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Perioperative Methadone Use and Postoperative Pain Control in Adult Patients

Undergoing Elective Spinal Fusion Surgery

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Abstract

Patients undergoing elective spinal fusion surgeries often experience moderate to severe postoperative pain (Murphy et al., 2017). The use of perioperative methadone has been suggested as an effective adjunct for patients to reduce postoperative pain, decrease opioid use, and improve patient satisfaction (Murphy et al., 2017). Traditional opioid management of orthopedic spine surgeries include intermittent injections or patient-controlled analgesia devices. These approaches may cause fluctuating levels of opioids or require patient education and cooperation to be effective (Murphy & Szokol, 2019). Methadone has a much longer elimination half-life when compared to other opioids, and therefore may provide patients with a stable blood concentration of opioid to improve postoperative pain control (Murphy & Szokol, 2019). In adult patients undergoing elective spine surgery, how effective is perioperative methadone use compared to traditional opioid management in controlling postoperative pain in the first 24 hours?

Keywords: methadone, postoperative pain, spinal fusion, literature review

Perioperative Methadone Use and Postoperative Pain Control in Adult Patients Undergoing Elective Spinal Fusion Surgery

Despite advances in multimodal pain management practices, postoperative pain control remains a significant issue within the United States. Around 80% of surgical patients report postoperative pain and, more concerning, 88% of those patients reporting pain would describe the pain as moderate to severe in intensity (Murphy et al., 2021). Patients undergoing spinal fusion surgery are at an elevated risk for moderate to severe postoperative pain, as well as increased risk for complications related to pain and opioid use (Murphy et al., 2021). In a study comparing the pain scores of 179 surgical procedures, one half of the surgeries that resulted in a pain score of 7 (on a rating scale of 0-10) on postoperative day one were major spinal surgeries (Murphy et al., 2021). Murphy & Szokol (2019) found that even after procedures that were deemed to be minor, more than 50% of patients experienced moderate to severe pain. Adding to the difficulties of controlling postoperative pain after spinal surgeries, many patients have chronic pain resulting in chronic opioid use prior to the added insult of surgical pain (Murphy et al., 2017). Despite improved technologies and techniques, uncontrolled postoperative surgical pain remains a considerable issue.

Inadequate postoperative pain control may have systemic physiologic effects such as arrhythmias, hypoventilation, and delirium. Adverse events from postoperative pain include increased hospital length of stay, costs, morbidity, and mortality (Machado et al., 2019). Patients with increased pain may also have decreased physical function, decreased patient satisfaction, reduced sleep, and prolonged use of opioids after surgery (D'Souza et al., 2020). During the early postoperative period, poorly controlled pain is a risk factor for the development of chronic postsurgical pain (D'Souza et al., 2020). Patients often have chronic pain prior to surgery and

may be sensitized to painful stimuli postoperatively (Murphy et al., 2017). Other factors contributing to postoperative pain include opioid-induced hyperalgesia and acute tolerance (Murphy et al., 2017). Further complications from uncontrolled pain affecting multiple organ systems including coronary ischemia, arrhythmias, hypoventilation, pulmonary infections, ileus, urinary retention, and delirium (D'Souza et al., 2020). Inadequately controlled postoperative pain has multiple deleterious physiologic effects for postoperative patients after undergoing spinal fusion surgery.

Poorly controlled postoperative pain leading to increased opioid consumption adds further complications. Side effects from increased narcotic use include respiratory depression, nausea and vomiting, constipation, pruritus, and urinary retention (Machado et al., 2019). Excessive use of opioids can also lead to misuse and addiction (Lobova et al., 2021). According to the Centers for Disease Control and Prevention (2022), more than 564,000 people have died from opioid overdoses from 1999 to 2020, from both prescription and illicit narcotics. Data also indicated that opioids were involved in over 68,000 deaths in 2020 alone, which was 8.5 times the number of opioid-related deaths that occurred in 1999 (Centers of Disease Control and Prevention, 2022). Acute postoperative pain risks progression to chronic pain syndromes, resulting in further complications and potential addiction.

Spinal fusion surgery is traditionally managed with short acting-opioids or a multimodal approach with opioids and non-opioids. Narcotic management of spinal fusion surgery include shorter acting narcotics, such as fentanyl, hydromorphone, or morphine given as either an intravenous (IV) bolus or with a patient-controlled analgesia device (PCA; Murphy & Szokol, 2019). Intravenous boluses of narcotic leave the patient with a large fluctuation of blood opioid concentration, which can result in variations from severe pain to oversedation and respiratory

depression (Murphy & Szokol, 2019). Narcotic management with a PCA pump requires patient cooperation and education, staff education, and specialized equipment (Murphy & Szokol, 2019). This method may result in variable drug concentrations as programmable bolus options that can be delivered to the patient who is experiencing pain (Murphy & Szokol, 2019).

Multimodal approaches of pain control combine synergistic analgesics to minimize postoperative opioid use and side effects (Murphy et al., 2021). Acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), long-acting local anesthetics, and N-methyl-D-aspartate (NMDA) receptor antagonists, such as ketamine, have often been used in conjunction with opioids (Murphy et al., 2021). Traditional narcotic management with short-acting opioids may not provide adequate postoperative pain control.

An alternative approach to pain management for spinal fusion surgery includes the use perioperative IV methadone. The use of methadone instead of short-acting opioids may provide a longer sustained blood concentration of opioid due to its long half-life (Murphy & Szokol, 2019). The elimination half-life of methadone is 24 to 36 hours with larger doses such as 20 milligrams (mg), when compared to smaller doses of 5 to 10 mg that produce analgesic effect for three to four hours (Murphy & Szokol, 2019). Methadone is a unique synthetic opioid that not only produces analgesic effects through mu receptor agonism, but also antagonizes NMDA receptors (Alexander, 2022). Methadone also inhibits the reuptake of serotonin and norepinephrine, which may provide a mood elevation effect in the postoperative period and thereby improve the patient's perception of pain (Murphy & Szokol, 2019). The addition of perioperative methadone to an anesthetic plan for spinal fusion surgery may provide improved postoperative pain control and recovery from surgery.

The use of perioperative IV methadone may provide patients undergoing elective spinal fusion surgery with improved postoperative pain control and reduced postoperative opioid consumption. This paper will investigate the efficacy and safety of perioperative methadone use in controlling postoperative pain during the first 24 hours after elective spine surgery.

Background

Chronic Back Pain

Outcomes for acute low back pain are typically positive, with improvement within the first month (Chou, 2022). However, low back pain persisting longer than three months is a problem for many people (Chou, 2022). Treatment for low back pain with degenerative lumbar disc disease may include a spinal fusion surgery (Chou, 2022). Whether the treatment is surgical or nonsurgical, limited numbers of patients have reported absolute symptom resolution (Chou, 2022). In a systematic review of disability outcomes between nonsurgical treatment and lumbar spinal fusions, three of four trials found no clinically relevant difference between surgery and nonsurgical treatment (Chou, 2022). Current practice guidelines from the American Pain Society recommends that surgical options are presented to patients who have had persistent (classified as greater than one year), disabling, non-radicular low back pain (Chou, 2022). Despite lack of evidence for long-term surgical outcomes for spinal fusion surgery and rising numbers of spine surgeries within the United States, surgical intervention represents only a small population of patients with chronic back pain (Chou, 2022). Treatment options for chronic low back pain vary between medical or surgical options such as a spinal fusion.

Surgical Procedure: Spinal Fusion

A spinal fusion is a procedure that fuses two or more vertebral bodies for the treatment of chronic nonspecific low back pain with degenerative lumbar disc disease (Chou, 2022). There

are a variety of fusion techniques that are practiced; however, the primary goal of any spinal fusion is to remove the disc with degenerative changes to relieve the painful symptoms (Chou, 2022). Surgery may be done with or without the insertion of hardware such as screws, plates, or cages (Chou, 2022). A bone graft is placed between the targeted vertebrae and hardware may be inserted to assist in stabilization and splinting as the bone graft heals (Chou, 2022). However, spinal fusions change the natural mechanics of the spine and an increase in long-term degenerative changes to the contiguous spinal segments may occur (Chou, 2022). Spinal fusion surgery is intended to provide relief from painful vertebral discs due to degenerative changes. There is debate as to the effectiveness of spinal fusion in patients with non-specific low back pain, which is categorized as chronic low back pain and degenerative lumbar disc disease with no radicular symptoms or symptoms attributable to a specific disease process (Chou, 2022).

Perioperative Analgesia: Opioids

Fentanyl

Fentanyl is a common opioid used in the perioperative period. It is a synthetic derivative of morphine, however, it is 100 times more potent than morphine (Alexander, 2022). Fentanyl is a highly lipophilic drug, which promotes rapid diffusion through the blood-brain barrier for a fast onset of action of three to five minutes for peak effect. Patients usually note a decrease in pain after about one minute (Alexander, 2022). Fentanyl has many uses within the perioperative period and for many different types of anesthetics. During induction of general anesthesia, fentanyl is used to blunt airway reflexes and the sympathetic nervous system response to laryngoscopy (Alexander, 2022). During maintenance, fentanyl is often considered for analgesia and to treat hemodynamic changes in response to surgical stimuli, such as tachycardia and hypertension (Alexander, 2022). Fentanyl may also be used for acute pain during the

postoperative phase (Alexander, 2022). Fentanyl is also a common adjunct during monitored anesthesia care (MAC) (Alexander, 2022).

There are several advantages to the usage of fentanyl. Rapid onset of action allows for quick analgesia and easy titration to effect (Alexander, 2022). Fentanyl has minimal effect on myocardial function and hemodynamics, lacks histamine-releasing properties, and is generally lower cost when compared to remifentanyl (Alexander, 2022).

Disadvantages of fentanyl include prolonged context-sensitive half-time that occurs when fentanyl is administered as an infusion (Alexander, 2022). This may cause delayed emergence and for this reason infusions are usually avoided during short or intermediate length surgical cases (Alexander, 2022). Fentanyl may also have synergistic effects when administered with other agents, such as serotonergic drugs or CYP3A4 inhibitors, including cimetidine, haloperidol, and metoprolol (Alexander, 2022). Administration of fentanyl with serotonergic agents may increase the risk of serotonin syndrome, and administration with CYP3A4 inhibitors may increase the plasma levels of fentanyl which could increase the incidence of adverse effects such as respiratory depression (Alexander, 2022).

Remifentanyl

Remifentanyl is a fentanyl derivative in the phenylpiperidine family with one to two times the potency of fentanyl and is ultrashort-acting (Alexander, 2022). Remifentanyl is also highly lipophilic and the diffusion through the blood-brain barrier takes just one to two minutes (Alexander, 2022). One unique property of remifentanyl is the short duration of action, which is five to ten minutes after infusion has been stopped, due to rapid metabolism through plasma esterases (Alexander, 2022). Remifentanyl is often used as an adjunct in a total intravenous

anesthetic (TIVA) technique due to rapid metabolism, however this also means the analgesic effect is terminated shortly after the infusion is discontinued (Alexander, 2022).

Advantages of remifentanyl include rapid onset, rapid offset, and a short context-sensitive half-time (Alexander, 2022). This makes remifentanyl an ideal agent for neuromonitoring spinal fusion cases where quick attainment of neurological exam is desired after emergence from anesthesia (Alexander, 2022). Remifentanyl may also have lower incidence of postoperative nausea and vomiting (PONV) when compared with fentanyl (Alexander, 2022).

Disadvantages of remifentanyl include the high costs when compared to other opioids (Alexander, 2022). There is also a risk of chest wall rigidity when administered rapidly and with high dosage (Alexander, 2022). There is data to indicate opioid tolerance and opioid-induced hyperalgesia after remifentanyl infusion, however, this is dose-dependent and most likely to occur with higher doses of 0.3 micrograms (mcg) per kilograms (kg) per minute (Alexander, 2022).

Sufentanyl

Similar to remifentanyl, sufentanyl is a phenylpiperidine opioid (Alexander, 2022). While remifentanyl is only one to two times more potent than fentanyl, sufentanyl is ten times more potent than fentanyl (Alexander, 2022). Sufentanyl is a highly lipophilic opioid that crosses the blood-brain barrier easily, resulting in a rapid onset of one to two minutes (Alexander, 2022). Like remifentanyl, sufentanyl is often used for a TIVA anesthetic technique, especially when surgery warrants neuromonitoring. Sufentanyl has a short context-sensitive half-time, however it is longer than that of remifentanyl (Alexander, 2022).

Advantages of sufentanyl include rapid onset (Alexander, 2022). Sufentanyl also has a lower cost when compared with remifentanyl (Alexander, 2022). Due to the longer context-

sensitive half-time when compared to remifentanyl, analgesic effects last longer once an infusion has been discontinued (Alexander, 2022).

Disadvantages of sufentanil are similar to those of other lipophilic opioids, such as fentanyl and remifentanyl (Alexander, 2022). Context-sensitive half time is longer than that of remifentanyl, but shorter than that of fentanyl (Alexander, 2022). For example, after 200 minutes of a continuous sufentanil infusion, a 50 percent decrease in concentration will occur in 30 to 45 minutes, while this same decrease would take approximately 200 minutes with fentanyl and only four minutes with remifentanyl (Alexander, 2022).

Morphine

Morphine is a phenanthrene opioid that is about 100 to 200 times less potent than fentanyl (Alexander, 2022). Unlike fentanyl and remifentanyl, morphine is less lipophilic resulting in slower diffusion across the blood-brain barrier and therefore a slower peak effect, about 15 to 20 minutes (Alexander, 2022). Morphine also has a longer duration than fentanyl or remifentanyl, about four to six hours (Alexander, 2022). Similar to fentanyl and remifentanyl, morphine is often used during the maintenance phase of anesthesia and to control postoperative pain.

Advantages of morphine include low cost and prolonged duration of action (Alexander, 2022). This prolonged duration of action is adventitious when moderate to severe postoperative pain is expected for any given procedure (Alexander, 2022).

Disadvantages of morphine include a prolonged context-sensitive half-time, which makes an infusion unfavorable due to difficulty titrating anesthetic depth (Alexander, 2022). Morphine has a higher occurrence of opioid-related adverse effects, such as urinary retention, constipation, nausea, and pruritus (Alexander, 2022). Histamine release also may occur, resulting in

hypotension and diaphoresis (Alexander, 2022). The metabolite produced during morphine metabolism, morphine-6-glucuronide, is renally excreted and may potentially be nephrotoxic in patients with a creatinine clearance of less than 30 milliliters (mL) per minute (Alexander, 2022). Morphine should also be used with care in patients with seizure disorders, as the metabolite may cause neuroexcitation leading to possible seizure activity (Alexander, 2022).

Hydromorphone

Hydromorphone is a semi-synthetic derivative of morphine, is five times more potent than morphine, and has a slightly faster onset of action, with peak effect within ten minutes of intravenous administration (Alexander, 2022). Hydromorphone has a shorter half-life of 2.4 hours, when compared to morphine (Alexander, 2022). Hydromorphone is used during maintenance of general anesthesia as well as for treatment of postoperative pain (Alexander, 2022).

Advantages of hydromorphone are the same as those for morphine, including low cost, and longer duration of action, up to four to six hours (Alexander, 2022). Additionally, hydromorphone has a slightly better analgesic effect than that of morphine and less histamine release (Alexander, 2022).

Disadvantages of hydromorphone include slower onset, especially when compared to synthetic agents such as fentanyl and remifentanyl (Alexander, 2022). Hydromorphone is metabolized primarily by the liver and may result in increased plasma levels in patients with liver disease (Alexander, 2022). Care should also be taken in patients with renal insufficiency due to accumulation of the metabolite, hydromorphone-3-glucuronide, that is renally excreted and may be nephrotoxic (Alexander, 2022).

Methadone

Methadone is a synthetic opioid that is uniquely different from other opioids. The mechanism of action is through mu receptor agonists, while also antagonizing N-methyl-D-aspartate (NMDA) receptors (Alexander, 2022). Methadone also inhibits the reuptake of serotonin and norepinephrine, which may provide a mood elevation effect in the postoperative period, improving perception of pain (Murphy & Szokol, 2019).

Onset of analgesic effects of intravenous methadone has been reported in as little as eight minutes, with duration extending 24 to 36 hours when doses exceed the redistribution half-life of about 20 mg (Alexander, 2022). When smaller doses of methadone are given, such as 5 to 10 mg, the clinical effect is determined by redistribution, however elimination half-life exceeds 24 hours when 20 mg or more are given (Murphy & Szokol, 2019). In this case, methadone acts as a shorter-acting opioid, with an analgesic duration of only 3 to 4 hours (Murphy & Szokol, 2019). Due to this rapid redistribution after initial bolus, smaller doses as single injections may be inadequate to provide effective analgesia due to lower plasma levels of the drug (Mok et al., 2021).

Methadone is metabolized in the liver by CYP2D6; medications that induce this metabolism include phenobarbital and phenytoin, which may increase the metabolism of methadone (Alexander, 2022). Medications that inhibit CYP2D6 include fluoxetine, sertraline, ticlopidine, which may result in reduced metabolism of methadone, increasing plasma levels and increasing incidence of adverse events (Alexander, 2022). Methadone also interacts with selective serotonin reuptake inhibitors (SSRIs), which may lead to elevated serotonin levels, increasing the risk of serotonin syndrome (Alexander, 2022).

Methadone is excreted by the kidneys, with about 20% of drug unchanged (Kreutzwiser & Tawfic, 2020). Metabolites of methadone include 2-ethylidene- 1,5-dimethyl-3,3-

diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (EMDP) which are both inactive metabolites (Kreutzwiser & Tawfic, 2020). There is also a small, but clinically insignificant, amount of methadol and normethadol produced from the metabolism of methadone (Kreutzwiser & Tawfic, 2020).

Literature Review

Methods

A literature search was conducted using the following major databases: Cochrane Database, PubMed, Scopus, and UpToDate. Systematic reviews, randomized control trials (RCT), and retrospective reviews were selected. Twenty-five studies were initially selected and, after review, five were excluded due to duplicated studies. Keywords for database search included *methadone*, *postoperative pain*, *pain control*, and *spinal fusion*.

The literature review yielded articles that compared postoperative pain with methadone and a variety of shorter acting narcotics. Primary studies that compared postoperative pain control of methadone to shorter acting opioids during spinal fusion surgeries were focused on, with broadening search to other types of surgeries. The secondary aims of the studies included postoperative complications or adverse events, sedations scores, and Post Anesthesia Care Unit (PACU) or hospital length of stay. Two studies specifically looked at the safety and adverse events of methadone use in the perioperative period.

Perioperative Dosing of Intravenous Methadone

Perioperative dosing of intravenous methadone has been studied to determine if dosage influences analgesic outcomes, or if the dosage adds to adverse events. UpToDate found most studies to dose 0.1 to 0.2 mg/kg of ideal body weight up to 20 mg, mostly with a single IV dose at the induction of anesthesia (Alexander, 2022). Komen et al. (2019) found that 30-day opioid

consumption was significantly decreased in patients who had received 0.15 mg/kg of methadone, but not for those who received 0.1 mg/kg of methadone, when compared with a control. This study also found that opioid consumption in the PACU was not lowered for those who received 0.1 mg/kg of methadone when compared to the control (Komen et al., 2019). However, in patients receiving 0.15 mg/kg of methadone, opioid consumption in the PACU was significantly lower than the control (Komen et al., 2019). This suggests the rapid redistribution of lower doses, such as 0.1 mg/kg, may not provide adequate levels of analgesia to reduce opioid consumption.

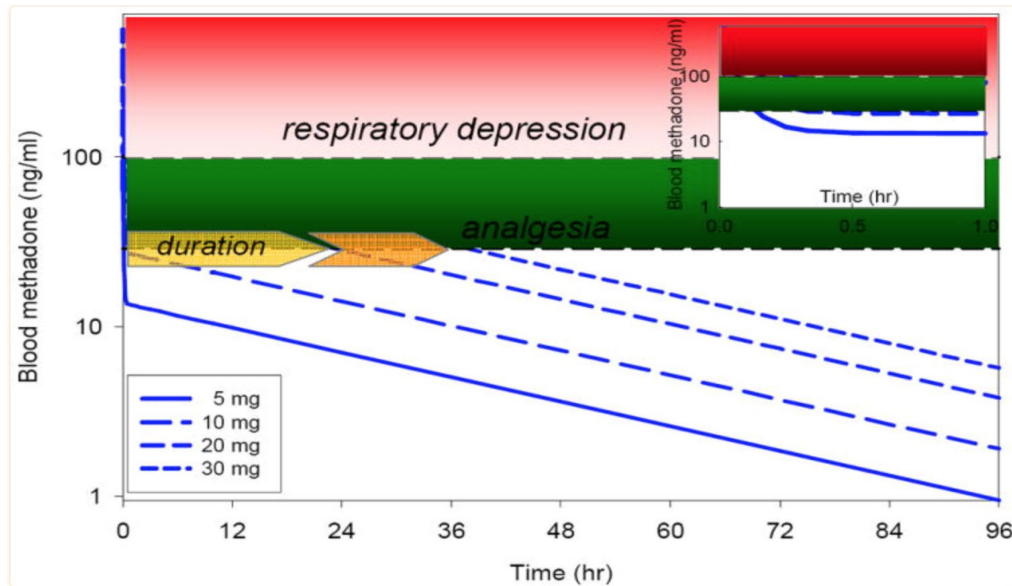
In a retrospective cohort study by Robinson et al. (2020) cardiac surgery patients received a total of 0.1-0.4 mg/kg with a maximum dose of 30 mg of methadone, and dosage was determined by the anesthesia provider delivering care. The study matched patients who underwent the same procedure but who did not receive methadone. This study reported that patients in the control group received three times more opioids in the first 12 hours when compared to those in the methadone cohort (Robinson et al., 2020). However, they did not find an association between higher methadone doses, such as 0.4 mg/kg, and further decreases in opioid consumption, suggesting an analgesic ceiling in methadone dosing, where lower doses may provide adequate pain control (Robinson et al., 2020).

In a clinical focus review by Murphy & Szokol (2019), the focus of intraoperative methadone dosing was to target a blood concentration of drug that would exceed the minimum analgesic concentrations during the slow elimination phase. This targeted level would also have to be below the threshold for respiratory depression (Murphy & Szokol, 2019). Figure 1 shows the simulated relationship between duration of methadone levels within the blood, compared at various doses. The rapid redistribution illustrates that anticipated respiratory depression with

higher single doses would be for 30 to 45 minutes (Murphy & Szokol, 2019). In this study subjects received 20 mg of methadone at induction of anesthesia, with no patients requiring naloxone infusions for prolonged respiratory depression (Murphy & Szokol, 2019).

Figure 1

Methadone Dose and Duration of Effect



Note. From Murphy, G. S., & Szokol, J. W. (2019). Intraoperative methadone in surgical patients: A review of clinical investigations. *Anesthesiology*, *131*(3), 678–692. <https://doi-org.une.idm.oclc.org/10.1097/ALN.0000000000002755>

These studies suggest that intraoperative methadone use does require a minimum dose to provide effective analgesia, with 0.15 mg/kg significantly reducing PACU opioid consumption as well as 30-day opioid consumption, when 0.1 mg/kg did not significantly reduce total opioid consumption (Komen et al., 2019). These studies also show that increasing doses does not increase analgesic control when compared to the lower doses (Robinson et al., 2020).

Safety of Intraoperative Methadone Use

Concern for the use of intraoperative methadone is due to side effects, including respiratory depression and QT interval prolongation, especially due to the prolonged elimination

half-life, which can be up to 30 hours (Alexander, 2022). In a retrospective study by Dunn et al. (2018), 1,478 patients who underwent major multilevel spine surgery received intraoperative methadone with doses ranging from 2 to 40 mg (0.1 to 0.2 mg/kg). Incidence of adverse events were reviewed, and the most common events presented were respiratory depression and hypoxemia at 36.8 and 79.8 percent, respectively. However only 2.3 percent of patients required treatment with naloxone for respiratory depression (Dunn et al., 2018). This study also reported postoperative cardiac arrhythmias observed in 30.1 percent of patients, with sinus tachycardia being the most common (Dunn et al., 2018). Respiratory depression and hypoxemia were the highest reported adverse events following multilevel spine surgery.

Respiratory Depression

Murphy et al. (2017), in a RCT for methadone use in elective posterior lumbar, thoracic, or lumbothoracic spinal fusions found that patients receiving larger doses of methadone, up to 0.2 to 0.4 mg/kg or 20 to 30 mg, were not at risk of developing a clinically significant respiratory depression when compared to a hydromorphone control group. In a separate RCT by Murphy et al. (2015), the use of 0.3 mg/kg intraoperative methadone was compared with fentanyl for elective cardiac surgery. This study found no differences in opioid related adverse events between the methadone and fentanyl group (Murphy et al., 2015). Both these studies suggest the safety of methadone with larger doses when compared to hydromorphone and fentanyl. In a systematic review by D'Souza et al. (2020), pooled results from ten studies found no differences in respiratory depression, hypoxemia, or hypoventilation compared to control groups. In a RCT by Pontes et al. (2021), intraoperative morphine use was compared to methadone in patients undergoing laparoscopic gastroplasty. This data found no episodes of respiratory depression were reported in PACU. The methadone group was found to have lowered incidence of

supplemental oxygen use and lower sedation scores at admission to PACU to 60 minutes, when compared to morphine (Pontes et al., 2021). These studies suggest safety of methadone compared to hydromorphone, fentanyl, and morphine.

QT Interval Prolongation

Prolongation of QT interval may increase the risk of a potentially lethal arrhythmia, torsade de pointes. Methadone use, especially with prolonged use such as with an opioid abuse disorder, has been associated with the development of prolonged QTc (Alexander, 2022). In a retrospective review by Dunn et al. (2018), postoperative arrhythmias were only observed in 30.1% of patients, with sinus tachycardia being the most common, and no incidences of polymorphic ventricular tachycardia, which can lead to torsade de pointes. Bastian et al. (2019) found no difference in postoperative QTc intervals between methadone and fentanyl groups. Similarly, Robinson et al. (2020) found no incidence of prolonged QTc with methadone cohort. Risk of QTc prolongation was not found to be increased in patients receiving perioperative methadone in any of the reviewed literature.

Postoperative Nausea and Vomiting

In a study conducted by Dunn et al. (2018), postoperative nausea and vomiting (PONV) was observed in 44 percent of patients receiving methadone and undergoing multilevel spine surgery. Machado et al. (2018) compared PONV incidence in patients receiving methadone with those receiving shorter acting fentanyl. This study found that in patients undergoing open bariatric surgery, PONV occurred significantly less in the methadone group than with the fentanyl group ($p = 0.001$; Machado et al., 2018). In the fentanyl group, nausea and vomiting occurred 75% and 31.3% respectively, while in the methadone group, incidence of nausea and vomiting occurred 6.3% and 0% respectively (Machado et al., 2018). Part of this improvement in

PONV may be due to a decrease in total opioid consumption, thereby minimizing the side effects of those medications. In another RCT, randomized patients received either intraoperative methadone or intraoperative morphine (Pontes et al., 2021). The aim of this study was to assess the quality of recovery after laparoscopic gastroplasty (Pontes et al., 2021). The study found that the single dose of 0.1 mg/kg of methadone was associated with an improved patient perceived quality of recovery when compared to 0.1 mg/kg of morphine (Pontes et al., 2021). A major complication after a laparoscopic gastroplasty is PONV, which can occur in up to 65% of patients (Pontes et al., 2021). Similarly, to Machado et al., in this study PONV incidence was lower in the methadone group both in PACU, and overall, during hospital stay when compared to the morphine control group (Pontes et al., 2021). Comparable to Machado et al., part of this may be attributed to the total lower dose of opioids as well (Pontes et al., 2021).

Outpatient Surgery

With over 60% of surgical cases in the United States now being done in same-day surgical centers, barriers to methadone use are increased due to concerns of adverse events after the patient has been discharged (Komen et al., 2019). These procedures carry the same risk for acute postoperative pain, with the potential of leading to chronic postoperative pain. This provides unique challenges for anesthesiologists since the same adequate analgesia is required as in an inpatient setting, but patient contact time is decreased (Komen et al., 2019). Komen et al. performed a randomized control trial to determine effective, yet safe, dosing for same-day surgical procedures (2019). The most common procedures included laparoscopic cholecystectomy, tubal ligation, and salpingectomy and/or oophorectomy (Komen et al., 2019). Groups were randomized and patients received escalating methadone doses of 0.1 mg/kg or 0.15 mg/kg, and additionally a control group received standard short-acting opioids (Komen et al.,

2019). Opioid consumption in the PACU was significantly less in the patients receiving 0.15 mg/kg of methadone, while readiness for PACU discharge and adverse respiratory events were not significantly different between either group receiving methadone and those receiving short-acting opioids (Komen et al., 2019). This pilot study demonstrated that methadone was safely used in ambulatory surgical setting by decreasing total opioid consumption without increased PACU stays or respiratory depression when compared to traditional opioid management.

Obese Patients

Machado et al. (2018) conducted a RCT to assess the safety and efficacy of intraoperative methadone use compared to fentanyl in the morbidly obese population. Patients undergoing elective open bariatric surgery were randomized to either receive 0.15 mg/kg ideal body weight (IBW) plus 20% of methadone upon induction of anesthesia or 6 mcg/kg IBW plus 20% of fentanyl (Machado et al., 2018). Patients continued to receive the same narcotic during surgery as originally randomized to, either 0.05 mg/kg IBW plus 20% of methadone or 2 mcg/kg IBW plus 20% of fentanyl (Machado et al., 2018). All patients received a postoperative PCA pump with morphine (Machado et al., 2018). Postoperative morphine consumption was significantly higher in the fentanyl group when compared to the methadone group, from hour two postoperatively to hour 48. Sedation scores and need for supplementary oxygen were similar between the two groups (Machado et al., 2018).

Similarly, Pontes et al. (2021) looked at obese patients undergoing bariatric surgery, comparing perioperative methadone use to morphine. The methadone group was found to have a shorter length of stay, lower requirements for supplemental oxygen, lower rescue requirements of narcotic in the PACU, and lower sedation scores both at admission to PACU and 60 minutes

later (Pontes et al., 2021). This suggests methadone may be as successful at controlling pain in the obese population compared to shorter acting narcotics, without risking safety.

Perioperative Methadone Use for Spinal Fusions

Postoperative pain management in patients undergoing spinal fusions can be severe and, pain control is frequently reported as inadequate (Murphy et al., 2021). Inadequate postoperative pain control may lead to chronic pain syndromes as well as prolonged hospitalizations, decreased patient satisfaction, and increased healthcare associated costs (Murphy et al., 2021). In a RCT, Murphy et al. (2017) examined postoperative pain control in patients undergoing elective posterior lumbar, thoracic, or lumbothoracic spinal fusions. In this study, patients were randomized to either receive 0.2 mg/kg (actual body weight) of methadone or 2 mg of hydromorphone intraoperatively (Murphy et al., 2017). Postoperatively patients were placed on a hydromorphone PCA pump. Data showed patients in the methadone group had reduced opioid requirements for the first three days after surgery (Murphy et al., 2017). On postoperative day three, patients were transitioned from a hydromorphone PCA to 10 mg hydrocodone and 325 mg acetaminophen tablets (Murphy et al., 2017). The study reported that fewer oral narcotics were required in the methadone group, and total oral opioid consumption was also reduced in this group as well (Murphy et al., 2017). The authors also found that overall patient satisfaction was higher in the methadone group from PACU admission through the morning of postoperative day three (Murphy et al., 2017). This study noted that the incidence of adverse events such as PONV, itching, hypoventilation, or hypoxemic events did not differ between the two groups (Murphy et al., 2017). This study demonstrates the analgesic effects and improved postoperative pain control with perioperative methadone use when compared to perioperative hydromorphone.

Comparably, in a retrospective review by Mok et al. (2022), the effects of hydromorphone and methadone on postoperative pain were assessed in adolescent patients undergoing spinal fusions for idiopathic scoliosis. However, unlike Murphy et al. (2017), this review included three groups, a hydromorphone PCA group (Group PCA), a preincisional methadone (0.2 mg/kg) plus a hydromorphone PCA group (Group PCA + methadone), and a group who received preincisional methadone (0.2 mg/kg) followed by 0.1 mg/kg intravenous methadone in PACU at first analgesic request (Group methadone; Mok et al., 2022). This study found that group methadone used significantly less opioid than both group PCA and group PCA + methadone. Group methadone consumed half as much opioid in the first 72 hours postoperatively when compared to group PCA (Mok et al., 2022). Both Mok et al. and Murphy et al. (2017), demonstrated the effectiveness of IV methadone 0.2 mg/kg in spinal fusions when compared to hydromorphone. However, unlike Murphy et al. (2017), Mok et al. used multiple doses of methadone, one intraoperatively and two smaller doses in the PACU, and this study reported a 45% reduction in opioid consumption when compared to the use of a hydromorphone PCA pump (Mok et al., 2022). With repeated doses of methadone, risks for increased side effects and adverse events may occur, however this study reported that no patients in the methadone group experienced QT prolongation on telemetry for the first 24 hours (Mok et al., 2022). However, it did find that time spent in the PACU was longer in the Group PCA + methadone and Group methadone when compared to the Group PCA (Mok et al., 2022). This literature shows that not only did intraoperative methadone use decrease total opioid consumption, but it may decrease the need for PCA pumps which requires special equipment, patient education, and skilled staff to operate.

Unlike Mok et al. and Murphy et al. (2017), who compared intraoperative methadone use to hydromorphone, a study by Gottschalk et al. (2011) intraoperative methadone use was compared to use of sufentanil in adult patients undergoing multilevel thoracolumbar spine surgery with instrumentation and fusion. In this study, when inadequate analgesia needed treatment, patients received a sufentanil bolus of 0.1 mcg/kg (Gottschalk et al., 2011). Randomized patients in the methadone group received a 0.2 mg/kg dose of methadone. Instead of hydromorphone as the control, in this RCT, postoperative pain control was managed at the discretion of the attending surgeon, using either fentanyl, morphine, or hydromorphone PCA (Gottschalk et al., 2011). In this study, the authors found that patients randomized to the methadone group reported less pain after surgery, and this difference became statistically significant 48 hours after extubation ($p < 0.05$; Gottschalk et al., 2011). The data also showed that the methadone group had lower postoperative opioid requirements, which again became statistically significant 48 hours after extubation ($p < 0.05$; Gottschalk et al., 2011). This study showed that postoperative opioid consumption and pain control was reduced with methadone use, which persisted 72 hours after surgery without a significant increase in adverse events (Gottschalk et al., 2011). This study helps to show methadone's effectiveness against different short acting narcotics.

In a retrospective matched cohort design by Ye et al. (2020), adolescent patients undergoing elective posterior spinal fusion for idiopathic scoliosis received methadone 0.1 to 0.3 mg/kg, compared to intraoperative morphine along with remifentanyl and ketamine infusions (Ye et al., 2020). Similar to Mok et al. (2022), the methadone group in this study received three more doses of methadone every 12 hours starting the evening after surgery (Ye et al., 2020). On postoperative day one opioid consumption was similar between the two groups, but by

postoperative day two the methadone group consumed 50% less opioids than the control group (Ye et al., 2020). Total hospital stay opioid consumption was about 30% less in the methadone group than in the control (Ye et al., 2020). The methadone group also had significantly shorter length of hospital stay when compared to the control group ($p < 0.001$; Ye et al., 2020). This study shows the analgesic control methadone can provide 24-48 hours postoperatively. Reduced opioid requirement 24-48 hours postoperatively was also found by Murphy et al. (2017).

Evoked Potentials and Methadone

Neuromonitoring is frequently utilized during spinal fusion surgeries, necessitating a total intravenous anesthetic (TIVA) technique to avoid potential interference by volatile anesthetic agents. In one RCT by Martin et al. (2018), adolescent patients presenting for posterior spinal fusion for idiopathic scoliosis were randomized into three groups, remifentanyl alone, remifentanyl and methadone (0.1 mg/kg), or remifentanyl and magnesium (50 mg/kg). Interestingly, the study only noted differences in opioid consumption between the remifentanyl alone and remifentanyl with methadone groups, none were noted with the magnesium group. Total opioid requirement, including administration in the operating room (OR), PACU, and inpatient units, were lower in the group receiving methadone, as well as decreased intraoperative requirements of remifentanyl and labetalol for controlled hypotension (Martin et al., 2018). The authors of this study also reported that no statistical differences were found in neuromonitoring, suggesting use of methadone can be safely given while not affecting quality of neuromonitoring technique (Martin et al., 2018). While this study was done in pediatric patients, it points to the benefits methadone could have in hemodynamic control and decreased overall anesthetic requirements for patients undergoing a TIVA anesthetic, commonly done with spinal fusions. Similarly, Mok et al. (2022) also used a TIVA technique to facilitate neuromonitoring of

somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) with no reported difficulties in monitoring in the methadone group.

Perioperative Methadone Use for Non-Spine Surgeries

Studies have shown that acute postoperative pain is the single greatest risk factor for chronic postsurgical pain (Komen et al., 2019). In a seminal investigation in 1986 by Gourlay et al., adult patients undergoing upper abdominal surgery either received methadone (20 mg) or morphine (20 mg) at the induction of anesthesia. Postoperatively, patients continued to receive the same opioid administered intraoperatively when additional pain medication was requested. The authors found that significantly less methadone was administered in the postoperative period when compared to morphine (Gourlay et al., 1986). The duration of pain relief following administration was also significantly longer in the methadone group than the morphine group (Gourlay et al., 1986). This was the first study that showed the efficacy of methadone use in the intraoperative period on reduction of postoperative opioid consumption.

In another seminal investigation in 2015 by Murphy et al., methadone use in elective cardiac surgery patients was examined. Patients were randomized to either methadone or fentanyl groups. The methadone group received 0.3 mg/kg of methadone (with a maximum dose of 30 mg) and the fentanyl group received 12 mcg/kg of fentanyl (with a maximum dose of 1,200 mcg). Half of each study drug was given at the induction of anesthesia with an infusion of the other half given over the first two hours of anesthesia (Murphy et al., 2015). Postoperative morphine requirements in the first 24 hours showed a significant reduction in opioid consumption in the methadone group when compared to the fentanyl group ($p < 0.001$; Murphy et al., 2015). Findings showed that 29.1% of patients in the fentanyl group required more than 20 mg of morphine in the first 24 hours postoperatively, while only 2.6% of those in the methadone

group required the same amount of morphine (Murphy et al., 2015). This early study also showed the analgesic effect of methadone on opioid consumption in the first 24 hours postoperatively, however unlike Gourlay et al. (1986), this study looked at perioperative methadone compared to fentanyl instead of morphine.

In a meta-analysis including RCTs and prospective observational studies by D'Souza et al. (2020), researchers showed that the methadone group consumed lower total opioids in all ten studies reviewed. Data from six of the trials showed no difference in time-to-extubation between methadone or control groups (D'Souza et al., 2020). Overall, four studies in this review showed that patients receiving methadone had significantly less total opioid requirements at 24 hours postoperatively ($p = 0.01$), when compared to traditional short-acting opioids (D'Souza et al., 2020). These findings are similar to those of Murphy et al. (2017), who also found lower opioid requirements in the first 24 hours after surgery.

Bastian et al. (2019) compared methadone to fentanyl use in moderate-to-severely painful surgery, including vascular, orthopedic, breast, and laparoscopic surgeries. Bastian et al. (2019) found that postoperative morphine consumption was significantly less in the methadone group on postoperative day one ($p < 0.05$), and lower on postoperative days two and three. This study placed all patients a morphine PCA pump postoperatively, and those in the methadone cohort never received further boluses of methadone (2019). This study showed improved postoperative pain control and decreased opioid consumption with the use of postoperative PCA pumps.

Similar to Bastian et al. (2019), a meta-analysis by Kendall et al. (2020) included patients undergoing a variety of surgical procedures. Unlike Bastian et al. (2019), this study compared intraoperative methadone use to intraoperative morphine use, instead of fentanyl (Kendall et al., 2020). The primary outcome of this study was postoperative opioid consumption in the first 24

hours postoperatively (Kendall et al., 2020). Opioid consumption was reduced in the PACU for those who received methadone in the operating room, as well as up to 24 hours after surgery (Kendall et al., 2020). This study showed the analgesic effect of methadone when compared to fentanyl and hydromorphone.

Similar to Kendall et al. (2020), in a systematic review by Lobo et al. (2021), postoperative pain outcomes with intraoperative methadone use were compared to intraoperative fentanyl and morphine use. Postoperative pain scores were found to be reduced with the use of intraoperative methadone when compared to fentanyl and morphine in three of four studies (Lobo et al., 2021). All studies in the systematic review reported that opioid consumption after receiving a single dose of methadone was reduced in the first 24 hours postoperatively when compared to patients receiving intraoperative morphine or fentanyl (Lobo et al., 2021). Similar to Kendall et al. (2020), this study found that opioid consumption was reduced and pain control was improved with a single dose of intraoperative methadone when compared to intraoperative morphine. Unlike Kendall et al., this study compared methadone to both fentanyl and morphine instead of morphine alone.

A pilot study was conducted to assess the potential long-term benefits of intraoperative methadone use by Murphy et al. (2020). This follow-up survey involved questionnaires sent to participants from two previous RCTs (Murphy et al., 2020). Questionnaires were mailed at 1, 3, 6, and 12 months after surgery. One group of participants were from a spinal fusion study and one group was from a cardiac surgery study. In each study patients either received methadone or were in a control group with a shorter-acting opioid; hydromorphone in the spine surgery group and fentanyl in the cardiac surgery group (Murphy et al., 2020). Questionnaires asked patients about frequency of surgical pain, pain level at the time of survey, and pain scores while at rest,

coughing, and with movement (Murphy et al., 2020). At three months following spinal fusion surgery, those in the methadone group reported pain a median of one time per week, while those in the hydromorphone group reported a median of daily pain (Murphy et al., 2020). Pain scores and frequency of pain were found to be lower at one month and three months, but no differences were found after 6 months (Murphy et al., 2020). This follow-up survey suggests methadone may assist in controlling postoperative pain for up to three months and may mitigate the risk for chronic postsurgical pain.

Multimodal Pain Management with Methadone

Due to the painful nature of spinal fusion surgeries, multimodal pain control is a common approach, and some studies have incorporated methadone into this multimodal approach to decrease postoperative opioid consumption. In a RCT by Murphy et al. (2021), the use of methadone and ketamine together when compared to methadone alone was studied in 127 patients. Patients in the methadone and ketamine group required significantly less hydromorphone on the first and second postoperative day ($p < 0.001$; Murphy et al., 2021). Total opioid consumption in the methadone and ketamine group was decreased by 50% over the first three days postoperatively (Murphy et al., 2021). This study shows the potential synergistic effect of methadone with other non-opioid agents to improve postoperative pain control even further. While both groups in this study received methadone, it shows growth opportunities for perioperative methadone use. Mok et al. (2022) demonstrated that the methadone group consumed almost half as many opioids than the hydromorphone PCA group, while maintaining equivalent pain scores, suggesting an opportunity to improve scores with the addition of multimodal anesthesia, as shown by Murphy et al. (2021).

Discussion

The idea of IV methadone use for postoperative pain control was first proposed over 30 years ago. In seminal investigations by Gourlay et al. (1986) and Gottschalk et al. (2011), both studies showed decreased postoperative opioid consumption in the methadone group when compared to sufentanil and morphine, respectively. Gottschalk et al. (2011) also found the methadone group to have significantly lower pain scores 48 hours after surgery. These early studies led to much more research on the use of perioperative methadone and its place in anesthesia practice and postoperative pain control.

Multiple studies found improved postoperative opioid consumption with the use of perioperative IV methadone. Murphy et al. (2017) and Mok et al. (2022) both concluded that consumption of postoperative hydromorphone was significantly decreased in the group receiving IV methadone at the induction of anesthesia for spinal fusions. Both studies found that reduction in postoperative opioids within the methadone group extended to postoperative day three, with Mok et al. (2022) noting a 50% decrease in opioid consumption in the first 72 hours compared to the hydromorphone group. Ye et al. (2020) also concluded opioid consumption to be significantly reduced 24 to 48 hours postoperatively, with a 50% reduction in opioid consumption in the methadone group on postoperative day two and a 30% reduction in total opioid consumption. Compared to intraoperative fentanyl administration, Bastian et al. (2019) found the methadone group to have significantly less postoperative morphine consumption on postoperative day one. When comparing postoperative opioid consumption with remifentanyl and methadone, Martin et al. (2018) found total opioid requirements (including OR, PACU, and inpatient units) to be decreased with the group receiving methadone. Both Martin et al. (2018) and Mok et al. (2017) used a TIVA technique to facilitate SSEPs and MEPs during spinal fusions, and both studies reported no difficulties in monitoring with the methadone groups.

These previously mentioned studies show that perioperative methadone use during spinal fusions provides decreased postoperative opioid consumption when compared to different short-acting opioids, without affecting neuromonitoring signals.

Postoperative patient satisfaction and quality of recovery were investigated in multiple studies. Murphy et al. (2017) and D'Souza et al. (2020) concluded patient satisfaction to be higher in the methadone group. Murphy et al. (2017) found the higher satisfaction in the methadone group on pain management to continue through the morning of postoperative day three. Similarly, in a systematic review by Machado et al. (2019), patient satisfaction was found to be higher in the methadone group at 24, 48, and 72 hours postoperatively, while Bastian et al. (2019) found patient satisfaction to be similar between the two groups. In a RCT by Murphy et al. (2021) comparing methadone and ketamine with methadone alone, patient satisfaction scores were determined to be higher in the methadone and ketamine group on postoperative day one. After that, satisfaction scores were high in both groups and did not significantly differ (Murphy et al., 2021). Pontes et al. (2021) had similar satisfaction findings, this RCT found a single dose of 0.1 mg/kg of methadone to be associated with an increased quality of recovery from surgery, when compared to 0.1 mg/kg of morphine. Not only does methadone show to decrease opioid consumption, but perceived patient satisfaction and quality of recovery was also improved with use of perioperative methadone.

Multimodal pain management in anesthesia is common practice to limit high doses of narcotics. The addition of methadone to a multimodal plan may provide superior postoperative pain control. Murphy et al. (2021) found a decrease in postoperative hydromorphone use by 57% in the group receiving methadone and ketamine compared to methadone alone in patients

undergoing spinal fusions. Further studies should be done to determine the effectiveness of methadone in multimodal anesthesia compared to short-acting multimodal techniques.

Several studies investigated the safety and side effects of methadone when compared to those receiving short-acting opioids. Both Machado et al. (2018) and Pontes et al. (2021) concluded PONV incidence to be lower in the methadone group when compared to fentanyl and morphine, respectively. Komen et al. (2019) found that respiratory adverse events did not differ significantly between the methadone group and those receiving short-acting opioids. Similarly, Pontes et al. (2021) found the methadone group to have lower requirements for supplemental oxygen and lower sedation scores upon admission to PACU and 60 minutes after arrival to PACU. Murphy et al. (2017) and Murphy et al. (2015) both concluded there to be no clinically significant differences in respiratory depression or difference in opioid related adverse events, respectively. In a RCT conducted to compare the use of methadone to fentanyl in morbidly obese patients, sedation scores and need for supplementary oxygen did not differ significantly between the two groups (Machado et al., 2018). Bastian et al. (2019) and Robinson et al. (2020) both found no statistically significant differences in incidence in QTc prolongation between methadone groups and short-acting opioids. These studies show the safety of perioperative methadone when comparing incidence of adverse events to short-acting opioids.

Limitations

Several studies reported small sample sizes. Gottschalk et al., (2011) reported a sample size of 29. Komen et al. (2019) and Martin et al. (2018) both reported a sample size of 60. Mok et al. (2022) reported a sample size of 87, while Robinson et al. (2020) reported a sample size of 74. These studies with lower sample sizes may result in higher variability and risks a larger margin of error.

While several studies used a standardized opioid for the control, a few studies allowed the control opioid to be at the discretion of the anesthesia provider. In Gottschalk et al., (2011) intraoperative opioid control was standardized to sufentanil, however postoperative pain control was varied between fentanyl, morphine, and hydromorphone. In Komen et al., (2019) patients in the control group received either fentanyl, sufentanil, morphine, or hydromorphone. No studies had two controls so that comparison could be made between methadone and two different shorter acting opioids.

Interestingly, studies found that despite lower pain scores and decreased opioid consumption, those in the methadone group still described pain as moderate in the first three days postoperatively, Murphy et al. (2021) was the only study to compare two methadone groups, one that received methadone alone, and one that received methadone and ketamine. Further studies should be done to determine the efficacy of non-opioid adjuncts to perioperative methadone and overall pain control and patient satisfaction.

No studies included patients with an American Society of Anesthesiologists (ASA) physical status score greater than two, meaning increased comorbidities and disease processes. Further research should be done to determine the safety of methadone use in patients with multiple comorbidities, as those patients often present as surgical candidates for spinal fusion surgery.

All studies only included opioid naïve patients. Further studies should also be done to determine the efficacy of methadone use in those patients with chronic pain and opioid use, since spinal fusion patients are often on an opioid regiment prior to surgery.

Finally, only a few studies compared various dosing of methadone to determine the most effective dose. Komen et al. (2019) aimed to determine the effective dose of methadone in an

outpatient surgical setting. However, the most common dosing of methadone for studies reviewed was 0.2 mg/kg and in Komen et al. (2019) the only two escalating methadone doses were 0.1 mg/kg and 0.15 mg/kg. Robinson et al. (2020) used intravenous methadone dosing 0.1 to 0.4 mg/kg; however, it was at the discretion of the anesthesia provider and doses were not standardized. More research is needed with varying standardized methadone dosing and higher ASA physical status scores, to better apply the use of perioperative methadone to a wider population.

Recommendations

This literature review supports the use of perioperative methadone for patients undergoing spinal fusion surgery for providing improved postoperative pain control and reduced opioid consumption. According to the study by Komen et al. (2019), at least a minimum dose of 0.15 mg/kg of methadone is required to provide effective analgesia and reduced PACU opioid consumption. Based on this literature review, perioperative IV methadone doses of 0.15 to 0.2 mg/kg of ideal body weight, up to 20 mg, provided adequate analgesic effect and reduced postoperative opioid consumption. Total opioid requirement and opioid consumption for those who received methadone was less when compared to those patients receiving traditional short-acting opioids (Murphy et al., 2017; D'Souza et al., 2020; Ye et al., 2020). When considering an anesthetic plan for spinal fusion surgery, the addition of 0.15 to 0.2 mg/kg, up to 20 mg, of perioperative methadone at the induction of anesthesia appeared to improve postoperative pain control and decrease total opioid consumption.

Conclusion

Postoperative pain for patients undergoing spinal fusions can be severe and often pain control is inadequate (Murphy et al., 2021). Poorly managed postoperative pain can lead to

chronic pain, prolonged hospitalizations, increased hospital associated costs, and decreased patient satisfaction (Murphy et al., 2021). Postoperative pain and opioid consumption were found to be significantly less in patients undergoing spinal fusions who received methadone perioperatively in comparison to hydromorphone (Murphy et al., 2021; Mok et al., 2022).

Decreased opioid consumption helps to reduce adverse effects such as PONV that can occur. Both Machado et al. (2018) and Pontes et al. (2021) found the incidence of PONV to be lower in the methadone group when compared to sole use short-acting opioids. Risks of perioperative IV methadone use include respiratory depression and QT prolongation. Murphy et al. (2017) and Murphy et al. (2015) both concluded that incidence of respiratory depression and adverse events postoperatively were not significantly increased in methadone cohorts compared to short-acting opioid groups. Both Bastian et al. (2019) and Robinson et al. (2020) found no incidence of prolonged QTc in the methadone cohort. The risks of IV methadone use for spinal fusion surgery do not outweigh the benefits of improved postoperative pain control and decreased opioid consumption.

This literature review supports the use of 0.15-0.2 mg/kg of intravenous methadone at the induction of anesthesia to improve postoperative pain control after spinal fusion surgery. Additional research should be done in patients with ASA physical status scores higher than two to better understand the application of methadone to different patient populations.

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