5-22-2019

Effect of Intraoperative Dexmedetomidine Infusion on Perioperative Opioid Use

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EFFECT OF INTRAOPERATIVE DEXMEDETOMIDINE INFUSION ON PERIOPERATIVE OPIOID USE

by

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Bachelor of Science in Nursing, University of North Dakota

An Independent Study

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

Grand Forks, North Dakota

December

2019

PERMISSION

Title: EFFECT OF INTRAOPERATIVE DEXMEDETOMIDINE INFUSION ON PERIOPERATIVE OPIOID USE

Department Nursing

Degree Master of Science

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AbstractTitle: Effect of Intraoperative Dexmedetomidine Infusion on Perioperative Opioid Use

Background: A 71-year-old female patient presented for robotic right hemicolectomy. The patient had a history of colon cancer, hypertension, and allergies to penicillin and propofol. The decision was made to approach the anesthetic plan with Enhanced Recovery After Surgery (ERAS) protocols in place. These protocols are intended to decrease or eliminate opioids, guide goal-directed fluid management, and speed recovery after surgery. Dexmedetomidine infusion was added as an adjunct to this protocol, and the patient was followed to assess opioid consumption post-operatively.

Purpose: To evaluate current data related to dexmedetomidine infusion to make evidence-based recommendations on the use of the drug for perioperative purposes.

Process: A systematic literature review was carried out using the University of North Dakota's Library of the Health Sciences. Databases used include Cochrane, PubMed, and searches of CDC statistics. The search was conducted using key words and publication date limits to include recent and applicable data. Literature was synthesized to develop recommendations for an evidence-based approach to use of perioperative dexmedetomidine.

Results: Randomized control trials, systematic reviews, and case reports were included in the final synthesis of literature. The literature suggests that dexmedetomidine may be used as part of an opioid-sparing anesthetic technique. Some of the strongest evidence advocates for a dexmedetomidine/opioid PCA post-operatively to decrease post-operative opioid consumption.

Implications: ERAS protocols are well-established as methods to increase patient satisfaction, decrease opioid consumption, and improve patient outcomes. Higher quality future research is needed to determine if dexmedetomidine should be used as an analgesic adjunct. Initial studies

suggest that dexmedetomidine infusion is a viable adjunct for opioid-sparing anesthetic techniques.

Keywords: Dexmedetomidine, ERAS, opioid-sparing, pain

EFFECT OF INTRAOPERATIVE DEXMEDETOMIDINE INFUSION ON PERIOPERATIVE OPIOID USE

Background

Epidemiologic data presented by the Center for Disease Control and Prevention (CDC) reports that in 2015, there were 174.6 per 100,000 non-fatal drug-related overdoses brought to Emergency Rooms (ERs) in the United States. Of these, opioids had the highest incidence, followed by heroin, methadone, and "other opioids", with all of these making up just over 50% of the total ER visits. Similarly, the CDC reported that 42,249 opioid-related overdose deaths occurred in 2016, which accounted for 66% of all drug-related deaths. What complicates this, and leads to great concern within the medical community, is that over 14,000 of those deaths (and possibly more) can be traced back to prescription opioids (CDC, 2018). Opioids are often prescribed to control post-operative pain.

Opioids have been a reliable and effective form of perioperative pain control for hundreds of years, stemming from the historical use of the opium poppy. While effective, they do come with an undesirable array of side effects including nausea, vomiting, constipation, urinary retention, respiratory depression, and dependence (Nagelhout & Elisha, 2018). A recent study demonstrated that interventions anesthesia professionals utilized intraoperatively had the potential to decrease the opioid requirement post-operatively, even in those who are already opioid-dependent prior to surgery (Nielsen, Fomsgaard, Nikolajsen, Dahl, and Mathiesen, 2018).

Opioids have been considered a primary analgesic in the practice of anesthesia due to both their efficacy in pain management and their low cost. This current opioid epidemic in the United States has created a unique situation for patients in the perioperative realm. Because the need exists for adequate intraoperative and post-operative pain control, anesthesia professionals must continue to consider opioid alternatives for analgesia. Enhanced recovery after surgery

(ERAS) protocols have begun to shape the way that anesthesia professionals approach their analgesic plans. In this paper, the author described current ERAS methods and sought to determine if there is a place for dexmedetomidine infusions within these protocols. Because of this, the author chose to research the question "In patients having outpatient surgery, does perioperative use of intravenous dexmedetomidine versus traditional opioid anesthesia produce decreased perioperative use of opioids?"

Case Report

A 71-year-old, 165 cm, 120 kg female patient presented for a robotic right hemicolectomy. Her past medical history included asthma, hypertension and LVEF of 55%, GERD, colon cancer, morbid obesity, and arthritis. Past surgical history included previous sigmoidectomy for colon cancer, as well as colonoscopy and esophagoduodenoscopy. Home medications included baby aspirin, losartan-hydrochlorothizide, multivitamin, and albuterol inhaler. She had drug allergies to penicillin, ketorolac, and propofol. Pre-anesthetic evaluation revealed history of post-operative nausea and vomiting, as well as history of difficult intubation. Airway evaluation showed a Mallampati score of 2, temporomandibular distance of greater than 3 fingerbreadths, full neck range of motion, and intact dentition. Baseline vital signs were within normal limits. The patient was classified as an ASA Physical Status 3. An l8-gauge IV was started in the preoperative holding room with LR infusing by gravity.

The patient was given midazolam 2 mg and taken back to the operating room. She was transferred to the operating room table and standard noninvasive monitors were attached along with bispectral index monitoring. The patient was preoxygenated with 15 liters per minute 100% O2 by mask. General anesthesia was induced with etomidate 12 mg, ketamine 30 mg, fentanyl 100 mcg, lidocaine 50 mg, and rocuronium 50 mg. The patient was successfully intubated on the

first attempt with a Macintosh 3 blade (Grade II Cormack-Lehane view), 7.0 endotracheal tube with stylet. Endotracheal tube placement was confirmed with $EtCO_2$ and bilateral breath sounds were auscultated. The tube was secured with tape, sevoflurane was initiated at ½ MAC, and fresh gas flows were decreased to O_2 0.5 L/min and air 0.5 L/min. Magnesium 3g was bolused over 30 minutes, and dexmedetomidine 0.5-0.7 mcg/kg/hr infusion was initiated along with lidocaine infusion at 1 mg/kg/hr LBW (60 mg/hr).

Clindamycin 900 mg and Metronidazole 500 mg were initiated after induction, and dexamethasone 8 mg and ondansetron 4 mg were administered for PONV prophylaxis. Vital signs remained within normal limits throughout the case with the use of a phenylephrine infusion, as well as 25 mg total of ephedrine. Intravenous fluids totaled 1,600 ml with 180 ml of urine output, and an estimated blood loss of 50 ml. Per the facility's ERAS protocol, ketamine 30 mg was administered each hour throughout the case for a total of 120 mg. The patient was reversed with sugammadex 300 mg. An awake extubation was performed, with the patient stating comfort upon arrival to the post-anesthesia care unit. No narcotic medications were given in the immediate post-operative period.

Post-operative pain control was discussed with the surgeon, and an agreement was made to put the patient on scheduled acetaminophen and gabapentin postoperatively with oxycodone-acetaminophen tablets for breakthrough pain. Within 24 hours postoperatively, the patient had received only two narcotic doses for breakthrough pain.

Methods

A search of the current literature was performed on several resource databases through the University of North Dakota Health Sciences Library, including PubMed, ClincalKey, and Cochrane. Each search was limited to include articles in the English language less than five years

old, and studies related the adult human population (19+ years of age). These limits were chosen to obtain relevant, recent data on adult patients. MeSH keywords such as dexmedetomidine, analgesia, postoperative, opioid, anesthesia, opioid free, multimodal, and postoperative opioids were used. The date limits were increased to include all articles 15 years or newer related to "intravenous dexmedetomidine analgesia" due to lack of recent evidence specific to the intravenous route of administration.

Cochrane database was searched to find Cochrane reviews and trials related to opioid-free anesthesia using the search terms opioid AND free AND anesthesia, as well as dexmedetomidine AND analgesia. During this search, only 7 Cochrane reviews were returned, only one of which was relevant to the current topic of decreasing post-operative opioid use.

Alternative websites were searched, including the American Association of Nurse Anesthetists website for position statements on opioid prescribing, the use of intraoperative and post-operative opioids, and opioid-free anesthesia. The United States Centers for Disease Control and Prevention website was searched for position statements on the opioid crisis, as well as epidemiologic data regarding drug poisonings and overdoses. Information was also found in a recently revised anesthesia textbook. Three total sources have been used outside of PubMed.

Discussion

Enhanced Recovery After Surgery

Enhanced recovery after surgery, or ERAS, is a growing movement of improving patient outcomes and shortening hospital stays through judicious use of pharmaceuticals and patient care techniques. As anesthesia professionals, one of the main roles that we play in ERAS involves the use of multimodal analgesia (MMA) intraoperatively. Multimodal analgesia means the use of non-opioid analgesics, as well as balanced use of opioids, to achieve perioperative pain control.

Lavand'homme and Estebe (2018) discussed undesirable side effects of opioid analgesia, including opioid-induced hyperalgesia, post-operative nausea and vomiting, constipation, ileus, and dependence. According to these authors, the side effects of opioids can lead to long-term chronic pain, as well as prolonged hospital stay.

Reagan, O'Sullivan, Gannon, and Steinberg (2017) explored the role of an opioid-free anesthetic (OFA) in post-operative opioid use for patients undergoing reconstructive pelvic surgery. In the randomized control study of 138 participants, MMA and opioid-sparing methods were found to provide equivalent pain control while decreasing post-operative opioid requirements. McLaughlin et al. (2018) found similar results when they paired multimodal analgesia with patients undergoing shoulder arthroplasty. Their prospective cohort study involved two groups of 75 participants each: one who received standard opioid anesthesia, and one who received a multimodal regimen. The multimodal group had lower pain scores on post-operative day 0,1, and 2 ($P < .01$), as well as shorter hospital stays ($P < .01$), and had no more complications than traditional opioid analgesia. The shorter hospitalization described by McLaughlin et al. (2018) also provided for an average of $1,000 USD less in overall hospital costs for patients undergoing MMA. While the figure was not found to be statistically significant, it stands to reason that the average patient may consider this a benefit.

So, what exactly is MMA? According to Brown, Pavone, and Naranjo (2018), this technique involves administering different drugs (with different mechanisms of action) together to achieve the anesthetized state. By doing this, the amount of each individual drug given is decreased versus a technique which uses only one or very few different agents. In the same way that a state of surgical anesthesia can be achieved with a multimodal approach, so can analgesia

during the perioperative period. To accomplish this, we must both define pain *and* understand the methods of pain transduction.

Brown et al. (2018) made a clear distinction between the definition of pain and nociception. Pain is considered a conscious perception of painful stimuli whose severity depends on patient perception. This definition, while broad, is in congruence with the well-known definition saying that pain is "whatever the patient says it is." Nociception is the actual transmission of painful stimulus within the nervous system. While nociception is sometimes what causes patients to perceive pain, it also can cause hemodynamic and humoral response changes such as hypertension, tachycardia, and cortisol release, even while patients are in the anesthetized state.

Mechanisms of Pain Modulation

Clarke et al. (2012) stated that pain can be classified as acute (less than 3 months duration) or chronic (lasting greater than 3-6 months). The cause of acute pain is generally known, which is what separates it from chronic pain, and these authors highlight the new knowledge that poorly treated surgical pain can be a precursor to chronic pain. Chronic post-surgical pain can be prevented with a multimodal approach using neuraxial techniques, peripheral regional techniques, and drugs with multiple mechanisms of action. Ideally, pain management would be proactive, or anticipatory.

Clarke et al. (2012) state that somatic and visceral pain are well-controlled by opioid analgesics, while neuropathic pain may be better treated by more unconventional pain medications such as antidepressants, gabapentinoids, muscle relaxants, and intravenous infusions such as lidocaine, ketamine, and dexmedetomidine.

Not all types of pain respond to the same pain medications. Lavond'homme and Estebe (2018) highlighted the multiple pathways and causes of nociception, including glutamate (fast onset, sharp pain), substance P (a peptide found in and released from peripheral afferent nociceptor C fibers), bradykinin, histamine, serotonin (5-HT), and prostaglandins among others, and discuss multimodal analgesic agents that may enhance both intraoperative and post-operative pain (Nagelhout & Elisha, 2018). With so many modes of pain transmission, it is important to note that the opioid pathway is only one of many that may be modulated to manage pain.

Non-Opioid Analgesic Methods

Ketamine. Ketamine is a phencyclidine that produces analgesia through antagonism of the N-methyl-D-aspartate (NMDA) receptor, as well as inhibition of mu, delta, and kappa opioid receptors. This drug generally provides analgesia and anesthesia without loss of respiratory reflexes (Nagelhout & Elisha, 2018). Aronsohn et al. (2018) wrote a case report on intraoperative use of ketamine to enhance analgesia for a morbidly obese patient (BMI 50.1 kg/m^2) undergoing a laparoscopic gastric sleeve procedure. The patient presented for surgery with a history of obstructive sleep apnea (OSA), non-compliant with her CPAP. With the goal of avoiding adverse respiratory events related to narcotics, the authors used ketamine as part of an opioid-free total intravenous anesthesia protocol. The case proceeded with a ketamine loading dose of 5 mg/kg and a maintenance infusion of 5 mcg/kg/min. This case report states that the patient had comparable analgesia to an opioid technique, but had no episodes of apnea, hypoxia ($SpO2 < 93\%$), or airway obstruction in the PACU. In addition to meeting outcomes for respiratory function, the patient was also ambulating unassisted at 90 minutes post-op.

There is evidence to show that intraoperative use of ketamine infusions is helpful for pain control, even in patients with chronic pain and opioid use. A randomized, double-blind study of

147 patients by Nielsen, Fomsgaard, Nikolajsen, Dahl, and Mathiesen (2018) showed that patients with chronic opioid-dependent pain undergoing spinal fusion have decreased use of opioids one year from surgery and have higher workforce association when intraoperative ketamine is used. While this does not relate immediately to postoperative or intraoperative analgesia, it shows that our nation's opioid crisis can be combated partially by what anesthesia professionals do intraoperatively.

Lidocaine. Boysen, Pappas, and Evans (2018) wrote a case comparison of two patients undergoing general anesthesia, one for bariatric surgery and one for endoscopic retrograde cholangiopancreatogram (ERCP). Both patients were administered intraoperative infusions of lidocaine and dexmedetomidine for pain control and sedation. As with many of the other studies, analgesics including subanesthetic doses of ketamine, as well as intravenous acetaminophen and ketorolac were used to maintain analgesia, and both patients were discharged having received no narcotics (Boysen, Pappas, & Evans, 2018). These examples, while few, are evidentiary to the possibility of a fully opioid-free anesthetic option, even for major surgeries such as bariatrics. Opioid-free analgesia can be achieved with modes such as these, in addition to administration of dexamethasone, selective cyclooxygenase-2 inhibitors such as celecoxib, and intravenous NSAIDS such as ketorolac can offer equivalent analgesia with potentially fewer undesirable side effects (Barazanchi, MacFater, Rahiri, Tutone, Hill, & Joshi, 2018).

Dexmedetomidine. Intraoperative infusions of dexmedetomidine have become an area of interest for anesthetists looking to decrease perioperative narcotic administration. A prospective, randomized, double-blind trial by Bakan et al. (2015) explored the use of dexmedetomidine infusions in patients undergoing laparoscopic cholecystectomy. Eighty patients of physical status I-II were allocated into two groups, one opioid free with propofol, dexmedetomidine, and

lidocaine infusions, and one with remifentanil and propofol infusions. These authors found that while dexmedetomidine can result in slower waking times, it is also associated with significantly lower pain scores, fewer rescue analgesic, and fewer rescue anti-emetics.

One of the most promising areas of research involves perioperative administration of dexmedetomidine, whether within intrathecal mixtures, nerve block mixtures, or as part of an intravenous anesthetic and analgesic cocktail. For the purposes of this case report, the intravenous method will receive primary focus as part of the MMA technique.

Mechanism of action. Dexmedetomidine is a relatively selective alpha-2 agonist whose anti-nociceptive effects can be explained by stimulation of alpha-2 adrenoreceptors in the brain (locus coeruleus) and spinal cord, as well as hyperpolarization of interneurons and reduction of substance P and glutamate. The analgesic effect has been shown to be minimal at doses intended for light sedation. However, Weerink et al. (2017) found that the opioid-sparing effect stemming from altered perception and reduced anxiety may still be beneficial. Dexmedetomidine has the added benefit of providing sedative, anxiolytic, and antiemetic properties, even more so than its less-selective alpha-2 agonist relative, clonidine (Blaudszun et al., 2012).

Dexmedetomidine is rapidly distributed, with an initial distribution half-life of 6 minutes and a terminal elimination half-life of 2 hours. It is metabolized into only inactive metabolites and excreted primarily through hepatic and renal modalities. Because of this, the initial dose of dexmedetomidine should be decreased in patients with chronic hepatic or renal insufficiency, or those at risk for developing these conditions (Nagelhout & Elisha, 2018).

According to Weerink et al. (2017), dexmedetomidine hydrochloride is generally diluted to a concentration of 4 mcg/ml or 8 mcg/ml prior to infusion. The drug comes in two brand names; Dexdor and Precedex. Dexdor's instructions state to start at an initial infusion rate of 0.7

mcg/kg/hr with no loading dose, and titrate to effect with dose range 0.2-1.4 mcg/kg/hr. Precedex's instructions state to begin with a loading dose of 1 mcg/kg over 10 minutes, and follow with maintenance infusion of 0.2-0.7 mcg/kg/hr. Procedural sedation allows the same loading dose of 1 mcg/kg over 10 minutes, with dose range 0.2-1 mcg/kg/hr.

Dexmedetomidine is FDA approved for intravenous use for up to 24 hours. It is highly protein-bound, with 94% bound to albumin and alpha-1-glycoprotein in plasma. It easily crosses the blood-brain barrier and placenta, and the apparent volume of distribution is related to body weight. Ingrande and Lemmens (2010) discussed that dosing in the morbidly obese should often be based on lean body weight, but there are no specific recommendations for dosing dexmedetomidine infusions. Dexmedetomidine undergoes an extensive first-pass effect when given orally, leaving only 16% bioavailable. Intranasally, it is well-absorbed (Weerink et al., 2017).

Adverse effects. Coadministration of dexmedetomidine in addition to other anesthetic modalities such as propofol, inhaled agents, and opioids can lead to compounding hemodynamic effects including bradycardia and hypotension. A balanced technique should be used to avoid these potential adverse effects.

Preoperative Applications

Pasin et al. (2015) provided a meta-analysis of dexmedetomidine versus midazolam for preoperative sedation in pediatrics. While this paper focuses on adult patients, it is worth noting that the authors noted the pediatric patients had significantly decreased anxiety on separation from the parents, decreased postoperative agitation, and more effective postoperative analgesia compared to midazolam. It should also be noted that the use of dexmedetomidine in pediatric patients is not FDA approved, and more research is required to gain approval for this use.

According to Weerink et al. (2017), preoperative sedation can be achieved in pediatric patients and uncooperative elderly patients by means of intranasal dexmedetomidine. While this is not currently an FDA-approved method of administration for the drug, it has been shown to be effective due to bioavailability of the drug through mucosal membranes. More research would need to be done to determine dexmedetomidine's usefulness in this way, and to determine whether this also has opioid-sparing effect.

Naaz and Ozair (2014) described a dosing regimen in their review of dexmedetomidine in practice. According to this review, a dose of dexmedetomidine 0.33-0.67 mcg/kg IV or 2.5 mcg/kg IM may be given 15 minutes preoperatively for sedation and reduction of oxygen consumption.

Intraoperative Applications

The subject of this case report was administered dexmedetomidine 0.5-0.7 mcg/kg/hr intraoperatively. While there are preoperative and postoperative indications for use of dexmedetomidine, the protocols at this hospital allowed only for intraoperative infusion. As stated previously, dexmedetomidine was used as an adjunct along with lidocaine 1 mg/min IV, as well as magnesium and ketamine boluses.

A meta-analysis by Singh et al. (2017) explored the role of intraoperative dexmedetomidine infusion for 24-hour post-operative analgesic requirements in obese patients undergoing bariatric surgery. The authors found that both intraoperative and postoperative infusions of dexmedetomidine resulted in an opioid-sparing effect in early and extended postoperative courses. These morbidly obese patient had not only improved pain control, but they also benefitted from lower incidence of postoperative nausea and vomiting than their placebo counterparts (Singh et al., 2017).

Another study by Bielka, Kuchyn, Babych, Martycschenko, and Inozemtsev (2018) discussed the use of dexmedetomidine infusion of 0.5 mcg/kg/hr vs saline placebo from induction of anesthesia until extubation in a group of physical status 1-2 patients undergoing laparoscopic cholecystectomy. These authors found that patients had lower incidence of postoperative pain, longer time to first use of rescue analgesia, and an overall decrease in postoperative opioid consumption.

During cervical spine cases, it is imperative that the patient have an adequate airway for extubation, which can often mean careful titration of narcotics. Gandhi et al. (2017) conducted a randomized controlled trial of 60 patients, split into two groups. One received a dexmedetomidine loading dose of 1 mcg/kg over 10 minutes, followed by an intraoperative infusion of 0.5 mcg/kg/hr, followed by a reduced infusion of 0.2 mcg/kg/hr for 24 hours postoperatively. The second group received a volume matched bolus and infusion of saline. The authors found that the dexmedetomidine regimen decreased anesthetic requirement intraoperatively and provided effective analgesia postoperatively (Gandhi et al., 2017).

While there are studies looking at adding dexmedetomidine to regional anesthesia to prolong the duration of peripheral nerve blocks, some studies have shown that an intravenous bolus of the drug may also prolong block duration. Kang et al. (2018) conducted a prospective, double-blind, randomized controlled trial of 72 patients. The goal of the study was to determine first pain at surgical site in patients having interscalene block (ISB) for shoulder surgery. Each patient received an ISB with 15 ml 0.5% ropivacaine, and then four groups (n = 18 in each) were assigned to receive a 50 ml bolus over 30 minutes of either saline placebo, or dexmedetomidine 0.5 mcg/kg, 1 mcg/kg, or 2 mcg/kg. The researchers determined that a 2 mcg/kg bolus provided superior block duration ($p < 0.001$) compared to the other groups.

Lastly, Shin et al. (2018) conducted a randomized controlled trial in which 48 patients undergoing total knee arthroplasty with spinal anesthesia were split equally into two groups. The first group was given a 1 mcg/kg bolus of dexmedetomidine followed by an infusion of 0.1-0.5 mcg/kg/hr for intraoperative sedation. The second group was given continuous propofol infusion. The dexmedetomidine sedation was associated with a small, but statistically significant difference in 24 and 48-hour post-operative opioid consumption.

Postoperative Applications

Postoperatively, dexmedetomidine may be used in conjunction with narcotic analgesics to decrease the total amount of narcotic received and improve analgesic effect and subjective sleep quality. Li et al. (2018) conducted a pilot randomized controlled trial of 58 adults 60 years of age or older after open abdominal surgery. These authors found that the primary outcome, 72-hour morphine consumption, was significantly lower when morphine patient-controlled analgesia was supplemented with dexmedetomidine versus morphine alone. The intervention group in this study received morphine 0.5 mg/ml with dexmedetomidine 2 mcg/ml in normal saline 100 ml. The patient-controlled analgesia was set to deliver a 2 ml bolus with an 8 minute lock-out period. Pertinent secondary outcomes were measured in this group, and pain intensity was significantly lower in the intervention group while sleep quality was significantly higher (Li et al., 2018).

The subject of this case study received no narcotic or other pain medication in PACU, and only two doses of oxycodone-acetaminophen 5-325 within 24 hours after surgery. She also had no significant post-operative hypotension or bradycardia. A Cochrane systematic review conducted by Lundorf, Nedergaard, and Moller (2016) included seven studies with a total of 492 participants. Most of the studies found a decrease in rescue opioids within 24 hours after surgery, but no significant decrease in postoperative pain. This is still significant, as it means that there

has been a decrease in opioid consumption. The review also found an increased risk of post-operative hypotension with high-dose infusions, relatively low risk with lower dose infusions.

In addition to lowering perioperative narcotic requirements, postoperative nausea and vomiting was shown to be less in patients receiving dexmedetomidine versus placebo. This review stated the evidence to be very low to low due to the heterogeneity and potential bias of the studies included. The authors of this review point out that additional studies of higher quality should be done to determine the full scope of effect for perioperative dexmedetomidine.

Recommendations

Recommendation #1

To improve patient experience and pain management, anesthesia professionals should administer preoperative membrane stabilizers (such as pregabalin or gabapentin), selective COX-2 inhibitors (such as celecoxib or meloxicam), and acetaminophen when not contraindicated. This recommendation is backed by several high-quality studies that show preoperative administration of these medications can provide enhanced recovery after surgery.

Recommendation #2

Anesthesia professionals should consider using dexmedetomidine infusions in the intraoperative period to enhance pain control, control the stress response to surgery, and assist in sedation. Further studies are necessary to confirm its efficacy, but the initial evidence is showing good results and better immediate postoperative pain control with the use of dexmedetomidine infusions.

Intravenous dexmedetomidine bolus of 2 mcg/kg over 30 minutes after induction may also have a role in prolonging the effects of peripheral and neuraxial anesthesia by increasing the time until first pain at surgical site requiring rescue analgesia. These techniques should be used

when prudent and possible to mitigate the use of intraoperative opioids and promote post-operative pain control. This recommendation is based on Grade A evidence showing that for as long as the peripheral nerve block lasts, pain is well-controlled without opioids or with minimal opioid administration. Use of peripheral regional anesthesia allows for up to 24 hours of postoperative analgesia, depending on the local anesthetic agent used (Nagelhout & Elisha, 2018; Kang et al., 2018).

Recommendation #3

Further research is needed to determine the true value of intraoperative and post-operative dexmedetomidine infusions for post-operative pain control. As ERAS protocols become more commonly used, a randomized controlled study for protocols with and without dexmedetomidine could be used. This would provide insight as to whether it is the other components of ERAS (such as lidocaine, ketamine, and magnesium) that are providing for improved pain management, or if dexmedetomidine itself has added benefit. Future research should also look to determine whether dexmedetomidine should be bolused and infused at total, ideal, or lean body weight, and whether there are specific effective dosing regimens for bolus and infusion.

Conclusion

While there are many non-opioid methods of analgesia that may be employed by a prudent anesthesia professional, the use of intraoperative infusion of dexmedetomidine should be considered when a multimodal analgesic technique is utilized to decrease opioid use and improve patient outcomes and satisfaction. This idea is consistent with the position statement made by the American Association of Nurse Anesthetists (AANA) regarding the opioid crisis in America. It is the responsibility of anesthesia professionals to collaborate with the interdisciplinary team to

create comprehensive post-operative pain management strategies. In doing this, the interdisciplinary team can decrease or eliminate the need for opioid pain medications throughout the perioperative period (AANA, 2018).

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Appendix

Effect of Intraoperative Dexmedetomidine Infusion on Perioperative Opioid Consumption

Lindsey Holter, SRNA

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Introduction

- CDC reported over 42,000 opioid-related overdose deaths in 2016
  - Over 14,000 of those deaths can be traced back to prescription opioids
- Opioids usually prescribed for postoperative pain
  - Effective, inexpensive
  - Many side effects
    - N/V, Constipation, urinary retention, respiratory depression, addiction

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Introduction

- Enhanced Recovery After Surgery (ERAS) protocols are changing the way anesthesia professionals approach analgesic plans
  - Non-opioid analgesic adjuvants such as ketamine, lidocaine, magnesium, acetaminophen, Toradol
  - Fluid balance, temperature management, post-op pain management also important
- Does perioperative use of IV dexmedetomidine produce decreased use of perioperative opioids?

(Lavand'homme & Estebe, 2018; Reagan et al., 2017)

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Case Information

- Robotic R Hemicolectomy
- 71 y/o Female
- 120 kg, 165 cm
- PS 3
- Allergy to Penicillin, Propofol, and ketorolac
- Pertinent Home Meds: losartan-HCTZ, Albuterol Inhaler

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Pre-operative Evaluation

- PMH: Asthma, HTN, LVEF 55%, GERD, colon cancer, morbid obesity, and arthritis.
- PSH: Sigmoidectomy, colonoscopy, EGD
- Pre-op VS were WNL
- EKG showed NSR, pre-op labs WNL
- MP II, TMD > 3, Full neck ROM, intact dentition

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Anesthetic Course

- GETA with 7.0 ETT
- Mac 3 blade
  - Grade II View
  - Confirmed with $EtCO_2$ and bilateral breath sounds
- Chosen due to robotic/laparoscopic surgery and paralytic requirement

- Pre-op
  - Midazolam 2mg
- Induction
  - Etomidate 12 mg
  - Ketamine 30 mg
  - Fentanyl 100 mcg
  - Lidocaine 50 mg
  - Rocuronium 50 mg
- Maintenance
  - Sevoflurane 0.5 MAC
  - Magnesium 3g over 30 min
  - Lidocaine 1 mg/min
  - Dexmedetomidine 0.5-0.7 mcg/kg/hr
  - 30 mg ketamine Q1H/total 120mg
- Emergence
  - Sugammadex 300 mg

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Intraoperative Issues

- Difficult induction, miscommunication with MDA
- Hypotension
  - Ephedrine 25 mg total
  - Phenylephrine infusion
- Otherwise, intraoperative course was smooth, no issues noted
- Surgeon had planned on scheduled narcotic, discussed making it only PRN for breakthrough, scheduling acetaminophen and gabapentin

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PACU

- Ran lidocaine through arrival at PACU
- PACU course was uneventful
- Patient was sleepy, but comfortable
- No narcotics required during PACU stay, patient stayed for about an hour and then transferred to the floor

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Enhanced Recovery After Surgery

- Goal of improving patient outcomes and shortening hospital stays
- Intraoperative Multimodal Analgesia
  - Biggest role that anesthesia professionals play
  - Judicious use of opioids, use of adjunct analgesics
- Reagan et al. (2017) found that MMA and opioid-sparing analgesics provided equivalent pain control, decreased post-op opioids
- McLaughlin et al. (2018) found a shorter hospital stay and decreased pain scores in patients undergoing shoulder arthroplasty with a multimodal analgesia regimen versus traditional opioid anesthesia

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Multimodal Analgesia

- Lavand'homme and Estebe (2018) highlighted multiple pathways of nociception
  - Glutamate, substance P, bradykinin, histamine, 5-HT$_3$, and prostaglandins
- Opioids are clearly not the only way to modulate the pain response in patients
  - ketamine (NMDA, mu, delta)
  - Magnesium (NMDA – adjunct)
  - Celecoxib (COX-2, prostaglandin inhibitor)
  - Local anesthetics on Na-channels, nerve blocks or intradermal

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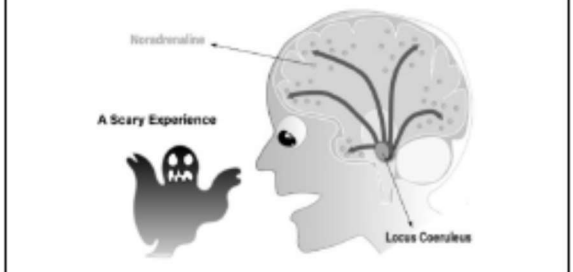
Dexmedetomidine



https://i2.wp.com/sltn.hms.harvard.edu/

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Perioperative Dexmedetomidine

- Dexmedetomidine is a selective alpha-2 agonist (much more selective than clonidine)
  - anti-nociceptive effect can be explained by stimulation of a-2 receptors in locus coeruleus and spinal cord
  - Hyperpolarization of interneurons, reduction of substance P and glutamate
  - Sedative, anxiolytic, and antiemetic properties as well
- Half-life of 6 minutes, terminal elimination half-life of 2 hours
  - Only inactive metabolites
  - Eliminated hepatically and renally
- Adverse effects:
  - Compounding hemodynamic effects with other anesthetics
  - Bradycardia and hypotension most frequent
  - Dose adjustments in patients with hepatic and renal dysfunction

(Blaudszun et al., 2012; Weerink et al., 2017)

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Perioperative Dexmedetomidine

- Bakan et al. (2015) described lower pain scores with opioid-free TIVA for lap chole
  - Dexmedetomidine, lidocaine, propofol
  - Added benefit of fewer rescue analgesics, fewer rescue anti-emetics
- A few ways to run this drug:
  - Brand name Precedex states to begin with a loading dose of 1 mcg/kg over 10 minutes, follow with infusion of 0.2-0.7 mcg/kg/hr
  - FDA approved for use up to 24 hours
  - Extensive first-pass effect orally
  - Well-absorbed intranasally

(Weerink et al., 2017)

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Pre-operative Applications

- Pasin et al. (2015) noted that pediatric patients had significantly decreased anxiety on separation from parents, decreased postoperative sedation, and more effective analgesia post-op when given dexmedetomidine versus midazolam.
- Dexmedetomidine not yet FDA approved for pediatric use.
- Naaz and Ozair (2014) suggest a dose of 0.33-0.67 mcg/kg IV or 2.5 mcg/kg IM may be given to adults 15 minutes preoperatively for sedation instead of midazolam.

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Intraoperative Implications

- Bielka et al. (2018) studied the use of dexmedetomidine 0.5 mcg/kg/hr vs saline placebo for patients undergoing lap chole.
  - Lower incidence post-op pain, longer time to first rescue analgesia, overall decrease in post-op opioid consumption
- Gandhi et al. (2017) studied patients undergoing c-spine surgery
  - LD 1 mcg/kg, infusion 0.5 mcg/kg/hr, post-op 0.2 mcg/kg/hr
  - Decreased intraop anesthetic requirement
  - Effective post-op analgesia compared to saline placebo

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Intraoperative Applications cont...

- Kang et al. (2018) found that dexmedetomidine bolus extended time to first pain at surgical site in patients undergoing ISB for shoulder surgery
  - Each patient 15 ml 0.5% ropivacaine for ISB
  - N=18 in each group, each got 50 ml bolus
  - 2 mcg/kg > 1 mcg/kg > 0.5 mcg/kg > saline placebo
- Implication for extending PNB duration

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Post-operative Applications

- Li et al. (2018) conducted an RCT of 58 adults age 60+ after open abdominal surgery.
  - Primary outcome was 72-hour morphine consumption
  - Intervention group received morphine 0.5 mg/ml with 2mcg/ml dexmedetomidine PCA
    - 2 ml bolus with 8 minute lockout period
  - Control had just 0.5 mg/ml morphine PCA
  - Morphine consumption was significantly decreased, secondary outcomes of pain intensity was significantly lower, and sleep quality significantly higher.

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Recommendations

1. To improve patient outcomes along ERAS guidelines, administer:
   - Preoperative gabapentinoids
   - Selective COX-2 inhibitors
   - Acetaminophen
2. Consider use of dexmedetomidine in the perioperative period.
   - Enhances pain control
   - Decreases stress response to surgery
   - Evidence that it prolongs regional anesthesia

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Recommendations

3. For Future Research:
   - Recommend trials with ERAS protocol plus/minus dexmedetomidine
   - Would allow a clearer picture as to whether it has beneficial effect
   - Could also focus on recommendations for infusions at ideal, total, or lean body weight
   - Determine specific effective dosing regimens

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Conclusion

- The subject of this case study went on to have adequate pain control within 24 hours post-operatively, and received only 2 doses of oxycodone-acetaminophen (5-325) for breakthrough pain within that 24 hour period.
- As anesthesia professionals, we should assimilate new data and collaborate with our interdisciplinary team to improve our practice and improve patient outcomes.
- Interdisciplinary discussions can help create comprehensive post-operative pain management strategies.

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Thank You
Are There Any Questions?

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