Case Series

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Opioid-free anesthesia with a mixture of dexmedetomidine, ketamine, and lidocaine in one syringe for surgery in obese patients

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Abstract

Recently, there has been a trend toward minimizing opioid use in obese patients to prevent opioid-related postoperative complications. Moreover, the use of opioid-free anesthesia has received growing interest. This case series reports the use of simple opioid-free anesthesia consisting of a mixture of dexmedetomidine, ketamine, and lidocaine in an obese male patient undergoing laparoscopic bariatric surgery and an obese pregnant woman undergoing cesarean section. These cases indicate that opioid-free anesthesia can be safely administered to obese patients and provides effective pain control without any postoperative adverse outcomes.

Keywords

Dexmedetomidine, ketamine, lidocaine, multimodal approach, obesity, opioid-free anesthesia

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Introduction

As a result of the opioid crisis in the United States, there has been increasing interest in minimizing opioid use. The Enhanced Recovery After Surgery Society recommends minimizing intraoperative opioid

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use in obese patients to reduce postoperative opioid-related side effects.[1] To achieve this, one emerging strategy is the use of opioid-free anesthesia, which is a multimodal anesthesia approach combining multiple non-opioid drugs with different targets.[2]

In this article, we present two challenging cases treated with opioid-free anesthesia. One was a severely obese patient with sleep apnea syndrome undergoing laparoscopic bariatric surgery, and the other was an obese pregnant woman undergoing cesarean delivery. Opioid-free anesthesia with a single syringe containing a mixture of dexmedetomidine, ketamine, and lidocaine achieved efficient postoperative pain control without any perioperative adverse events. Therefore, this strategy appears safe and clinically applicable.

Case reports

Before the patients arrived in the operating room, 50 μg of dexmedetomidine were added to a 50-mL syringe, and normal saline was added to a total volume of 50 mL (Syringe 1). Second, 50 μg of dexmedetomidine, 50 mg of ketamine, and 500 mg of lidocaine were added to an additional 50-mL syringe (Syringe 2), and normal saline was added to a total volume of 50 mL. The patient characteristics, alternative dose scales, and dose calculation formulas are summarized in Table 1. This case report was approved by the Institutional Review Board (EMC 2019-11-005) and performed in compliance with the Declaration of Helsinki. Written informed consent was obtained from the patients for the publication of this report.

Case 1

A 35-year-old man with a body mass index (BMI) of 64.4 kg/m^2 (height 168 cm, weight 182 kg) attended our center for laparoscopic sleeve gastrectomy. The patient was at a high risk of obstructive sleep apnea and had a score of 7 out of 8 on the STOP-BANG questionnaire. The patient also underwent polysomnography for further assessment and was found to suffer from severe obstructive sleep apnea/hypopnea syndrome with an apnea-hypopnea index > 30. Therefore, the patient was prescribed a positive pressure ventilation device set to continuous positive airway pressure mode during sleep. The pre-anesthetic evaluation revealed no abnormal findings on the electrocardiogram (ECG), chest radiography, or laboratory tests, and his vital signs were stable.

After arriving in the operating room, the patient was placed in a ramped position. After adequate preoxygenation and before the induction of anesthesia, the contents of Syringe 1 were infused at a rate of 240 mL/hour over 10 minutes, corresponding to 40 μg of dexmedetomidine at a dose of approximately 0.5 μg/kg of lean body weight (LBW). For the induction of anesthesia, Syringe 1 was replaced with Syringe 2, and 8.0 mL of the contents in Syringe 2 (dexmedetomidine 0.1 μg/kg + ketamine 0.1 mg/kg + lidocaine 1 mg/kg) were administered as a loading dose, followed by a bolus injection of 150 mg of propofol, corresponding to approximately 2 mg/kg of ideal body weight (IBW). After the loss of consciousness, succinylcholine was administered at a dose of 180 mg or 1 mg/kg of total body weight (TBW). Tracheal intubation was successful on the first attempt, as observed with a videolaryngoscope prepared in advance. To maintain anesthesia, the contents of Syringe 2 were infused at a rate of 8.0 mL/hour (dexmedetomidine 0.1 μg/kg/hour + ketamine 0.1 mg/kg/hour + lidocaine 1 mg/kg/hour). Desflurane was titrated to maintain a bispectral index scale (BIS) score between 40 and 60. Fifty milligrams of rocuronium (0.7 mg/kg of IBW) were administered, and an additional 10 mg of

Table 1. Patient characteristics and dose scalars used in dexmedetomidine, ketamine, and lidocaine dosing.

	Case 1	Case 2
Age (years)/Sex	35/M	34/F
Height (cm)	168	166
Weight (kg)	182	146
BMI (kg/m^2)	64.4	53.0
IBW (kg)	68	56
LBW (kg)	81.9	62.3
ABW (kg)	113.6	92

TBW (kg) = Patient's actual body weight

IBW (Broca's formula)

$$\mathbf{IBW\ (male)} = \mathbf{Height} - 100$$

$$\mathbf{IBW\ (female)} = \mathbf{Height} - 110$$

LBW (Janmahasatian's formula)

$$\mathbf{LBW\ (male)} = \frac{9.27 \times 10^3 \times \mathbf{TBW}}{6.68 \times 10^3 + 216 \times \mathbf{BMI}}$$

$$\mathbf{LBW\ (female)} = \frac{9.27 \times 10^3 \times \mathbf{TBW}}{8.78 \times 10^3 + 244 \times \mathbf{BMI}}$$

$$\text{ABW (kg)} = \mathbf{IBW} + 0.4 \times (\mathbf{TBW} - \mathbf{IBW})$$

ABW, adjusted body weight; BMI, body mass index; F, female; IBW, ideal body weight; LBW, lean body weight; M, male; TBW, total body weight.

rocuronium were given if the patient showed a T_1 response to a train-of-four (TOF) stimulus or a post-tetanic count $\geq$ 10 for deep neuromuscular blockade intraoperatively. At the beginning of the surgery, dexamethasone (5 mg) was injected, and an appropriate depth of anesthesia was maintained with a 0.7 minimum alveolar concentration of desflurane without the use of opioids. The patient's vital signs were stable, indicating no need for additional drugs. When the closure of the abdominal wound began, the rate of infusion from Syringe 2 was lowered to 4 mL/hour (dexmedetomidine 0.05 μg/kg/hour + ketamine 0.05 mg/kg/hour + lidocaine 0.5 mg/kg/hour). The total operating time was 3 hours, and there was almost no blood loss. After surgery, desflurane was washed out, and neuromuscular blockade was reversed using 220 mg of sugammadex, which is approximately 2 mg/kg of adjusted body weight (ABW), when the patient showed a T_3 response to a TOF stimulus. The patient was extubated when he was found to be alert and capable of spontaneous respiration. The patient was transferred to the intensive care unit (ICU) with close monitoring for respiratory complications and hemodynamic changes while maintaining the infusion from Syringe 2 at a rate of 4 mL/hour.

Immediately after being transferred to the ICU, the patient was connected to an intravenous (IV) patient-controlled analgesia (PCA), and Syringe 2 was stopped. At that time, the patient complained of pain and was found to have a numeric rating scale score of 7. Thus, he received an IV administration of paracetamol (1 g). However, the patient

continued to complain of pain, which resolved 30 minutes after the administration of an additional 50 μg IV bolus of fentanyl. Thereafter, no opioids or any other analgesics were used for pain control. The patient was moved to a general ward after postoperative day 2 with no respiratory complications and discharged on postoperative day 5 without further complications.

Case 2

A 34-year-old pregnant woman (gestational age 37 weeks and 6 days) with a BMI of 53.0 kg/m^2 (height 166 cm, weight 146 kg) visited the center for an elective cesarean section. The patient was a primigravida who had been diagnosed with gestational diabetes and had well-controlled preoperative blood glucose levels in the range of 100 to 150 mg/dL. The patient had no other specific medical history, and there were no abnormal findings on her preoperative ECG, chest radiography (performed while the abdomen was shielded), or laboratory tests. Although the risks and benefits of regional and general anesthesia were explained to the patient, she resolutely refused to receive regional anesthesia for fear of the operating room.

After arriving in the operating room, the patient was placed in a ramped position. Before the induction of anesthesia and while performing preoxygenation, Syringe 1 was infused at a rate of 180 mL/hour over about 10 minutes until the cord clamp, corresponding to 30 μg of dexmedetomidine (0.5 μg/kg [LBW]). After placing the surgical drape and completing preparations for surgery, 120 mg of propofol (2 mg/kg [IBW]) and 150 mg of succinylcholine (1 mg/kg [TBW]) were administered. Following successful intubation, a minimum alveolar concentration of 0.7 for desflurane was used to keep the BIS score between 40 and 60 for the maintenance of anesthesia, and 40 mg of rocuronium were also administered. Immediately after clamping of the umbilical cord, 6.0 mL of the contents in Syringe 2 (dexmedetomidine 0.1 μg/kg + ketamine 0.1 mg/kg + lidocaine 1 mg/kg) were administered as a loading dose followed by infusion at a rate of 6.0 mL/hour (dexmedetomidine 0.1 μg/kg/hour + ketamine 0.1 mg/kg/hour + lidocaine 1 mg/kg/hour). Three minutes after making the skin incision, a female neonate was delivered with 1-minute and 5-minute APGAR scores of 9 and 10, respectively. A catheter was placed between the rectus muscle and rectus sheath during wound closure, and 250 mL of 0.2% ropivacaine were infused at a constant rate of 5 mL/hour. Approximately 10 minutes before the end of surgery, the rate of infusion from Syringe 2 (dexmedetomidine 0.05 μg/kg/hour + ketamine 0.05 mg/kg/hour + lidocaine 0.5 mg/kg/hour) was decreased to 3.0 mL/hour. At the end of the surgery, desflurane was washed out, and when the patient showed a T_3 response to a TOF stimulus, 200 mg of sugammadex (2 mg/kg [ABW]) were administered. Following extubation, the patient was transferred to the postanesthetic care unit (PACU) while still receiving an infusion from Syringe 2 at a rate of 3.0 mL/hour.

After arrival to the PACU, she complained of pain with a numeric rating scale score of 4, which resolved after the administration of an IV injection of paracetamol (1 g) and ketorolac (30 mg). After 30 minutes of monitoring in the PACU, infusion from Syringe 2 was stopped, and the patient was moved to a general ward. She did not require any further analgesics.

Discussion

Opioid-free anesthesia provides certain advantages, including smooth and fast recovery during emergence from anesthesia and the prevention of acute opioid

tolerance after surgery.[2,3] This is especially useful for obese patients who have a higher risk of opioid-related complications, such as exacerbation of sleep apnea disorder and postoperative respiratory depression, ileus, nausea, and vomiting due to particularly high basal endogenous opioid levels and increased opioid sensitivity.[4] The slope of the concentration-effect curve steepens with the synergistic interactions between anesthetic drugs with different mechanisms when using a multimodal approach, meaning that small decreases in drug concentrations result in larger decreases in drug effects, thereby facilitating the emergence from anesthesia.[3] By attenuating opioid-induced hyperalgesia with opioid-free anesthesia, postoperative opioid use and their adverse effects can be reduced.[2] Furthermore, opioid-free anesthesia can help to prevent addiction following the liberal use of opioids during the perioperative period.[5] In the above two cases, opioid-free anesthesia was successfully administered to obese patients and contributed to enhanced recovery and the absence of opioid-related complications. However, sufficient pain relief after surgery is equally as important as reducing opioid consumption.

Without appropriate postoperative pain control, patients cannot breathe deeply or cough efficiently, leading to increased rates of postoperative atelectasis or pneumonia.[6] In this regard, even low opioid doses can be effective after surgery as a rescue measure in the treatment of refractory pain that is unresponsive to other non-opioid analgesics by sparing μ-opioid receptors during opioid-free anesthesia.[2] In case 1, the patient complained of severe acute pain after surgery, and low doses (50 μg) of fentanyl were used to manage this refractory pain that was unresponsive to other analgesics. This pain was effectively alleviated within 30 minutes without observed side effects.

Mulier, who has extensively studied opioid-free anesthesia since 2009, reported a new opioid-free anesthesia protocol in 2017.[6,7] We performed opioid-free anesthesia using a mixture of dexmedetomidine, ketamine, and lidocaine according to the recent protocol published by Mulier.[7] Mixing specific doses of these three drugs in a single syringe improved the feasibility and convenience of this approach, even for cesarean sections. Furthermore, this method helps to save time as the dosages of the three drugs can be modified at once by adjusting the infusion rate. Using this method, opioid-free anesthesia was performed conveniently and simply, allowing more time and attention for other challenging considerations in obese patients, such as airway management.

Dexmedetomidine, ketamine, and lidocaine have an analgesic effect without causing significant respiratory depression and a postoperative opioid-sparing effect, thereby reducing the risk of opioid-related postoperative complications.[8] Dexmedetomidine is a highly selective α_2-adrenergic agonist that blocks sympathetic nervous system activity by directly acting on spinal preganglionic sympathetic neurons. It is widely used for sedation, anxiolysis, and analgesia to reduce the requirement of anesthetics during general anesthesia.[8] Ketamine and partially lidocaine act on N-methyl-D-aspartate receptors to prevent opioid-induced hyperalgesia.[9] Lidocaine is known to have anti-inflammatory and immunomodulatory effects in patients undergoing abdominal surgery, which can reduce postoperative ileus, nausea, and vomiting and improve the rate of recovery of bowel function, thereby shortening the hospital stay.[10]

Regarding safety, all three drugs have side effects. These include severe hypotension and bradycardia induced by suppression of the sympathetic nervous system by dexmedetomidine;[4] central nervous system-related adverse events, such as

hallucination, dizziness, and blurred vision, caused by IV ketamine;[9] and neurological changes (lidocaine plasma concentrations > 8 μg/mL) and even cardiac dysrhythmias (lidocaine plasma concentrations > 20 μg/mL) induced by perioperative lidocaine infusion.[10] However, these side effects are exceedingly rare. The three-drug mixture was administered at a minimal dose considering the possibility of synergistic interactions between the three drugs, and according to the literature,[6,9–12] there have been no significant drug-related side effects of the doses suggested by Mulier.[7] Dexmedetomidine is commonly administered as a loading dose by infusion over 10 minutes at various doses in the range of 0.1 to 1.0 μg/kg. Following the recommendations of Ingrande and Lemmens,[13] 0.5 μg/kg were used as a loading dose and later verified for safety in several clinical trials in obese patients. In cesarean sections, potential side effects of dexmedetomidine crossing the placenta is a concern, but the neonate in case 2 showed good APGAR scores. It was assumed that this was because the proportion of dexmedetomidine that crossed the placenta was smaller than that of remifentanil, and most of it was retained in the placental tissue because of its lipid solubility. Additionally, dexmedetomidine only induces a natural sleep state from which neonates can be awakened by physiological stimuli.[8] Dexmedetomidine has also been demonstrated to effectively blunt hemodynamic fluctuations during laryngoscopy for intubation or surgical stimulation and achieve sedation and anxiolytic effects without compromising spontaneous respiration of mothers in the pre-induction phase or affecting the APGAR score of neonates.[8]

As there are no universally established dose scales for dexmedetomidine, ketamine, and lidocaine, previous reports have used different dosage protocols. These dosages were administered to patients according to the LBW, which is a metric of body weight that excludes body fat. Although relatively simple and widely used to calculate the LBW, the James formula tends to underestimate the body weight of individuals weighing ≥ 120 kg. Therefore, we used the Janmahasatian formula to overcome this shortcoming of the James formula.[13,14] Based on the research of Elfawy et al.,[15] sugammadex was administered at a dose of 2 mg of ABW when the TOF count was ≥ 2 and achieved complete reversal of neuromuscular blockade in both patients in this report.

Other useful non-opioid adjuvants can be considered in opioid-free anesthesia. Magnesium is a useful adjuvant but was not administered in these two cases because of concerns regarding residual neuromuscular blocking effects after surgery in obese patients requiring complete reversal.[16] Dexamethasone, regarded to have an impact on postoperative analgesia, was administered in case 1 as a single 5-mg bolus dose but not in case 2 with gestational diabetes because of concerns with increasing perioperative blood glucose levels.[17] After surgery, acetaminophen was used in both cases, whereas the non-steroidal anti-inflammatory drug ketorolac was not used in case 1 because of the theoretical possibility of increased rates of gastric perforation.[4] Additionally, a continuous loco-regional block was performed in case 2 by placing a catheter between the rectus sheath and muscle but not in case 1 because of severe acute postoperative pain. If an appropriate loco-regional block was performed in case 1, the acute postoperative pain that occurred immediately after ICU transfer might have been preventable.

Recently, there has been an increase in the number of case reports and studies on opioid-free anesthesia as a new paradigm. Nevertheless, many areas require further investigation. First, there is still a shortage of large, prospective, randomized clinical

trials on opioid-free anesthesia and limited data on the long-term outcomes.[2,3] Second, it is not possible to verify whether sufficient anti-nociception can be achieved without the intraoperative use of opioids.[6] Third, further research is required to determine what combination of drugs should be used and at what dose when performing opioid-free anesthesia.[2]

In conclusion, opioid-free anesthesia in the form of a mixture of dexmedetomidine, ketamine, and lidocaine was used to reduce postoperative opioid consumption in obese patients. This strategy was safe and effective for laparoscopic bariatric surgery in a morbidly obese patient who had severe obstructive sleep apnea/hypopnea syndrome and for cesarean section in a pregnant obese patient. Further research on the safety and usefulness of this method as a form of opioid-free anesthesia is warranted.

Declaration of conflicting interest

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