Some surgeries present increased challenges for adequate perioperative pain management, which require innovative methods to prevent development of chronic postsurgical pain (CPSP). Ketamine is an adjunct to traditional pain management methods and is an effective analgesic. The potent antihyperalgesic effects of ketamine represent an interesting option for those searching for multimodal approaches. This case report describes pain management for a 73-year-old man scheduled for surgical excision of a sacral chordoma who was at high risk of development of CPSP. The intraoperative pain management plan consisted of T9-10 epidural anesthesia with continuous infusion of ropivacaine and hydromorphone, intravenous low-dose ketamine infusion, and intermittent intravenous hydromorphone boluses for breakthrough pain. Postoperatively the epidural infusion was continued for 4 days. The ketamine infusion rate was decreased on transfer to the intensive care unit and titrated to off by postoperative day 3. An intravenous hydromorphone patient-controlled analgesia pump was available to the patient for breakthrough pain postoperatively. This multimodal approach controlled the patient’s pain postoperatively without reported complications. At his 1-year postsurgical follow-up visit, the patient reported some generalized “dull aching pain” that was well controlled with oral ibuprofen. Overall, the patient was satisfied with his pain control, and CPSP did not develop.

Keywords: Chronic postsurgical pain, ketamine, postoperative pain management, sacral chordoma.
repeated activation of C fibers and alter the action of glutamate at the N-methyl-d-aspartate receptor (NMDAR). The NMDAR is an important modulator of pain perception and transmission in humans. In patients experiencing CPSP, the nociceptive pathway becomes unbalanced with increased NMDAR excitatory function and decreased γ-aminobutyric acid and glycine inhibitory function. This, combined with increased sensory input in the dorsal horn, results in an ongoing state of hypersensitivity and a sensation of pain. Additionally, NMDARs are ionotropic glutamate and glycine receptors permeable to sodium, potassium, and calcium ions and are blocked by magnesium ions. Inhibition of phosphatases or increased kinase activity upregulates NMDAR currents and increases pain sensation. Long-term stimulation of NMDARs sensitizes the channels, increasing the amplitude and prolonging the late phases of the excitatory currents, which potentiates transmission and results in nociception. Antagonism of the NMDAR is thought to provide the beneficial pain-relieving effects of drugs such as ketamine, gabapentin, pregabalin, and nitrous oxide. Preventing sensitization of the NMDAR is an important part of any plan to manage postoperative pain in a patient at high risk of CPSP developing. Ketamine reduces the sensation of pain by antagonizing NMDARs, therefore decreasing central excitability. At higher doses, ketamine also affects monoamine, µ-2, and muscarinic receptors, as well as voltage-gated calcium channels.

The following case report describes pain management for a surgical patient who was at high risk of the development of CPSP.

Case Summary

A 73-year-old man, weighing 77 kg and 1.8 m tall, was scheduled for surgery. He had a history of hypertension that was managed with metoprolol as well as coronary artery disease and implantation of 3 drug-eluting stents (2 in 2007 and 1 in 2011). He was receiving clopidogrel, 75 mg, which was held for 1 week before surgery, and 325 mg of aspirin, which was reduced to 81 mg daily but continued. He also had obstructive sleep apnea and stated he was compliant with wearing a continuous positive airway pressure mask. His type 2 diabetes mellitus was well controlled with metformin (hemoglobin A1c concentration of 6.8%). His only previous surgical procedure was a transurethral resection of the prostate in 2005, which was uneventful.

The patient presented to his primary care physician with a 3-year history of sacral pain, increasing in intensity in the most recent 6 months. Magnetic resonance imaging (MRI) revealed a sacral mass measuring 8.6 × 9.8 × 5.8 cm located between the coccyx and sigmoid colon. A specimen obtained from an MRI-guided biopsy found the mass to be a sacral chordoma. Chordomas are benign, slow-growing bone tumors typically found at the base of the skull but have also been reported along the spinal cord and in the sacrum. Chordomas are more frequently reported in men aged 30 to 70 years old and can grow undetected for years at a time during which calcification and destruction of bone is known to occur.

The surgery involved a distal S3-4 sacrococcygeal excision with bowel resection and colostomy. The patient had been using increasing doses of acetaminophen and ibuprofen as needed for pain management, but no opioids preoperatively. Because of the planned surgical approach, high potential for nerve transection, length of the surgery, and structures involved, there was a clear need for an innovative, multimodal plan for postoperative pain management to prevent the development of CPSP.

The acute pain service (APS) was consulted, and before the day of surgery, the APS, the surgical team, and the anesthesia team developed a plan for managing this patient’s anticipated pain throughout the perioperative period. The intraoperative pain management plan included T9-10 level epidural anesthesia with a continuous infusion of 0.05% ropivacaine with hydromorphone, 2.5 µg/mL infusing at 7 mL/h. The T9-10 level was chosen to allow for coverage in case of cephalad extension of the planned abdominal surgical incision and to ensure the catheter was located away from the posterior surgical incision. An intravenous (IV) ketamine infusion of 10 mg/h was started during induction and continued throughout the procedure. Boluses of IV hydromorphone 100 to 300 µg were used as needed to treat acute increases in hemodynamics believed to result from pain.

The postoperative pain management plan included continuation of the epidural infusion at 7 mL/h and reduction in the IV ketamine infusion to a rate of 5 mg/h to be titrated to off over 3 days. A PCA infusion with hydromorphone, 0.2 µg every 10 minutes as needed, was added postoperatively. No basal rate was administered to reduce the risk of respiratory depression. The epidural, PCA, and ketamine infusions were titrated postoperatively according to the patient’s pain rating (Table).

The patient agreed to the pain management plan, and the epidural anesthesia was administered the morning of surgery without difficulty. Induction of anesthesia was completed with 2 µg of midazolam, 100 µg of fentanyl, 160 mg of propofol, and 50 µg of rocuronium. The trachea was intubated via direct laryngoscopy with a 7.5-mm oral endotracheal tube. An arterial line and 2 additional 16-gauge peripheral IV lines were placed before patient positioning. The patient’s vital signs remained stable throughout induction and maintenance of general anesthesia.

This surgical procedure required the patient to be positioned supine in a modified lithotomy position for the first 6 hours, followed by turning the patient prone to complete the tumor removal and sacral laminectomy. The initial midline incision was made by general surgery on the patient’s lower anterior abdominal aspect, which
allowed identification and resection of the mass around the sigmoid colon and rectum. After the abdominal incision was closed, the patient was turned to the prone position, and a midline incision along the sacral spine down the intergluteal line 3 to 4 cm from the anus was made by the neurosurgeons. The neurosurgeons opted to dissect laterally on both sides to increase their chances of removing the whole mass. Because the mass had infiltrated around the S3 through S4 vertebrae, an osteotomy through the S4 vertebra was also performed. Surgery progressed for 8 hours without complications. On emergence, the patient was extubated and transported to the surgical intensive care unit on a regimen of 4 L of oxygen via nasal cannula.

On postoperative day 1, the patient reported adequate pain control and was transferred to the surgical unit. The epidural, ketamine, and PCA infusions were continued through postoperative day 4. He was discharged home on postoperative day 7 and given a prescription for 2 to 4 mg of oral hydromorphone every 4 hours as needed.

This patient returned for additional surgery the following year to remove residual chordoma involvement, which was less invasive and was managed with an epidural infusion and PCA but without a ketamine infusion. At his 1-year surgical follow-up, he reported some generalized “dull aching pain” that was well controlled with oral ibuprofen taken every 4 to 6 hours while he was working. Overall, he was very satisfied with his pain control. As of his last postoperative visit, the patient did not have a diagnosis of CPSP.

### Table: Patient’s Daily Pain Management Plan and Evaluation

<table>
<thead>
<tr>
<th>Postoperative day</th>
<th>Pain rating</th>
<th>Ketamine</th>
<th>Epidural</th>
<th>PCA</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No patient complaints of nausea, vomiting, or pain</td>
<td>Infusion at 5 mg/h</td>
<td>2.5 µg hydromorphone with 0.05% ropivacaine epidural infusion at 7 mL/h</td>
<td>Held overnight as patient denied pain</td>
<td>Patient transferred from surgical intensive care unit to the surgical unit</td>
</tr>
<tr>
<td>2</td>
<td>4/10 at rest and 7/10 with activity</td>
<td>Infusion at 5 mg/h</td>
<td>2.5 µg hydromorphone with 0.05% ropivacaine epidural infusion at 7 mL/h</td>
<td>Hydromorphone PCA started at 0.2 mg every 10 minutes as needed</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2/10 at rest and 7/10 with activity</td>
<td>Titrated down to 2.5 mg/h</td>
<td>Changed to only 0.1% ropivacaine at 7 mL/h</td>
<td>Switched to morphine at 1 mg every 8 minutes as needed</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2/10</td>
<td>Discontinued</td>
<td>0.1% ropivacaine at 7 mL/h</td>
<td>Discontinued</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2-4/10</td>
<td>X</td>
<td>Epidural catheter removed with tip intact</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2/10</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Denies pain</td>
<td>X</td>
<td>X</td>
<td>Discharged to home with prescription for 2 mg oral hydromorphone, 1-2 tablets every 4 hours as needed</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; PCA, patient-controlled analgesia; X, none.

Discussion

The postoperative pain scores for anterior abdominal and posterior sacral/lumbar incisions required to resect this tumor averaged 7 of 10 and 9 of 10, respectively. Common reasons for posterior sacral pain arise from direct pressure applied to the sacral area while the person is sitting or lying supine, but anterior pain is believed to be due to intestinal wall peristalsis as well as myofascial and cutaneous nerve root irritation. The surgery required substantial manipulation of the abdominal structures to check for metastasis, and portions of the sacrum were removed because of erosion and destruction from the tumor. These factors increased the likelihood of major levels of postoperative pain leading to the development of CPSP.

When conventional methods are insufficient to control a patient’s anticipated or actual pain, alternative methods should be sought. Despite a consistent record of effectiveness in reducing postoperative pain in the difficult-to-manage patient, ketamine is often overlooked. This may be because of fear of ketamine’s various side effects such as psychotomimetic tendencies, feelings of inebriation, nausea, impaired cognition, memory or mood effects, or catecholamine depletion, or simply provider unfamiliarity with the drug. Regardless of the
reason, ketamine has been shown to be a very effective analgesic, adjunct to opioid analgesia, potent antihyperalgesic, and preventer of CPSP in multiple types of surgeries and difficult-to-treat patients.23-26 Ketamine was synthesized in the early 1960s, noted to have anesthetic properties in 1965, and approved by the US Food and Drug Administration in 1970 as a dissociative anesthetic.18,27 One of its first documented uses for anesthesia was in American soldiers during the Vietnam War.18 Ketamine has been used to induce and maintain general anesthesia; as an adjunct for regional and monitored anesthesia; and for pediatric, emergency, and intensive care unit sedation.22 Additional uses include treatment for migraine headaches, neuropathic pain, chemotherapy-induced neuropathy, complex regional pain syndrome, fibromyalgia, phantom limb pain, spinal cord injury, and certain psychiatric conditions.22,27

**Intraoperative and Postoperative Uses of Ketamine.** More recently, ketamine has been increasingly used to reduce postoperative pain and opioid consumption in patients receiving long-term opioid therapy.13,22 Ketamine is also becoming more popular in the postoperative setting to achieve optimal pain control for the difficult-to-manage postsurgical patient because it reduces the incidence of opioid tolerance and hyperalgesia, and decreases the need for postoperative opioids during the first 24 hours.10 It is also a potent adjunct to a morphine PCA, reducing opioid consumption in patients undergoing major abdominal surgery.22 Ketamine infusions have been used successfully to reduce morphine consumption and pain levels in the postoperative anesthesia care unit (PACU) and 6 weeks postoperatively in patients with chronic pain who are undergoing back surgery.15 The major analgesic properties of ketamine occur through downregulation of NMDARs and reduced central sensitization.6,16,18 Ketamine also acts indirectly with several neurotransmitters, which contribute to many of the unwanted side effects.18

Patients undergoing major orthopedic, thoracic, and upper abdominal procedures had the greatest improvement, with 78% reporting less pain after ketamine than a placebo group.23 Intra-abdominal and lower-abdominal surgical patients also required less opioid following ketamine administration during their procedure.23 Intravenously administered ketamine is an effective supplement to spinal anesthesia during caesarean deliveries, with no difference observed in neonatal Apgar scores.28 Ketamine also reduces opioid use during dental, tonsillectomy, and head and neck surgeries, but less so than for other procedures.23 Ketamine appears most effective for patients reporting pain scores greater than 7 of 10.23 There also appears to be a maximal effect, with no further reduction in opioid use for patients who reported pain scores of less than 4 of 10.23 In a systematic review, Laskowski and colleagues23 found that ketamine was most effective in the immediate 4 hours after surgery and that patients reported less pain for 24 to 72 hours postoperatively. Although approximately 16% of the studies reviewed found no significant reduction in pain for patients treated with ketamine, the patients in the placebo groups reported increased pain despite using more opioid than the ketamine groups.23 Timing of ketamine administration (before or after incision) and method of administration (IV bolus, PCA, infusion) did not show statistical significance in the overall effectiveness of ketamine in reducing pain or opioid consumption.23

Intraoperative use of ketamine may affect commonly used monitors in the operating room. Bispectral index scores were found to have a direct correlation with ketamine plasma concentrations.29 Ketamine also increases the amplitude of motor evoked potentials, making it preferred over propofol and volatile anesthetics, which dampen the amplitude.30 No changes in amplitude or latency of cortical somatosensory evoked potentials were observed.30 Although there are no contraindications to using ketamine during evoked potential monitoring, the anesthetist should be aware of the changes it produces. Continuing the ketamine infusion postoperatively decreases hyperalgesia and improves pain control postoperatively.24 However, because of unfamiliarity with ketamine infusions in this setting, both the PACU and unit nurses required some additional education to ensure that the patient received adequate pain control, while maintaining patient safety. Information regarding ketamine was sent electronically to all staff caring for this patient, and the APS was available at all times via pager. Policies and procedures may vary between hospitals regarding use of continuous ketamine infusions outside the operating room and should be reviewed before relying on ketamine as part of a postoperative pain management plan.

**Ketamine Pharmacology.** The recommended intraoperative dosing of IV ketamine for treatment of pain varies greatly in the published literature and ranges between 0.15 and 7 mg/kg.10,15,18,22-28,31 Although higher doses are associated with increased side effects, they are not always correlated with a greater reduction in pain score than lower doses.23 Unfortunately, the definition of high-dose and low-dose ketamine is inconsistent between studies. Suggested starting doses for sedation are between 0.25 and 1 mg/kg for adults and 0.25 to 2 mg/kg for children. At these doses, airway reflexes, spontaneous respirations, and cardiovascular stability are maintained.31 Induction of anesthesia and a dissociative state occurs above dosages of 1 to 2 mg/kg. A continuous IV infusion of 0.06 to 5 mg·kg⁻¹·h⁻¹ has also been shown to reduce pain with limited adverse psychotomimetic effects.18,26 However, larger doses of ketamine are not always necessary. Low-dose ketamine infusions less than 1 mg·kg⁻¹·h⁻¹ have also been shown to reduce pain at rest, decrease analgesic requirement, and improve patient satisfaction.22
continued postoperatively, infusion rates may be started between 85 and 120 μg·kg⁻¹·h⁻¹ for 24 hours, and then reduced to 60 μg·kg⁻¹·h⁻¹ for 48 hours.²⁴

Analgesia and sedation may also be achieved with 4 to 5 mg/kg of intramuscular ketamine and 3 to 15 mg/kg of oral ketamine to a maximum dose of 500 mg.³¹ Oral ketamine tastes bitter and may not be tolerated well; intramuscular ketamine results in pain at the injection site and, compared with IV administration, has prolonged recovery time and increased risk of vomiting.³¹ Intranasal administration results in rapid absorption with a bioavailability twice that of oral routes, and therefore may be the preferred route for the pediatric population.³¹ Recommended intranasal dosages range between 0.25 and 4 mg/kg for analgesia and sedation. Sedation may also be achieved with a rectal administration of 50 mg of ketamine diluted in 0.4 mL/kg of 0.9% saline.³¹ Topical 10% ketamine has minimal to no sedation effects and has been shown to reduce pain after a single dose for up to an hour with no reported side effects.³⁸ Diluted preservative-free ketamine injections in the caudal and epidural spaces reduced pain and opioid requirement in patients undergoing major upper abdominal surgery and those with chronic low back pain.²⁴,²³,³²,³³ Intrathecal ketamine results in toxicity, and subcutaneous administration may cause irritation or infection at the injection site; therefore, administration via these routes is not recommended.²⁴,³²,³³,³⁵

The major undesirable side effects of ketamine are psychotomimetic, including hallucinations and nightmares.²³,²⁴,³²,³³ Coadministration of a benzodiazepine, such as midazolam, has been shown to attenuate the psychotomimetic effects of ketamine.²³,³⁰ Ketamine’s effects on perceptual abnormalities, such as body surroundings and time awareness, as well as abnormal thought processes were also reduced by midazolam.²⁹ No change was noted in the level of sedation or changes in mood with coadministration of midazolam.²⁹ Other common side effects of ketamine include salivation, hypertension, difficulty sleeping, severe headache, nausea, muscle weakness, dizziness, blurred vision, and a feeling of inebriation, all of which have a direct correlation with higher dosages.²³,²⁴ Most of the undesirable effects are limited to the time of administration or subside shortly thereafter, with the highest incidence of central nervous system side effects following bolus IV doses.³⁴ Overall, ketamine use is associated with decreased postoperative nausea and vomiting possibly due to a reduction in opioid administration.²⁵ The low oral bioavailability of ketamine poses additional obstacles for chronic use.¹⁸ Abuse and prolonged systemic use of ketamine are associated with liver injury, which, although reversible if discovered early, is profound.¹⁸ Regardless, ketamine is often preferred over other pain medications, such as opioids, because it does not reduce blood pressure or produce respiratory depression, and it may improve respiration by dilating the bronchioles, making it an ideal analgesic choice for cardiac and respiratory-compromised patients.¹⁸

Conclusion
A ketamine infusion was added as part of a multimodal pain management plan for this case because of the sensitivity of the surgical areas being resected, the invasive and extensive nature of the surgical procedure, and the strong desire to prevent CPSP. Epidurals are effective for managing pain from anterior incisions; however, because of the occasional sacral-sparing effect, complete relief would not have been achievable in this patient. Opioids such as hydromorphone and morphine are most effective for pain at rest, with increased pain expected during patient activity.³⁵ A patient’s pain rating of 7 of 10 with activity does not negate the effectiveness of the opioid, but rather confirms the true pharmacokinetics of the drugs and their lessened ability to relieve pain during movement.³⁵ Adding a ketamine infusion to the epidural anesthesia and PCA allowed broader, more consistent pain control. Uptake of epidural opioids into the systemic circulation and redistribution to the brainstem opioid receptors combine with the respiratory depressant effects of the PCA opioids and increase the potential for respiratory depression.³⁶ The ketamine infusion allowed for a reduction in the dose of both epidural and IV opioids, decreasing this risk. Continuous pulse oximetry was used to monitor for hypoxia in the event of oversedation related to the dual forms of opioid administration.

This case report described the perioperative pain management for excision of a sacral chordoma, which posed a high risk of the development of CPSP. Defined as postoperative pain lasting greater than 3 months after surgery, CPSP frequently results from inadequately treated acute perioperative surgical pain. Ketamine is effective in reducing postoperative pain and overall opioid consumption, and has been shown to be an effective adjunct to general, regional, and monitored anesthesia. In this case, a continuous ketamine infusion was started intraoperatively and was continued for 4 days postoperatively as an adjunct to an epidural infusion and PCA. This multimodal plan for pain management aggressively treated the patient’s acute pain and thereby successfully prevented the development of CPSP.

REFERENCES
5. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk fac-


