. Hydromorphone 0.4 mg was administered intravenously. The remifentanil infusion was discontinued. To stimulate spontaneous respirations, ventilation settings were adjusted to a tidal volume of 450 and a rate of 8 breaths per minute to allow $PaCO_2$ to rise. Spontaneous respirations with adequate tidal volumes were achieved within 5 minutes. The patient was rotated to a supine position. The endotracheal tube was removed, and the airway remained patent. The patient was transported to the post-anesthesia care unit with oxygen at 8 L/min via facemask. Postoperative vital signs were as follows: pulse, 87; blood pressure, 117/71 mm Hg; respiratory rate, 12; SpO_2, 100%; and temperature, 36.2°C. Hydromorphone 1.5 mg was administered intravenously at 5-minute intervals in 0.5-mg doses in the post-anesthesia care unit. The patient was admitted to the hospital for continued evaluation. During a follow-up visit 24 hours postoperatively, the patient stated that his pain was well controlled except for a 30-minute interval when his pain was 7 on a 10-cm VAS. This interval of increased pain intensity occurred 3 hours postoperatively. No other adverse outcomes were noted.

DISCUSSION

The use of remifentanil infusions during general anesthesia has been associated with hyperalgesia in the postoperative period. In the first systematic review and meta-analysis concerning OIH in surgical patients, treatment with high doses of intraoperative remifentanil was associated with higher pain intensity during the first 24 hours after surgery.[1] In the 27 studies included in the systematic review, a high dose of remifentanil was typically considered an infusion of 0.3 mcg/kg/min. Some of the studies used higher or lower doses, but in each study a comparison was made between an opioid, predominately remifentanil, and either a lower dose of the same opioid or a placebo. The study included oropharyngeal, neurosurgical, cardiothoracic, and abdominal surgeries. The study acknowledged that a possible cause of the increase in pain intensity was an acute opioid tolerance after remifentanil infusion, because patients experiencing OIH also consumed more morphine in the first 24 hours after surgery.[1] Another possible explanation is that remifentanil causes long-term potentiation of C-fibers through activation of mu-opioid receptors and *N*-methyl-D-aspartate (NMDA) receptors.[3] Although the exact mechanism is still being determined, anesthetic management of patients receiving remifentanil should include techniques that will lower the incidence of OIH in the postoperative period.

Ketamine infusion

It is postulated that OIH is due to central sensitization through activation of NMDA receptors.[3] In support of this hypothesis, the NMDA receptor antagonist ketamine has been shown to decrease postoperative pain intensity and morphine requirements in patients receiving remifentanil infusion during general anesthesia.[4,5] Hong and colleagues used a 0.3-mg/kg intravenous bolus of ketamine during induction followed by a 3-mcg/kg/min ketamine infusion during surgery to effectively prevent OIH and decrease the total amount of opioids required in those undergoing general anesthesia utilizing sevoflurane and remifentanil.[4] A separate study set out to determine the effective dose of ketamine to prevent OIH. For a ketamine bolus delivered intravenously before skin incision, the ED_{50} was determined to be 0.24 mg/kg and the ED_{95} was determined to be 0.33 mg/kg.[5] If used in this case, ketamine could potentially have lessened postoperative pain intensity and opioid consumption.

Pregabalin

In 93 patients undergoing general anesthesia for laparoscopic urologic surgery where a remifentanil infusion was utilized, a single dose of 300 mg pregabalin orally before surgery was

found to increase the time from the end of surgery to the first analgesic requirement, to decrease the amount of pain medication via patient-controlled analgesia pump during the first 24 hours postoperatively, and to decrease postoperative pain intensity for 24 hours.[6] The study confirmed the existence of OIH by first comparing 2 groups who did not receive pregabalin. Patients receiving 0.3 mcg/kg/min remifentanil had increased pain intensity for 24 hours following surgery compared with patients receiving 0.05 mcg/kg/min remifentanil. Furthermore, by adding a third group who received the high dose of remifentanil and pregabalin, the results of this study showed that a single dose of pregabalin could help to prevent OIH resulting from remifentanil infusion.[6] The pregabalin dose was given 1 hour before anesthesia. The likely mechanism is prevention of central pain sensitization and increased spinal nerve excitability as opposed to direct analgesic activity.[6] The patient in this case report did not indicate any history of gastroesophageal reflux during the preoperative assessment, making this oral drug a viable option for prevention of OIH.

Nitrous oxide

The use of nitrous oxide, an NMDA antagonist, has been associated with a significant reduction in postoperative OIH in those receiving total intravenous anesthesia using propofol and remifentanil. The study showed that administering nitrous oxide at 70% decreased postoperative OIH for 12 to 18 hours when compared with an anesthetic using 100% oxygen.[7] It is of note that postoperative pain intensity and opioid consumption were similar among the 2 groups and that the decrease in OIH was measured by using mechanical pain thresholds on the arm.[7] Therefore, nitrous oxide is an option for preventing OIH but may be a less potent preventive. Furthermore, in the present case it would not have been a viable alternative because total intravenous anesthesia was used for ideal neuromonitoring conditions.

Gradual withdrawal of remifentanil infusion

Avoidance of sudden cessation of a remifentanil drip has been associated with prevention of OIH.[8,9] Rodent studies have demonstrated that when an intravenous infusion of 7.5 mcg/kg/min remifentanil was gradually decreased over 30 minutes, the long-term potentiation of C-fibers that accompanies OIH was prevented.[10] A 2014 study in patients undergoing spinal surgery found that abrupt cessation of a remifentanil drip was associated with a higher incidence of OIH compared with slow cessation over 90 minutes after surgery.[9] These results indicate that an abbreviated but still pronounced withdrawal beginning at the start of surgical wound closure when nociception is typically lower could prevent OIH. This method may be effective but not practical in fast-paced anesthesia settings. Another alternative in longer procedures would be a weaning of a remifentanil infusion toward the end of surgery while introducing longer-acting opioids to assist in prevention of OIH. This plan would incorporate remifentanil dosing guidelines which state that adequate postoperative analgesia should be achieved before discontinuation of remifentanil infusion.[11]

SUMMARY

The development of OIH is a concern in patients receiving a remifentanil infusion as a component of a general anesthetic.[1] Anesthesia professionals should be aware of this risk. While this case report did not involve a patient with excessive hyperalgesia postoperatively, there was a 30-minute period during which the patient experienced an increased pain intensity. When remifentanil infusions are used, it may be prudent to include medications that could prevent OIH. Pregabalin 300 mg given orally 1 hour before surgery, 0.3 mg/kg ketamine administered as an intravenous bolus with or without a 3-mcg/kg/min infusion, and 70% inhaled nitrous oxide are viable options for prevention of OIH. After the anesthesia professional weighs the risk-benefit ratio, these medications may be incorporated. If pharmacologic interventions are contraindicated, a gradual withdrawal of the remifentanil infusion may aid in the prevention of OIH.

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Lauren Gray is completing the final year of a Doctor of Nursing Practice at Texas Christian University. Gray graduated summa cum laude from the University of Texas Health Science Center in San Antonio with a Bachelor of Science in Nursing. Before beginning her doctoral education, Gray was an intensive care nurse at Methodist Hospital in San Antonio where she actively participated in the largest heart failure and heart transplantation program in South Texas. Her current professional interests include pharmacology, cardiovascular physiology, regional anesthesia, and infection prevention.