CLINICAL REPORT

Opioid-Free Perioperative Analgesia for Hemicolectomy in a Patient With Opioid-Induced Delirium: A Case Report and Review of the Analgesic Efficacy of the Alpha-2 Agonist Agents

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■ **Abstract:** Surgical pain in patients with documented opioid-induced delirium can be difficult to treat. We present a case of a patient undergoing laparoscopic hemicolectomy effectively treated with an opioid-free, alpha-2 adrenoreceptor agonist analgesic regimen.

Case report: A 21-year-old woman with persistent abdominal pain presented to the operating room for laparoscopic hemicolectomy for redundant right colon. Her medical history included a recently diagnosed postoperative opioid-induced delirium. Epidural infusion with local anesthetic offered partial pain relief with sensory levels of T9-L2. With the addition of dexmedetomidine infusion in the immediate postoperative period, the patient was comfortable with pain scores of 1 to 2/10 on Numerical Rating Scale (NRS). On postoperative day 1, the infusion was discontinued and the clonidine, 12 μg/hours was added to the epidural bupivacaine. With increased sedation 48 hours later, neuraxial clonidine was discontinued in favor to transdermal clonidine 0.1 mg/week, which was maintained until hospital discharge. Pain scores were maintained at 2 to 3/10 on NRS for the next 3 days when increased abdominal distention because of abscess formation rendered a new surgical intervention. The analgesia for the exploratory laparoscopy was maintained using epidural clonidine and bupivacaine infusion as well as intravenous dexmedetomidine, which were maintained another 2 days. Pain scores remained minimal until discharged home 3 day later. Discussion: Nonopioid analgesic regimens are beneficial in patients at risk of postoperative cognitive dysfunction attributable to opioids. Successful postoperative analgesia was achieved in our patient by alternating various routes of administration of alpha-2 adrenoreceptor agonists. ■

Key Words: dexmedetomidine, epidural, delirium, clonidine, bupivacaine, alpha-2 agonists

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INTRODUCTION

As antiquity, surgical interventions have been associated with severe pain and discomfort in the immediate perioperative period. Surgical anesthesia and the perioperative analgesic regimen aim toward complete intra-operative amnesia, profound analgesia, effective control of autonomic responses and rapid emergence. However, many of the anesthetic and analgesic agents used perioperatively have severe and profound side effects. Perioperative delirium with or without cognitive decline appears frequently immediately after surgery. Its prevalence can range anywhere from 9% to 87%.[1] With prevalence primarily in the elderly population, delirium is associated with many triggering factors such as infection, metabolic derangements, dehydration, and polypharmacy. Opioids, widely used in the immediate perioperative period for their profound analgesic effect, also have a variety of side effects that may limit their use. Opioid analgesic agents are among the most important causes of delirium in postoperative patients.[2] Alternative modalities to treat surgical pain have been used in various combinations but so far no single analgesic agent had the ability to substitute opioids as the analgesic of choice for moderate to severe postoperative pain.

Balanced anesthetic techniques using multiple synergistic agents combined with perioperative multimodal analgesia was introduced in the last decade as an effective technique to reduce the incidence of side effects associated with the medications involved.[3] The pharmacological principle of multimodal analgesia consists of combining different analgesics that act by different mechanisms and at different sites in the nervous system to produce additive or synergistic analgesia for the surgical patient in the perioperative period. Medications currently used as part of multimodal analgesia are nonsteroidal anti-inflammatory medications, alpha-2 adrenoreceptor agonists, NMDA receptor antagonists, local anesthetics, glucocorticoids and anticholinergics.[3]

The use of alpha-2 adrenoreceptor agonists as analgesics and sedatives was first studied in veterinary medicine.[4] Introduced as a potent nasal decongestant in the 1960, clonidine, the first specific alpha-2 adrenoreceptor agonist has been subsequently used as an antihypertensive, sedative and analgesic.[4] Neuraxial application of clonidine provides adequate analgesia and extends the sensory block regression of concurrent local anesthetics [5,6] by stimulating the presynaptic alpha-2 adrenoreceptors in the spinal cord. The resultant norepinephrine reuptake inhibition is responsible for the negative feedback on the receptors in the substantia gelatinosa of the dorsal horns. Subsequent stimulation of those structures inhibits firing of nociceptive neurons stimulated by peripheral A-delta and C fibers as well as halting the release of substance P thus altering neuronal firing in nociceptive pathways. Dexdemetomidine, the newest agent in this class has specific and selective alpha-2 adrenoreceptor agonist. The central nervous system effects of this medication consist on activation of the alpha-2 adrenoreceptors in the brain and spinal cord and consequent inhibition of neuronal activation and transmission causing hypotension, bradycardia, sedation and analgesia. The alpha-2 receptors are present in high density at the level of locus coeruleus primarily in the pons. The majority of sedative and antinociceptive effect of dexdemetomidine and clonidine are likely manifesting by activation of neurons at this level. The higher specificity for dexmedetomidine (alpha-2:alpha-1 ratio of 1680:1) when compared with clonidine (alpha-2:alpha-1 ratio of 220:1) may be responsible for the improved sedative and analgesic effects of the dexmedetomidine.[4] However, clonidine can be administered in various preparations (oral, transdermal, intravenous, and neuraxial) making this medication more versatile and useful on an outpatient basis.[7]

Given their potent antinociceptive effect, alpha-2 adrenergic agonists have been used as adjuvants to opioid regimens in the postoperative period to treat surgical pain. In various situations when opioid analgesic may be contraindicated or restricted (severe opioid side effects such as delirium, excessive sedation, severe constipation, ileus, etc.)[8] anesthesiologists rely on alternate regimens for perioperative analgesia. We present a case of a patient with a history of opioid-induced delirium after a celiac artery decompression that underwent a hemicolectomy followed by an emergency exploratory laparotomy. Nonopioid effective analgesia was achieved throughout both perioperative periods with a regimen consisting on alpha-2 adrenergic receptor agonist agents in various routes of administration (intravenous dexmedetomidine, transdermal clonidine, neuraxial clonidine) and a thoracic epidural infusion of bupivacaine and clonidine.

CASE REPORT

A 21-year-old woman with persistent abdominal pain was scheduled for a laparoscopic hemicolectomy. Her

medical history was significant for longstanding (5 years) abdominal pain from median arcuate ligament syndrome. Four months before her present admission, she underwent celiac artery decompression and median arcuate ligament release that resulted in partial alleviation of epigastric pain. She continued to complain of right lower quadrant pain, and CT confirmed fecal impaction of the right colon suspected to be related to a redundant, dysfunctional and dilated right colon, nonresponsive to more conservative measures (laxatives, stool softeners, and frequent endoscopies). She was subsequently scheduled for hemicolectomy after colonoscopic decompression had failed multiple times.

The preoperative anesthesia assessment identified a history of postoperative opioid-induced delirium from her previous surgery. When asked about the details, both the patient and her parents described episodes of agitation, aggressiveness and increased emotional manifestations (inconsolable crying) as well as altered mental status in the immediate postoperative period after her median arcuate ligament release. She had been given 200 μg of intravenous fentanyl and 0.6 mg of intravenous hydromorphone during the surgery. In the recovery room, documentation by the anesthesia providers indicated that the symptoms worsened with the administration of 0.4 mg of hydromorphone. After 30 minutes of verbal and physical aggression, the patient became nonresponsive for 20 minutes that prompted head CT scan; it was negative for any pathology. Extensive laboratory workup was negative for any electrolyte imbalance, signs of infection, hypoglycemia, hypoxia or dehydration. Upon consultation by both psychiatry and the pain service, the patient was diagnosed with opioid-induced delirium.

Given her documented adverse reaction to intravenous opioids, the analgesic plan for the scheduled hemicolectomy was a thoracic interlaminar epidural catheter at T12-L1 for postoperative pain control. The intra-operative course was uneventful, and anesthesia was maintained with a propofol infusion at 250 μg/kg/minutes, a dexmedetomidine infusion at 0.4–0.7 μg/kg/hours, cisatracurium, and desflurane. Before surgical incision, an epidural bolus of 10 cc of 0.25% bupivacaine was administered and an infusion of bupivacaine 0.125% was started at 6 mL/hours and continued postoperatively.

In the immediate postoperative period, the patient complained of pain 6/10 on the Numerical Rating Scale (NRS) which prompted increased epidural infusion to 10 mL/hours. Her pain scores decreased to 4/10 on NRS and the patient reported decreased cold sensation in the T9 to T12 dermatomes. Addition of intravenous demedetomidine rendered the patient comfortable with reported pain scores of 1 to 2 on a 10-point Numeric Rating Scale (NRS). The analgesic regimen was maintained with the continuous epidural bupivacaine (0.125%) infusion at 10 mL/hours and intravenous dexmedetomidine infusion, 0.7 μg/kg/hours. The patient was sedated but easily arousable in the intensive care unit where vital signs and sedation scores were monitored. On postoperative (POD) 1, the dexmedetomidine infusion was discontinued and the patient was transitioned from the intensive care unit to the floor. In anticipation of postoperative visceral pain and to avoid rescue medications, neuraxial clonidine was added to the epidural solution. In addition to epidural bupivacaine, 12 μg neuraxial clonidine was administered hourly through the existing epidural catheter by changing the epidural solution to bupivacaine (0.125%) and clonidine 1 μg/mL at 12 mL/hours.

The patient remained comfortable and pain free but sedation increased on POD 3. She was given transdermal clonidine (0.1 mg/week), and epidural clonidine was discontinued. During this transition, she became less sedated and was comfortable with an NRS score of 2 to 3/10 with continuous epidural bupivacaine and a clonidine patch. Pain scores remained at 2 to 3 for another 2 days. At that time the patient underwent a second surgical intervention for abdominal distension and evacuation of an abdominal abscess.

With the second intervention, intra-operative anesthesia was maintained with intravenous propofol (200 μg/kg/minutes) and dexmedetomidine (0.8 μg/kg/hours). The epidural catheter remained in place. An aggressive analgesic regimen was initiated intra-operatively with an epidural bolus of 100 μg of clonidine, followed by a continuous epidural infusion of 0.125% bupivacaine and 2 μg/mL clonidine at 10 mL/hours. Transdermal and epidural clonidine, as well as IV dexmedetomidine, were used at the intra-operative doses for 2 days. After 2 days, the epidural catheter was removed, dexmedetomidine (0.5 μg/kg/hours) was discontinued, and transdermal clonidine was increased to 0.2 mg/week. Pain scores remained low until the patient was discharged home 3 day later. Throughout her hospital course, blood pressure varied between 80 to 100/40 to 60 seconds mmHg and heart rate between 60 and 110 beats per minute (Table 1). The

Table 1. Analgesic Regimen and Vital Signs During Hospitalization

	Medication				
Postoperative Day	Epidural	Intravenous	Transdermal	Pain Scores (NRS)	Vital Signs
1	B	D		1–2/10	BP 112/69, HR 95
2	B+C			2–3/10	BP 116/46, HR 93
3	B		C	2–3/10	BP 107/68, HR 82
4	B		C	3–4/10	BP 120/86, HR 80
5*	B+C	D	C	4/10	BP 112/77, HR 73
6	B+C	D	C	4/10	BP 114/77, HR 74
7			C	2–3/10	BP 110/71, HR 89
8–11			C	2	BP 113/61, HR 67

B, bupivicaine 0.125%; D, dexmedetomidine; C, clonidine; NRS, Numerical Rating Scale; BP, blood pressure; HR, heart rate.
*Patient underwent a second surgical intervention.

patient remained hemodynamically stable and suffered no adverse events.

DISCUSSION

In patients with a well-documented history of opioid-induced delirium, other alternatives for analgesia must be considered for the perioperative period. Delirium is defined by the American Psychiatric Association's Diagnostic and Statistical Manual. 4th edition (DSM IV) as a complex psychiatric syndrome that includes disturbance of consciousness with reduced ability to focus, a change in cognition or development of a perceptual disturbances, events that can develop over hours or days and are caused by a medical condition, substance intoxication or medication side effect. Medications alone may account for 12% to 39% of all cases of delirium.[9,10] Some medications frequently associated with delirium include opioids, anxiolytics, antidepressants, and corticosteroids.[11]

Opioid-induced delirium has been described in patients with advanced cancer, typically after escalation of opioid doses to relieve intractable pain.[11–13] The accumulation of active metabolites in patients receiving morphine, hydromorphone, or meperidine may contribute to the psychotic features encountered in terminally ill patients.[14,15] Fentanyl-induced delirium also has been reported in patients after dose escalation. In 1 case report, a 55-year-old woman experienced delirium after morphine and fentanyl doses were increased. Her delirium was successfully treated with intravenous physostigmine, an acetylcholinesterase inhibitor.[16] Patients with well-documented opioid-induced delirium present a challenge for the anesthesiologist for several reasons. In addition to the known metabolic, endocrinologic or infectious causes of an acute delirium, surgical pain itself can contribute to acute cognitive dysfunction manifesting as agitation, confusion or combativeness.[17,18] In the setting of surgical pain during emergence from anesthesia, it is often unclear whether observed delirium is a result of acute pain or administered medications. The difficulty arises when rescue medications to treat pain and agitation increase the psychiatric symptoms. In cases of known opioid-induced delirium, several treatments have been used with good results. Among them are reversal of metabolic derangements, opioid rotation, hydration, and the elimination of additional analgesics. Those techniques are more often utilized in debilitated cancer patients taking chronic opioids, in which this form of delirium is more readily encountered.

Unlike many situations described in the literature, our patient was young and taking no oral analgesic medication before her initial surgery. She had an acute episode of delirium that followed opioid (fentanyl and hydromorphone) administration and worsened with additional doses of hydromorphone. It is unclear which medication was responsible for our patient's psychotic reaction, although her symptoms were aggravated with repeated doses of hydromorphone, suggesting that it may have been the triggering agent.

When the patient needed another surgical intervention, we decided to avoid opioids entirely. Using a multimodal analgesic approach, our available options for perioperative analgesia were local anesthetics, nonsteroidal anti-inflammatory medications, alpha-2 agonists, NMDA receptor antagonists. Neuraxial blocks have been successfully used to limit the incidence of postoperative cognitive dysfunction, primarily in the elderly population.[9,15,19,20] It also has been shown to be superior to parenteral opioids for postoperative analgesia.[21,22] As our patient had a history of documented and diagnosed opioid-induced delirium and because she was expected to be strict NPO following

her surgery, we chose a regional technique as part of perioperative nonopioid analgesic regimen. However, the epidural catheter placed at T12-L1 provided only a T9-L2 sensory level in our patient despite an infusion rate of 10 mL/hours bupivicaine 0.125%. Therefore, a concurrent intravenous analgesic technique was considered. Alpha-2 adrenergic receptor agonists, such as dexmedetomidine and clonidine, are potential antinociceptive agents.[7] In addition, their routes of administration are varied, an advantage for a patient who was NPO for several days. Several small randomized studies have suggested that dexmedetomidine may decrease the incidence of delirium, although other studies have concluded no significant benefit.[23] In children, dexmedetomidine decreased the incidence of anesthesia emergence agitation.[24,25] Dexmedetomidine does not cause respiratory depression and even enables conscious awareness. In a randomized trial of 34 patients, dexmedetomidine plus morphine for postoperative analgesia reduced the need for morphine significantly compared with analgesia in the control group that received morphine alone.[26] Other studies also have demonstrated the analgesic and opioid-sparing effects of dexmedetomidine.[26,27]

Like dexmedetomidine, clonidine is an alpha-2 adrenergic receptor agonist. In animal studies, its peripheral analgesic properties were previously reported to be mediated by inhibition of the I_h cation channel, which enhanced activity-dependent hyperpolarization and decreased neuronal transmission.[28] Clonidine may have selectivity for C fibers, which mediate painful stimuli while sparing motor neurons. It has been administered via enteric, neuraxial, and intravenous routes for management of acute and chronic pain. It also has been used as an adjuvant to opioids or local anesthetics. In a study of patients with complex regional pain syndrome, epidural clonidine provided effective pain relief and sedation. Blood pressure and heart rate decreased after bolus epidural injection at doses of 300 and 700 μg. At 300 μg, the side effects including sedation were mild.[29] In the same study, epidural clonidine infused in 19 patients at a mean rate of 32 μg/hours produced good pain relief. In a randomized double-blind, controlled trial of 60 patients who had total hip arthroplasty, clonidine 15 μg was added to intra-operative spinal anesthesia with bupivacaine 17.5 mg. Postoperative epidural analgesia was achieved with ropivacaine 4 mg/hours and clonidine 40 μg/hours. Anesthesia was superior and analgesia was longer-lasting in the clonidine group compared with the patients who had regional anesthesia with a local anesthetic alone. Clonidine also had a ''morphine-sparing effect'' compared with local anesthetic alone.[30] Other studies have shown that clonidine decreased anesthetic requirements for opioids [31] and had analgesic properties.[32] Administered postoperatively, clonidine had opioid analgesic sparing effects in surgical patients.[33]

In a double-blind trial conducted in 40 male children, intravenous clonidine (2 μg/kg) prevented agitation after sevoflurane anesthesia.[34] In a small randomized trial, infusion of clonidine reduced the incidence of delirium during weaning from mechanical ventilation in the ICU.[35]Potential negatives of clonidine and dexmedetomidine are hypotension and sedation, and thus patients who receive an infusion of these agents may need to be monitored carefully. Respiratory drive is not inhibited and neurologic status is not depressed; therefore a cooperative sedation can be achieved with these medications.

The dexmedetomidine's high affinity for the alpha-2 adrenoreceptors, especially 2A subtype accounts for the more effective sedative and analgesic properties when compared with clonidine.[4] However, it can be administered only intravenously. Clonidine has multiple routes of administration making it a more useful analgesic formulation in more distant perioperative period in patients with opioid intolerance and postoperative pain. Within 48 hours, transdermal clonidine elicits same blood concentration level as the oral formulation and the effect is maintained for 7 days after a single patch application.[36,37] Epidural clonidine, acting as an antinociceptive agent on locus coeruleus neurons in spinal cord and in brain stem, has also been shown to quickly restore bowel function postoperatively by decreasing inflammatory cytokine levels in patients undergoing colorectal surgery.[38] The therapeutic goal with our patient was effective opioid-free analgesia perioperatively. Our method demonstrates the progressive use of intravenous, epidural, and transdermal administration of alpha-2 agonists for pain management as an alternative therapy in a patient with opioid-induced delirium.

In general, multimodal analgesia for the treatment of postoperative pain involves a variety of medications aiming toward various mechanisms of action. An NMDA receptor antagonist like ketamine as well as an intravenous nonsteroidal anti-inflammatory agent (NSAIDs) such as ketorolac are usually combined with alpha-2 adrenoreceptor agonists to provide

adequate analgesia. In our case, ketamine was avoided because of possible psychotropic effects and thus difficult to distinguish from a medication induced delirium. As the epidural catheter provided only partial pain relief, we used alpha-2 adrenoreceptor agonists for effective perioperative analgesia. To our knowledge, this is the first report where opioid-free analgesia was achieved with single class agents by transitioning various routes of administration. Our patient was young with no other comorbidities and was able to tolerate the titration of those agents with no change in vital signs. However, hypotensive episodes and excessive sedation can appear with administration of alpha-2 adrenoreceptor agonists even with transdermal formulation. This analgesic technique can be useful in patients at risk of developing postoperative cognitive dysfunctions, patients with opioid addiction and dependence as well as obese patients with obstructive sleep apnea at risk of respiratory depression from opioids. It may be avoided when the patients are at risk of developing postoperative hypotension such as extensive bleeding, dehydration, and cardiac dysfunction.

This case report describes an effective alternative perioperative analgesic treatment when patients are intolerant to opioids. However, it has a number of limitations. Although psychiatry consult service diagnosed our patient with postoperative opioid-induced delirium during recovery from a previous surgical intervention, it is still unclear whether her behavior with altered perception, agitation and hallucinations was a reaction to the opioids administered postoperatively, a delayed reaction to inhalational anesthetics or an underlying, undiagnosed comorbid psychiatric condition such as somatoform disorder. The diagnosis was made by clinical appearance, in the absence of metabolic, fluid and electrolytes derangements as well as a noncontributory past medical history. Another limitation of the study is that we did not use a plasma assay to identify the therapeutic levels of the medications administered. We guided our pain management regimen based on clinical and vital signs as well as daily physical examination. In addition, we used multiple interventions simultaneously, which makes it challenging to know which intervention was responsible for the observed effect. Despite these limitations, our case study showed that the analgesic properties of dexmedetomidine and clonidine, which decrease the central sympathetic discharge through alpha-2 adrenoreceptors, might prove advantageous in opioid-intolerant patients. Future prospective studies may be necessary to establish optimal transition and/or combination of alpha-2 adrenoreceptor agonists with various routes of administration to consistently achieve opioid grade analgesia using a nonopioid regimen for moderate to severe postsurgical pain.

CONCLUSION

Opioid-induced delirium is often observed with escalating doses of opioids in cancer patients. The case we describe is unique in that our patient was young and was on no opioid regimen before surgery. Her surgical pain was severe enough to require rescue analgesic intervention. We chose to avoid opioids and used alpha-2 agonist agents for her intra-operative and postoperative surgical pain. Based on her clinical presentation and vital signs, in addition to daily physical examination, we transitioned the analgesic regimen through various routes of administrations (intravenous, neuraxial, and transdermal) to maximize the antinociceptive effect of alpha-2 adrenoreceptors agonists used for perioperative pain control. This technique, effective in our case, may prove beneficial for patients in whom opioid analgesia is best avoided such as those with known delirium, dementia or opioid addiction. However, because only a single class of analgesics is used in this opioid-free regimen, medical staff should carefully monitor vital signs and pain scores to ensure maximal analgesic benefit with minimal side effects and discomfort.

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