DEVELOPMENT AND IMPLEMENTATION OF AN INTRAOPERATIVE METHADONE GUIDELINE FOR COMPLEX SPINAL SURGERY

by

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Abstract

Background: The recent and ongoing opioid epidemic in the United States has been very detrimental to the country's overall health and has led to devastating patient outcomes. There is a responsibility on the part of healthcare providers to do their part in reducing these negative consequences.

Purpose: This quality improvement project was to develop and implement an evidence-based guideline for intraoperative methadone administration during complex spine surgery. Data was collected to evaluate whether this intervention correlated with reduced postoperative pain and narcotic use.

Methods: Education was provided to the clinical associates of Kalamazoo Anesthesiology regarding the guideline components and associated benefits of methadone. The guideline was implemented for all patients undergoing complex spine surgery at Bronson Methodist Hospital. At the conclusion of the implementation period, provider adherence to the guideline was assessed as well as patient outcomes for patients who received all components of the methadone guideline.

Results: Complete provider adherence to the methadone guideline occurred in five out of 22 (22.7%) opportunities. A Wilcoxon test showed a statistically significant finding in patients who received methadone who reported decreased pain scores ($p = .015$) post-operatively. This test showed that patients who did not receive methadone reported a pain score of well over double (mean = 9.57) as compared to those who received intraoperative methadone (2.67).

Conclusion: Despite knowledge of current literature and the methadone guideline components, anesthesia providers had a low level of adherence to the protocol, overall. Patients who did receive all elements of the methadone guideline demonstrated decreased consumption of opioids and pain levels in the postoperative period.

Key Words: methadone, intraoperative, spine surgery, opioid epidemic

Table of Contents

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Background and Significance

Chronic opioid use is an ongoing public health concern and has even been declared a public health emergency due to its detrimental impact on public health and socioeconomic welfare (Centers for Medicare & Medicaid Services, 2020). Recently, the crisis has seen a precipitous and alarming spike during the COVID-19 pandemic, causing the American Medical Association to urge state legislators and governors to implement and support all harm reduction strategies (American Medical Association, 2021).

Surgery is a known risk factor for the development of chronic opioid use (Dunn et al., 2018). This conclusion is underscored by a study by Quinlan et al. (2019), in which it was demonstrated that the risk of opioid use at 90 days post-surgery, in patients who were previously opioid naive, may be as high as 6.5%. Thus, perioperative providers play an instrumental role in developing alternative strategies to decrease opioid use in the perioperative setting and beyond.

A decrease in opioid use after surgery could potentially be accomplished via the administration of an intraoperative intravenous dose of methadone. Methadone is a mu-receptor agonist and NMDA receptor antagonist with the longest elimination half-life of the clinically used opioids (Kharasch, 2011). Due to methadone's extended half-life, one dose administered intraoperatively by an anesthesia provider has the potential to provide extended pain relief beyond the postoperative period (Murphy & Szokol, 2018).

The literature review below and the corresponding literature table (Appendix F) aims to address the following question: in adult patients undergoing complex thoracolumbar spinal surgery (defined as a spinal fusion of at least two levels with instrumentation) under general

anesthesia, does the implementation of a methadone guideline correspond with decreased postoperative pain scores and opioid consumption, or does it reveal no impact or even increased postoperative pain scores and opioid consumption? Additionally, in our quest to include an educational component to this project, we ask the following question: for anesthesia providers with Kalamazoo Anesthesiology, does formative education impact guideline adherence, knowledge base, and attitude toward methadone administration for patients having complex thoracolumbar spine surgery, or does it show no significant impact?

Purpose Statement

The purpose of this quality improvement project was to develop and implement an evidence-based guideline for intraoperative methadone administration during complex thoracolumbar spinal surgery (defined as a spinal fusion of at least two levels with instrumentation). The project consisted of the following four components:

1. Development of an evidence-based Intraoperative Methadone Administration Guideline;
2. Assessment of knowledge and attitude of anesthesia providers on using methadone during surgery;
3. Implementation of the Intraoperative Methadone Administration Guideline; and
4. Formative evaluation of the Intraoperative Methadone Administration Guideline as it is being implemented.

Literature Review

The aim of this literature review is to explore the impact of utilizing a single dose of intravenous methadone intraoperatively in patients undergoing complex thoracolumbar spine surgery, defined for this project as a spinal fusion with instrumentation of at least two levels or

more. The primary outcome investigated was the impact on postoperative pain and opioid requirements. Secondary outcomes examined included methadone's impact on post-operative nausea and vomiting (PONV), hemodynamic stability, and respiratory stability.

Methods

A systematic search of current literature was conducted, utilizing the following databases: CINAHL, the Cochrane Library, and PubMed. Key search terms included "intraoperative methadone," "postoperative pain," "spinal surgery," and "spinal fusion." Criteria for inclusion consisted of peer-reviewed articles which specifically contained data evaluating the impact of methadone on postoperative pain control and opioid consumption. Excluded articles were those that did not measure postoperative pain or opioid requirements. Articles were all published within the last ten years with the exception of one (Grourlay et al., 1984), which was retained due to its relevance to this project.

Results

The search of the medical databases yielded 732 results. After applying the inclusion and exclusion criteria outlined above, 24 studies remained. Ultimately, 16 articles were chosen, with the remaining seven excluded based on relevancy. Of the 16 included studies, 10 are randomized controlled trials (RCTs) (Murphy et al., 2020; Bolton et al., 2019; Friesgaard et al., 2019; Gottschalk et al., 2011; Gourlay et al., 1984; Korman et al., 2019; Murphy et al., 2017; Pacreu et al., 2012; Sharma et al., 2011; Udelsmann et al., 2011), four are meta-analyses (D'Souza et al., 2019; Kendall et al., 2020; Karasch. 2011; Murphy & Szokol, 2019), one was a cohort study/quality improvement project (Ye, et al., 2020), and one was an observational study (Dunn et al., 2018). The literature review table is presented in Appendix F.

Primary Outcomes

Sixteen research articles were chosen for the purpose of this review, all of which support the administration of intraoperative methadone for improving postoperative pain control. A further examination of the study methods and population characteristics will illuminate a potential rationale and guide the anesthesia provider in the best use of this therapy.

Patient Reports of Pain. One measure of pain control was patient-reported intensity of pain. All studies included in this review contain data on this outcome. Only one RCT (Bolton et al., 2019) found no difference in postoperative pain scores in the methadone group versus control group; however, it is the only study in this literature review in which oral methadone was administered, rather than intravenous methadone. In one RCT (Friesgaard et al., 2019), while postoperative pain score was listed as a primary outcome, the study had not been conducted at the time of this literature review and, therefore, results are unknown.

Of the nine RCTs that have been conducted, seven examined methadone administration on spinal surgery patients, and two examined methadone administration on cardiac patients (Bolton et al., 2019; Udelsmann et al., 2011). One study (Sharma et al., 2011) evaluated methadone administration on adolescents, rather than adults. Doses of methadone were not consistent. Most studies were conducted with weight-based intravenous (IV) dosing, ranging from 0.1mg/kg to 0.3mg/kg, though one study (Udelsmann et al., 2011) administered a standard dose of 20mg IV to patients. Finally, some studies compared pain scores of patients who received methadone to scores of patients who received a short-acting opioid (e.g., hydromorphone or morphine), while other studies compared them to a placebo group, in which patients did not receive any type of opioid. Nonetheless, the results remained consistent, and overall, the studies were supportive of methadone leading to improved postoperative pain scores.

Opioid Usage. Of the RCTs that have been carried out, nine found that the use of intraoperative methadone results in decreased postoperative opioid consumption. One study (Pacreu et al., 2012) further evaluated the effect of methadone both with and without concurrent administration of Ketamine, and it was discovered that when patients received both, there was a 70% decrease in methadone requirements by PCA. Interestingly, however, there were increased remifentanil requirements when patients received both, compared to when they only received methadone. This is thought to be attributed to a significant increase in Bispectral Index (BIS) values that accompany Ketamine. Sharma et al. (2011) evaluated the administration of different doses of methadone, ranging from 0.1mg-0.3mg/kg, and found that postoperative pain scores and opioid consumption were improved by methadone, but they were not affected by dose. It should be noted, however, that this study was conducted in adolescents, which is in contrast to the aim of this proposed quality improvement project which focuses on adults. In contrast, the study performed by Korman et al. (2019) found that dose affected total opioid consumption. It was discovered that opioid consumption in the PACU was significantly less in subjects who received methadone 0.15mg/kg, but not in subjects who only received 0.1mg/kg.

Two meta-analyses evaluated the effect of intraoperative methadone on postoperative opioid requirements and reached different conclusions. D'Souza et al. (2019) found that postoperative opioid consumption in the first 24 hours was decreased in patients who received methadone, while Kendall et al. (2020) found the effect of intraoperative methadone on postoperative opioid consumption did not reveal a significant effect ($p=0.42$). The quality improvement project conducted by Ye at al. (2020) found that morphine consumption postoperatively was lower (29.3mg versus 9.9mg) in the intervention group where subjects received methadone, versus the control group where they did not ($p < 0.001$).

Secondary Outcomes

Postoperative Nausea and Vomiting (PONV). One RCT (Udelsmann et al., 2011) found that the prevalence of PONV was lower in patients who received methadone 20mg with induction than it was in patients who received morphine. The RCT concluded that there was an obvious decrease in PONV observed in the methadone group and therefore "it is a low-cost option available that should be utilized." Other RCTs (Murphy et al., 2020; Bolton et al., 2019; Gottschalk et al., 2011; Koman et al., 2019; Murphy et al., 2017) and meta-analyses (D'Souza, et al., 2019 and Murphy & Szokol, 2019), although not explicitly listing PONV among outcomes, indicate that methadone does not cause increased prevalence of adverse effects such and PONV, or at the very least, causes no change when compared to the control group. Friesgaard et al. (2019) is a RCT to be conducted in the future that will evaluate the difference in PONV at 6, 24, and 72 hours postoperatively. The study by Pacreu et al. (2012), which evaluated methadone alone versus methadone with Ketamine, found that there was no statistical significance in PONV between the two groups ($p < .05$).

Hemodynamic Stability. Murphy & Szokol (2018) evaluated the mechanism of action of methadone and also addressed safety concerns. Here, cardiac QT interval was discussed, and it was proposed that patients receiving large doses of oral methadone for longer periods of time are at risk for QT prolongation, torsades de pointes, and cardiac death. However, "the effect of a single dose of methadone on the risk of prolonged QT interval has not been examined, although no adverse cardiac events related to methadone administration have been described in clinical trials or case reports." The observational study conducted by Dunn et al., (2018) on 1,478 patients who underwent spinal surgery and received an IV dose of intraoperative methadone of 0.14 ± 0.07mg/kg found that cardiac complications including arrhythmias (29.9%), QTc

prolongation (58.8%), and myocardial infarction (1.1%) occurred, as well as two in-hospital deaths (0.14%).

RCTs by Gottschalk et al. (2011) and Murphy et al. (2017), and a meta-analysis by Murphy & Szokol (2019), did not explicitly evaluate hemodynamic effects, but generally evaluated adverse events and outcomes that were associated with intraoperative methadone administration. It was summarized that methadone does not appear to increase the risk of hemodynamic side effects, and the consensus was that there were no differences between the methadone group and the control group with respect to adverse events.

Respiratory Stability. In the article by Murphy & Szokol (2018), which evaluated the mechanism of action of methadone and addressed safety concerns, it was noted that, at the present time, no adverse respiratory events related to methadone use have been found in the clinical trials to date. It was pointed out, however, that past studies are limited by small sample sizes and "a lack of close postoperative respiratory monitoring to assess the incidence of hypoxemic events and airway obstruction" (p. 82). Respiratory depression was defined as a respiratory rate less than 8-12 breaths per minute, while a hypoxemic event was defined as oxygen saturation dropping below 90-92%. It was recommended that further studies, with larger sample sizes and more diligent monitoring, be conducted to assess these outcome measures. The RCTs that evaluated respiratory parameters (Bolton et al., 2019; Gottschalk et al., 2011; Gourlay et al., 1984; Murphy et al., 2017; Udelsmann et al., 2011) reached similar conclusions: there was no difference in opioid-related respiratory effects between the methadone group and the control or placebo groups.

The observational study conducted by Dunn et al. (2018) evaluated hypoxemia and reintubation rates as secondary outcomes. The results found that, of the 1,478 subjects, 77.4%

were extubated in the operating room, 36.8% experienced respiratory depression, 79.8% experienced hypoxemia, and 1.5% required reintubation. It was concluded that, while the incidence of respiratory depression and hypoxemia were common, they were also easily managed.

The meta-analysis by Karasch (2011) recommended targeting doses and concentrations as high as possible above the minimal analgesic concentration, but below the threshold for respiratory depression. It is claimed that this will achieve the longest-lasting analgesia while preventing adverse respiratory side effects. Notably, the authors of this study estimate a methadone dose of greater than, or equal to, 20 milligrams. Relatedly, the meta-analysis performed by Murphy & Szokol (2019) found that "the dose of methadone that will result in prolonged analgesia without inducing respiratory depression has not been clearly defined in the literature" (p. 688). The authors point out that clinical trials have not supported the belief that the long half-life of methadone contributes to prolonged sedation and respiratory depression. Respiratory depression has occurred, but generally speaking, it can be deduced from the literature that methadone has not led to significant and detrimental respiratory events.

Theoretical Framework

Conceptual Framework

Melzack and Wall's (1965) gate control theory of pain was used as a framework for the implementation of the identified quality improvement project.

Gate Control Theory of Pain

The basis of the pain theory is that, like vision and hearing centers, the brain possesses a completely unique system for pain perception (Hua et al., 2020). Pain is transmitted from nerve endings on the skin along specific pathways to the pain center of the brain, where the sensation

of pain is processed. The brain therefore generates the experience of pain in the body (Melzack, 1999).

Specific to chronic spinal pain, the gate control theory of chronic pain recognizes pain as it pertains to both aspects of the nervous system: the central nervous system and the peripheral nervous system. As initially researched by Melzack and Wall (1965), pain is detected by multiple nerve endings in the back which are present in muscles, ligaments, disks, vertebrae and joints. With any irritation or inflammation, the perception of pain is transmitted through the spinal cord and up to the brain. Various treatments override these signals, including but not limited to: medication, massage, transcutaneous nerve stimulation, heat, and cold. In the gate control theory, these sensational impulses travel through large-diameter fibers and cause the gate in the spinal cord to close off to small-diameter fibers that carry pain impulses, thereby inhibiting the sensation of pain (Melzack & Wall, 1965), as represented in the model in Appendix C. The inverse is also true, i.e., an open gate will enable the pain sensation. There is a link between the open gate theory and the question presented in this project, which can be captured as follows: the project assesses the effect of long-duration opioid methadone on overriding pain perception signals when the body's recognition of pain occurs and continues following complex thoracolumbar spine surgery.

Project Methodology

Sample and Setting

This quality improvement project was conducted at Bronson Methodist Hospital in Kalamazoo, Michigan for a time period of one month. There was no financial compensation or any conflicts of interest. The evidence-based literature guideline used is available in Appendix A.

Adults 18-80 years old undergoing complex thoracolumbar spine surgery performed at Bronson Methodist Hospital were eligible for inclusion. Patients were included in the study regardless of preoperative medication administration, including any medications given as part of an Early Recovery After Surgery (ERAS) protocol. Exclusion criteria included known hypersensitivity to methadone hydrochloride or any other ingredient in Dolophine, current Methadone use, pregnant women, and known prolonged QTc interval preoperatively (>460 msec).

Key Personnel/Stakeholders

Key personnel involved in this project were anesthesia professionals with Kalamazoo Anesthesiology. The pharmacy department was also notified of this guideline implementation to prepare them for a likely increase in methadone preparation and consumption.

Recruitment Strategies

This DNP project was not a clinical trial and therefore there were no challenges with patient recruitment or anticipated challenges that would warrant the need to develop a detailed recruitment strategy. The proposed recruitment strategy involved eligible patients subjected to the Intraoperative Methadone Administration Guideline for a one-month period and then followed through PACU discharge.

Study Design and Implementation Plan

Development of Evidenced-Based Intraoperative Methadone Administration Guideline. After extensive evaluation of the current evidence-based literature, the Intraoperative Methadone Guideline was created (Appendix A). Due to the evidence-based beneficial effects discussed in the literature review above, a dose of 0.2mg/kg based on ideal body weight (IBW) was chosen. It was requested that fentanyl (if desired), be limited to 100mcg with induction, with

a goal to withhold further narcotic. Methadone 0.2mg/kg (IBW) was to be administered intravenously over five minutes after induction, but before incision. The anesthetic plan beyond the foregoing was performed at the discretion of the anesthesia provider.

Education of the Anesthesia Team. Prior to initiation of the quality improvement project, an educational presentation was provided to all anesthesia providers. This presentation took place during a department monthly meeting. The anesthesia providers were asked to take a pre-education assessment (Appendix E). A link to the survey, created in Survey Monkey, was provided to all anesthesia providers. This helped determine baseline knowledge and areas for education. After the completion of the pre-survey, a PowerPoint presentation was provided on the use of methadone for spine surgery. The intraoperative methadone administration guideline (Appendix A) was presented and explained to the anesthesia team. Time was allotted to answer any questions or concerns. At the conclusion of the presentation, the anesthesia providers were asked to take a post-survey (identical to the pre-survey found in Appendix E), to assess if there was adequate education provided. In addition, all Kalamazoo Anesthesiology employees received an e-mail correspondence with the guideline attached.

Implementation of the Intraoperative Methadone Administration Guideline. Implementation of the Intraoperative Methadone Administration Guideline began in February 2022. Prior to implementation, the anesthesia providers were presented with education about the guideline as well as an opportunity to address questions and concerns during a department meeting, as stated above. After the conclusion of the education session, the guideline was emailed to all anesthesia providers. Another e-mail was sent to all anesthesia providers one week before implementation of the guideline to remind them of the initiation date. To further assist with ease of implementation, a copy of the guideline was placed on the anesthesia workstation in

all operating rooms where spine surgery occurs. Our contact information was provided on the guideline to assist with availability if any questions arise.

Anesthesia and Airway Management. Induction, maintenance and emergence of anesthesia were performed at the discretion of the anesthesia provider. Aside from the intraoperative methadone administration guideline, we did not attempt to control for any aspects of the anesthetic technique. Anesthesia providers were free to manage anesthesia and administer analgesics as they deemed appropriate for their patient.

Surgical Technique. All procedures were performed at the discretion of the surgeon. We did not attempt to control for any aspect of the surgical technique or postoperative surgical management.

Evaluation of the Results. Descriptive statistics was used to find meaningful conclusions of the data. A professional Oakland University statistician was consulted. Without recording any identifying data, chart reviews were conducted on all applicable surgical procedures that occurred during the pre-established timeframe. Data collected included:

- Procedure type
- Pre-operative medications administered
- QTc interval, if pre-operative ECG performed
- Dose of methadone administered, if applicable
- Oxycodone administered pre-operatively (yes/no)
- Dose of fentanyl administered with induction, if applicable
- Any additional intraoperative narcotics administered
- Pain Score on admission to Post Anesthesia Care Unit (PACU)
- Post-operative narcotics administered in PACU

Measurement Methods and Data Collection. Upon completion of the intraoperative methadone guideline, we accessed the surgical record for data collection. Kalamazoo Anesthesiology provided a Letter of Support (Appendix D) indicating approval for chart reviews. Data was collected via electronic medical chart review. Guideline adherence data was collected on all patients who underwent a complex thoracolumbar spine surgery between January 31, 2022 until February 25, 2022. Patient outcome data was collected on any patient meeting the inclusion and exclusion criteria who underwent an applicable procedure. Patient outcomes were measured and evaluated from the time the patient arrived in the PACU.

Guideline adherence data collected included:

- Randomly assigned patient number
- Methadone 0.2mg/kg IBW was given prior to incision per the guideline (yes/no)
- Fentanyl limited to 100mcg or less (yes/no)
- Complete adherence to the guideline (yes/no)

Patient outcome data included:

- Initial pain score recorded in PACU
- Post-operative narcotic requirements in PACU

Evaluation Plan. For data management, IBM SPSS Statistics Version 24 software was utilized as a centralized repository for ease of computation of data sets. After data collection was complete, descriptive statistics was conducted on all major study variables. A computerized statistical software and professional statistician was consulted. All statistical computations were performed by the professional statistician.

Dissemination of the findings occurred during another anesthesia department meeting in May 2022, where we also discussed project limitations and possible explanations for lack of adherence.

Barriers and Project Limitations. This study was limited by a few factors. While there was education provided and a clear guideline to follow, there was no way to ensure the anesthesia providers strictly adhered to the guideline. Our low adherence rate and inconsistent sample size in survey participation decreased the strength of our findings. In addition, we were unable to control for all variables throughout the patient's surgical experience, thereby also limiting the generalizability of the results. Finally, a specific sample size could not be guaranteed over the allotted time period, which limited the potential for statistical significance and generalizable findings. Finally, matched pre-and post- surveys would produce stronger results and we believe that a focus group would facilitate some insight in determining why providers used the medications they did and why they chose not to use methadone for applicable cases.

In the planning phase of this project, we discovered three additional populations that we neglected to address for consideration of the methadone guideline. These included critical care patients, patients undergoing emergent procedures (e.g., trauma victims), and those with spinal cord injuries. We were appreciative of the anesthesiologists and CRNAs caring for these patients for reaching out to ask us how our guideline fits their specific disease processes. We regretfully did not have an answer, but perhaps future research can determine the best plan of care for these patients. Without supporting literature, we modified our patient population and placed these conditions into our exclusion criteria. We also did not find in our literature review any information about the impact of methadone administration for the various thoracolumbar

approaches. All of our chart reviews were conducted on posterior approaches, and we therefore cannot generalize our findings in relation to the oblique or anterior approaches.

Project Resources

There was no financial burden or cost involved in the implementation process. While there were no increased overhead costs from the perspective of the anesthesia department, there was the potential for increased labor and material costs in the pharmacy department, due to the sudden need for increased methadone preparation and use.

Approvals for Implementation

Prior to the implementation of this project, we received exemption from the Oakland University IRB and Institutional letter of support from Bronson's research compliance department (Appendix D).

Evaluation of the Results

Anesthesia provider adherence to the Intraoperative Methadone Administration Guideline was assessed during the month of February, 2022. Throughout this time period, 22 patients were eligible to receive the protocol, and were evaluated for adherence to the protocol. Adherence to the protocol components as well as the protocol in its entirety was evaluated on a yes/no basis. Complete adherence to the guideline occurred in five of the 22 patients, for an adherence rate of 22.7%.

We conducted our chart reviews systematically utilizing a data collection tool (Appendix B) to ensure consistency. Upon completion of the chart reviews, we met with a statistician with Oakland University, and utilized his assistance and expertise to find a meaningful analysis of both the results of our chart review and of our pre- and post-survey results.

An analysis of the results of the surveys revealed no strong correlation between pre-and post-surveys. In other words, the surveys did not reveal a statistically significant difference in methadone knowledge or attitude toward using methadone during complex spinal surgery. This may have been partially due to decreased participation rates in the post-survey, but it ultimately indicates that our presentation did not have a significant impact on provider knowledge and attitude toward methadone.

In the results that we analyzed with our statistician, we found that provider role was not predictive of either attitude toward methadone, nor of knowledge base in pre- vs post- education results. When looking at experience and familiarity with methadone, the results displayed a "signal," indicating that providers with more experience felt more familiar with methadone. This was not a statistically significant finding, but the statistician pointed out that this result was trending significant. Likewise, there was also a trending significant result in improved knowledge regarding methadone's onset of action between pre- and post-surveys, at $p = 0.052$.

Overall, it was difficult to extrapolate any generalizations from the data we collected via the surveys. In the future, it would be helpful to have linked survey results, where we can anonymously link a provider's pre-and post-survey. We believe it would also be helpful to receive feedback from KA providers on where the perceived barriers or reluctance lied in participating in one or both of the surveys, as a larger, more consistent sample size would have provided more valid and reliable results.

Utilizing SPSS Statistics and the expertise of a professional statistician, a Wilcoxon test showed a statistically significant finding in patients who received methadone who reported decreased pain scores ($p = .015$) post-operatively. The Wilcoxon test is a non-parametric analysis that we utilized on this data because this test accounts for smaller sample sizes. This test

showed patients who did not receive methadone (whether they received oxycodone, or no pre-operative narcotic at all) reported a pain score of well over double (mean = 9.57) as compared to those who received intraoperative methadone (2.67).

In a comparison between patients who received oxycodone versus those who did not receive any preoperative narcotic, we again ran a Wilcoxon test and found that there was no statistical difference in pain scores among patients who received oxycodone pre-operative versus those who did not. Of the 20 applicable procedures during our implementation timeframe, 10 patients received oxycodone, while five did not receive any preoperative narcotic and six patients received methadone. The patients who received oxycodone reported no significant effect on pain scores in PACU ($p = .165$) compared to those who received no preoperative narcotic. Again, due to a small sample size and low adherence rate, it is not possible to make broad generalizations from the results of this study. More research is needed with a larger sample size in order for generalizations to be made.

Recommendations for Future Research

Recommendations for future quality improvement projects will include strategies to improve anesthesia provider adherence to the evidence-based protocol. Future projects may explore ways to increase anesthesia staff engagement in the earlier stages of the project. This may include identifying areas of interest or need and earlier implementation of staff education. This would likely improve staff engagement and willingness to adhere to the proposed protocol. Additionally, it would be beneficial for future projects to aim to remove all barriers that may prevent providers from adhering to the components of an evidence-based protocol. For example, having eligible procedures flagged in the charting system would ensure that the provider had an instant reminder and confirmation of eligibility.

Implications for Nursing Practice

While the use of intraoperative methadone has direct implications for nursing practice, the overall implementation of this DNP project will also affect the practice of nursing and the goals of nursing in a variety of ways. A main goal in the practice of nursing is to improve a patient's overall health experience. Through the implementation of this DNP project, the evidence suggests that a patient's post-operative pain will be improved, post-operative opioid requirements will be reduced, and a high level of patient satisfaction will be maintained with the use of intraoperative methadone. With the reduction of post-operative pain and opioid consumption, patients will additionally benefit from a reduction of side effects such as nausea and vomiting and opioid-induced hyperalgesia.

Moreover, enhancing the patient's experience results in an anticipated reduction in length of stay. Since evidence shows that intraoperative methadone administration reduces opioid consumption and improves post-operative outcomes, this guideline would logically prove to be beneficial for both patient and hospital reimbursement. The cost savings for patients would directly correlate to the evidence that suggests implementation of this DNP project will lead to quicker recovery times and decreased length of stay.

While the use of intraoperative methadone administration could provide a tool for decreasing opioid use, dissemination of the benefits of intraoperative methadone and the findings of this study will contribute to an overall increase in the knowledge of nursing practice and will ultimately help improve patient outcomes. The findings from this study could then be applied to other procedures such as open-heart surgery or extensive open abdominal surgery. There is an obligation on behalf of the nursing profession to advocate for the health of patients and

communities. Nursing interventions that are evidence-based, cost-effective, and safe result in improved patient outcomes should be adopted by the nursing profession.

Contributions to the Doctor of Nursing Practice Essentials

The American Association of Colleges of Nurses (AACN) developed competencies that must be addressed in the curriculum of all Doctor of Nursing Practice (DNP) programs. These eight essentials of doctoral education tackle the increasingly complex needs of the healthcare system. The development and implementation of this DNP project addressed all of these essentials, but Essentials I, III and VIII specifically were met repetitively and consistently (*The essentials of doctoral education for advanced nursing practice*, 2006).

Essential I, Scientific Underpinnings for Practice, is met by incorporating a nursing theory which enhances healthcare delivery and improves patient outcomes. As discussed above, the Gate Control Theory of pain was utilized in this project to help guide the nursing interventions used throughout the DNP project.

Essential III, Clinical Scholarship and Analytical Methods for Evidence-Based Practice, is achieved by facilitating evidence-based initiatives into patient care to promote better outcomes. The overarching purpose of this project was to implement meaningful change using current best evidence and practice guidelines regarding intraoperative methadone administration, thereby improving the care of patients.

Essential VIII, Advanced Nursing Practice, is met by working alongside multiple healthcare disciplines to facilitate a large systematic change. Essential VIII can be seen throughout this project through discussions and collaborations with pharmacy staff, anesthesia providers, and recovery nurses in the development of the methadone guideline, feasibility of the project, and the identification of barriers for implementation.

Conclusion

This quality improvement project aimed to reduce the detrimental consequences of the national opioid epidemic by shifting the practice of anesthesia providers. This effort was comprised of multiple phases including an extensive review of current literature, development and implementation of an evidence-based guideline, evaluation of provider adherence to the guideline, and the evaluation of patient outcomes. Current literature reveals that the intraoperative administration of methadone to patients undergoing a complex spine surgery is associated with decreased opioid administration in the postoperative period, as well as decreased post-operative reports of pain. Therefore, a guideline was developed to assist anesthesia providers in the administration of intraoperative methadone during complex spine surgery with instrumentation. The evidence-based guideline was presented to the providers of Kalamazoo Anesthesiology in an educational staff meeting. Although many providers failed to adhere completely to the methadone guideline, patient outcomes still demonstrated reduced opioid consumption with the administration of methadone. Future quality improvement projects should address barriers to protocol adherence with a goal to strengthen the quality of post-intervention data.

References

American Medical Association. (2021). *Issue brief: Reports of increases in opioid- and other drug-related overdose and other concerns during COVID pandemic*. https://www.ama-assn.org/system/files/2020-12/issue-brief-increases-in-opioid-related-overdose.pdf

Batras, D., Duff, C., & Smith, B. J. (2016). Organizational change theory: Implications for health promotion practice. *Health Promotion International, 31*(1), 231-241.

Bolton, T. M., Chomicki, S. O., Mckay, W. P., Pikaluk, D. R., Betcher, J. G., & Tsang, J. C. (2019). Preoperative oral methadone for postoperative pain in patients undergoing cardiac surgery: A randomized double-blind placebo-controlled pilot. *Canadian Journal of Pain, 3*(1), 49-57. https://doi.org/10.1080/24740527.2019.1575695

Cho, I., & Min, S. (2015). *Korean Association of Urogenital Tract Infection and Inflammation*, *10*(2), 98.

Coluzzi, F., Bifulco, F., Cuomo, A., Dauri, M., Leonardi, C., Melotti, R. M., Natoli, S., Romualdi, P., Savoia, G., & Corcione, A. (2017). The challenge of perioperative pain management in opioid-tolerant patients. *Therapeutics and Clinical Risk Management*, *13*, 1163–1173.

De Boer, H. D., Detriche, O., and Forget, P. (2017). Opioid-related side effects: postoperative ileus, urinary retention, nausea and vomiting, shivering. A review of the literature. *Best Practice & Research Clinical Anaesthesiology*, *31*(4), 449-504.

D'souza, R. S., Gurrieri, C., Johnson, R. L., Warner, N., & Wittwer, E. (2019). Intraoperative methadone administration and postoperative pain control. *Pain, 161*(2), 237-243.

Dunn, L. K., Yerra, S., Fang, S., Hanak, M. F., Leibowitz, M. K., Alpert, S. B., Tsang, S., Durieux, M. E., Nemergut, E. C., & Naik, B. I. (2018). Safety profile of intraoperative methadone for

analgesia after major spine surgery: An observational study of 1,478 patients. *Journal of Opioid Management*, 14(2), 83–87. https://doi.org/10.5055/jom.2018.0435

Dunn, MD, PhD, L., Yerra, MBBS, S., Fang, MSc, S., Leibowitz, M., Tsang, S., Durieux, M., Nemergut, E., and Naik, B. (2018). Incidence and risk factors for chronic postoperative opioid use after major spine surgery. *Anesthesia & Analgesia, 127*(1), 247-254.

Friesgaard, K. D., Brix, L. D., Kristensen, C. B., Rian, O., & Nikolajsen, L. (2019). Intraoperative methadone for postoperative pain after laparoscopic hysterectomy: Protocol for a randomised, double-blind trial. *Acta Anaesthesiologica Scandinavica, 63*(9), 1257-1261.

Gottschalk, Antje, Durieux, Marcel, MD, PhD & Nemergut, Edward. (2011). Intraoperative methadone improves postoperative pain control in patients undergoing complex spine surgery. *Anesthesia & Analgesia*, *112*, 218-223.

Gourlay, Geoffrey, Willis, Richard & Wilson, Peter. (1984). Postoperative pain control with methadone: Influence of supplementary methadone doses and blood concentration-response relationships. *Anesthesiology*, *61*(1), 19-26.

Higgs, M., Hackworth, R., John, K., Riffenburgh, R., Tomlin, J., & Wamsley, B. (2017). The intraoperative effect of methadone on somatosensory evoked potentials. *Journal of Neurosurgical Anesthesiology*, *29*(2), 168-174.

Hua, T., Chen, B., Lu, D., Sakurai, K., Zhao, S., Han, B. X., Kim, J., Yin, L., Chen, Y., Lu, J., & Wang, F. (2020). General anesthetics activate a potent central pain-suppression circuit in the amygdala. *Nature Neuroscience*, 23(7), 854–868. https://doi.org/10.1038/s41593-020-0632-8

Kendall, M. C., Alves, L. J., Pence, K., Mukhdomi, T., Croxford, D., & Oliveira, G. S. (2020). The effect of intraoperative methadone compared to morphine on postsurgical pain: A meta-analysis of randomized controlled trials. *Anesthesiology Research and Practice, 2020*, 1-9.

Kharasch E. D. (2011). Intraoperative methadone: Rediscovery, reappraisal, and reinvigoration? *Anesthesia and Analgesia*, *112*(1), 13–16.

Komen, H., Brunt, L. M., Deych, E., Blood, J., & Kharasch, E. D. (2019). Intraoperative methadone in same-day ambulatory surgery: A randomized, double-blinded, dose-finding pilot study. *Anesthesia and Analgesia*, *128*(4), 802–810.

Melzack, R. (1999). Pain – an overview. *Acta Anaesthesiologica Scandinavica*, 43(9), 880-884.

Melzack, R., & Wall, P. (1965). Pain mechanisms: A new theory. *Science*, *150*(3699), 971-978.

Murphy, G. S., Avram, M. J., Greenberg, S. B., Shear, T. D., Deshur, M. A., Dickerson, D., . . . Szokol, J. W. (2020). Postoperative pain and analgesic requirements in the first year after intraoperative methadone for complex spine and cardiac surgery. *Anesthesiology, 132*(2), 330-342.

Murphy, G. S., & Szokol, J. W. (2019). Intraoperative methadone in surgical patients. *Anesthesiology, 131*(3), 678-692.

Murphy, G., & Szokol, J. (2018). Use of methadone in the perioperative period. *Anesthesia Patient Safety Foundation (APSF), 32*(3), 81-82.

Murphy, G., Szokol, J., Avram, M., Greenberg, S., Shear, T., Deshur, M., Vender, J., Benson, J. and Newmark, R., (2017). Clinical effectiveness and safety of intraoperative methadone in patients undergoing posterior spinal fusion surgery. *Anesthesiology*, 126(5), pp.822-833.

Pacreu, S., Candil, J. F., Moltó, L., Carazo, J., & Galinski, S. F. (2012). The perioperative combination of methadone and ketamine reduces post-operative opioid usage compared with methadone alone. *Acta Anaesthesiologica Scandinavica, 56*(10), 1250-1256.

Quinlan, J., Rann, S., Bastable, R., & Levy, N. (2019). Perioperative opioid use and misuse. *Clinical Medicine*, *19*(6), 441-445.

Sharma, A., Tallchief, D., Blood, J., Kim, T., London, A., & Kharasch, E. D. (2011). Perioperative pharmacokinetics of methadone in adolescents. Anesthesiology, 115(6), 1153–1161.

The Association. (2006). *The essentials of doctoral education for advanced nursing practice*. Washington, D.C.

Udelsmann, A., Maciel, F. G., Servian, D. C., Reis, E., de Azevedo, T. M., & Melo, M. (2011). Methadone and morphine during anesthesia induction for cardiac surgery. Repercussion in postoperative analgesia and prevalence of nausea and vomiting. *Revista brasileira de anestesiologia*, *61*(6), 695–701.

Wilson, L., & Kolcaba, K. (2004). Practical application of comfort theory in the perianesthesia setting. *Journal of PeriAnesthesia Nursing, 19*(3), 164-173.

Ye, J., Myung, K., Packiasabapathy, S., Yu, J.S., Jacobson, J.E., Whittaker, S.C., Castelluccio, P., Drayon-Jackson, M., Sadhasivam, S. (2020). Methadone-based multimodal analgesia provides the best-in-class acute surgical pain control and functional outcomes with lower opioid use following major posterior fusion surgery in adolescents with idiopathic scoliosis. *Pediatric Quality & Safety, 5*(4), 1-8.

Appendix A

Guideline for Intraoperative Methadone

Intraoperative Methadone Guideline for Complex Thoracolumbar Spine Surgery

- Background: Severe pain after complex spine surgery is a common and undertreated problem that can be difficult to manage and may lead to poor postoperative outcomes and even opioid dependence. Chronic pain (commonly neuropathic in nature) is prevalent among patients undergoing complex spine surgery, as is the existence of a long-standing pain management regimen that often includes the use of opioids. Consequently, these patients often present with opioid-induced hyperalgesia, elevated tolerance levels to medications, and increased requirements of pain medication to treat their postoperative pain. As such, patients who undergo complex spine surgery are at an increased risk of both postoperative pain and postoperative opioid dependence, and potentially even increased morbidity and mortality.

  Perioperative pain control has traditionally been accomplished via opioids with shorter half-lives intraoperatively (e.g., fentanyl, sufentanyl, remifentanil), which is then transitioned to opioids with longer half-lives postoperatively (e.g., morphine or dilaudid). The problem with this pain regimen is that it often creates a "peak and valley" effect, where significant fluctuations in opioid concentrations lead to reports of inadequate pain control. Methadone has been proven to provide potential advantages as a perioperative analgesic, decreasing the need for opioids with shorter half-lives, such as those listed above.

- Study: The Oakland University SRNAs are implementing a practice guideline derived from evidence-based literature in which methadone will be administered intra-operatively for thoracolumbar complex spine surgery (defined as a spinal fusion involving at least **two** levels with instrumentation).

- Rationale: A decrease in opioid use after surgery can potentially be accomplished via the administration of an intraoperative intravenous dose of methadone. Methadone is a mu-receptor agonist and NMDA receptor antagonist with the longest elimination half-life of the clinically used opioids. Due to methadone's extended half-life, one dose administered intra-operatively by an anesthesia provider has the potential to provide extended pain relief beyond the postoperative period.

- Population:
  - Inclusion criteria: Adults 18-80 years old undergoing thoracolumbar spinal fusion surgery of two or more levels with instrumentation at Bronson Methodist Hospital are eligible for inclusion
  - Exclusion criteria:
    - Hypersensitivity to methadone hydrochloride or any other ingredient in Dolophine
    - Current methadone use
    - Pregnant women

- Patients with a known prolonged QTc > 460 msec preoperatively

- Instructions

Pre-operatively:

- Pre-operative medications to be administered via Bronson's Neurosurgical ERAS protocol, and per provider discretion
-

Intra-operatively:

- Fentanyl (if desired), limited to 100mcg with induction, with efforts maintained to withhold any further narcotic throughout the duration of the procedure.
- Methadone 0.2mg/kg ***(IBW)*** IV push over 5 minutes, administered with induction but *before* incision
- Induction drugs and anesthetic plan (beyond what is listed above) is at the discretion of the anesthesia provider

Post-operatively:

- Routine post-operative monitoring per hospital policy
- Post-operative care, including medication administration, to be administered per policy and PACU provider discretion based on patient status

** This project will not control for any aspects of the anesthetic technique during the induction, maintenance, or emergence phases beyond the components of this guideline. The anesthetic delivery will be at the discretion of the anesthesia provider. Similarly, the surgical technique and postoperative management will be solely at the discretion of the surgeon.
Contact Information: Please feel free to contact us with any questions

Kelsey Fobbe
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(517) 282-1295
*Also available via TigerText

Thomas Hart
Thart@oakland.edu
(810) 813-5020

Appendix B

Data Collection Tool

Patient #: _____
Procedure: _____
Date: _____
Age: _____
Gender: Male Female

Inclusion Criteria Met (see guideline)? Yes No
Exclusion Criteria Met (see guideline)? Yes No

PRE-OP
Medications given per Bronson's Neurosurgical ERAS protocol, per provider discretion

Dramamine: Yes No
Acetaminophen: Yes No
Celecoxib: Yes No
Gabapentin: Yes No

EKG:
QTc Pre-op: _____ms
QTc Post-op: _____ms

INTRA-OP
Methadone 0.2mg/kg IV Used? Yes No Dose: _____mg
Oxycodone 5mg PO Used? Yes No Dose: _____mg

Induction Dose of Fentanyl: _____mcg

Additional Narcotics Intra-op? Yes No

Medication	Dose

POST-OP
Pain score on admission to PACU: ____/10

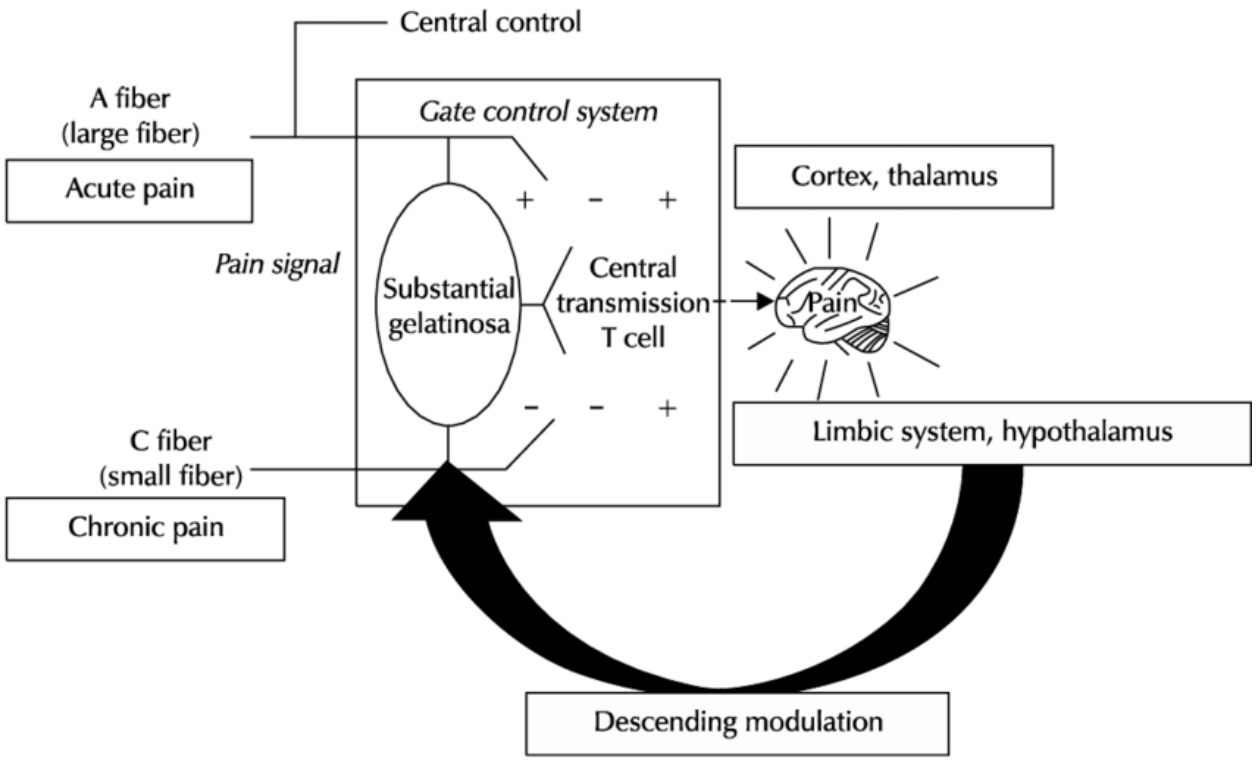
PACU Narcotics Given? Yes No

Medication	Dose

Guideline Adherence: **Yes** **No**

Appendix C

The Gate Control Theory of Pain



Note: The neurophysiologic events that gate (modulate) the pain impulse may be influenced by numerous peripheral and central factors (Cho & Min, 2015).

Appendix D

Approvals for Implementation

OAKLAND UNIVERSITY

Institutional Review Board

Date: October 28, 2021

Study #: IRB-FY2021-400

Study Tile: Intra-operative Methadone Administration for Complex Spine Surgery

Submission Type: Initial

IRB Decision: Not Research

Research Team:
Kelsey Fobbe
Toni Glover
Mary Golinski
Thomas Hart

The above referenced study has been has been determined to be Not Research according to federal regulations.

The IRB decision is based on the following:

This is not research. This is a quality improvement project to develop and implement an evidence-based guideline for intra-operative methadone administration during complex spinal surgery.
The results of this project are not intended to be generalized and the results of this QI project will be disseminated only to the anesthesia providers with Kalamazoo Anesthesiology at Bronson Hospital.

Please note the following:

- Before the project is initiated, permission must be obtained from all locations listed in the IRB submission.
- You must keep copies of all such permission letters for your files.
- It is the responsibility of each investigator to follow all applicable policies and procedures of any outside institution

Please retain a copy of this correspondence for your records.
If you have any questions, please contact the IRB staff.

The Oakland University IRB

NOTICE OF QUALITY IMPROVEMENT PROJECT APPROVAL

11/16/2021

Kelsey Fobbe
Kalamazoo Anesthesiology
900 Peeler St., #B
Kalamazoo, MI 49008

TYPE OF REVIEW: QUALITY IMPROVEMENT PROJECT

PROTOCOL TITLE: DNP-NA Quality Improvement Initiative: Development and Implementation of an Intraoperative Methadone Guideline for Complex Spinal Surgery.

Dear Kelsey

On 11/16/2021, it was determined the proposed activity does not meet the definition of research as defined by the Common Rule and FDA *[45 CFR 46.102(d)].* Therefore, review and approval by our local Western Michigan University Homer Stryker School of Medicine Institutional Review Board (IRB) is not required. Please be remindful when presenting or publishing the collected data that it is presented as a Bronson-specific Quality Improvement project and not as research.

This approval only applies to activities described in the proposed protocol submitted for approval and does not apply should any changes be made. If there are changes to the protocol, please re-submit for review and approval prior to implementation. If there are questions about whether these activities constitute research involving human subjects, please submit a new request to our local IRB for a determination utilizing the electronic submission system at https://med.wmich.edu/irbesubmit.

Your project will remain on file within the Research Compliance Office. If you should have any questions please feel free to contact me at 269-341-6662 or by email at ferrisp@bronsonhg.org.

Sincerely,

Pamela Ferris

Pamela Ferris, RN, BSN
Research Compliance Specialist
Bronson Methodist Hospital
601 John Street
Kalamazoo, MI 49007

Cc Toni Glover, Dr. Robert Nicholson, Kate Pratley, Dr. Larson

BRONSON

Appendix E

Pre- and Post-Education Survey

Intraoperative Methadone Administration for Complex Spine Surgery: A Pre- & Post-Assessment

1. I am a(n):
    a. Anesthesiologist
    b. Certified Registered Nurse Anesthetist

2. Number of years in practice:
    a. <1 year
    b. 1-<5 years
    c. 5-<10 years
    d. 10-<20 years
    e. >20 years

3. Please indicate the option that best describes your familiarity with methadone
    a. I routinely administer methadone to complex spine surgery patients
    b. I administer methadone to spine patients most of the time (>50%)
    c. I rarely administer methadone to spine patients (<50%)
    d. I have never administered methadone to spine patients

4. Compared to shorter-acting opioids, I currently feel that methadone in the post-operative period:
    a. is more effective
    b. is less effective

5. How likely is it that you would administer methadone to a patient undergoing a complex spinal surgery? (Defined above)

Not at all Likely
Extremely Likely

0	1	2	3	4	5	6	7	8	9	10

6. How comfortable are you in administering methadone?
    a. I am not comfortable administering intraoperative methadone
    b. I am reluctant to use methadone
    c. I am comfortable with methadone
    d. I think methadone is an effective method of pain management

7. Methadone has an onset of action of:
    a. 1-2 minutes
    b. 6-8 minutes
    c. 15-30 minutes
    d. 45-60 minutes

8. The half-life of Methadone is:
    a. 1-2 hours
    b. 6-8 hours
    c. 10-12 hours
    d. 24-60 hours

9. Methadone's primary mechanisms of action are: (select 2)
    ☐ Mu-receptor agonist
    ☐ GABA receptor agonist
    ☐ Alpha-2 receptor agonist
    ☐ NMDA receptor antagonist

10. Methadone is contraindicated in all of the following patients except:
    a. Pregnant women
    b. Pulmonary pathophysiology (e.g. asthma/COPD)
    c. Chronic Kidney Disease
    d. Prolonged QT interval

11. An appropriate loading dose for intraoperative methadone is _____, and is based on ideal body weight/actual body weight: (select two)
    ☐ 0.2mg/kg
    ☐ 0.4mg/kg
    ☐ Actual Body Weight
    ☐ Ideal Body Weight

Author (Year)	Design/Method	Sample/Setting	Major Variables Studied	Measurement	Data Analysis	Findings	Appraisal: Worth to Practice

Appendix F:

Literature Evaluation Table

1. Murphy, et al. (2020), Anesthesiology (132), 330-342.	Follow up to RCT evaluating 0.2mg/kg Methadone at induction vs 2mg hydromorphone at surgical closure	N= 120 Allocated to Methadone: n=63 Allocated to Hydromorphone : n= 57	InV1: Methadone 0.2mg/kg InnV2: Hydromorphone 2mg/kg DV1: Pain Frequency DV2: Pain Intensity DV3: Oral Opioid Requirements DV4: Opioid Frequency DV5: Need to contact physician DV6: Pain interference with sleep DV7: Pain interference with daily activities	Questionnaire at 1,3,6, and 12 months after surgery Primary Outcome: Frequency (scale 0-4) and Intensity (scale 0-10) of pain during first post-operative year Secondary Outcomes: requirements for any oral opioid analgesic medications (yes/no), as well as the frequency of use (scale 0-3); Patients recorded whether they had sought the care of a physician to treat pain directly related to the surgery; pain interference with sleep (scale 0-10) and pain interference with daily activities (scale 0-10	Mann-Whitney U Test or Fisher exact probability test	Three months after surgery, patients randomized to receive methadone reported the weekly frequency of chronic pain was less (median score 0 on a 0 to 4 scale [less than once a week] vs. 3 [daily] in the hydromorphone group, P = 0.004). Methadone is a unique opioid with a long half-life that provides prolonged stable blood concentrations after a single intraoperative dose, without the fluctuations associated with repeated injections of higher clearance opioids like morphine or hydromorphone	**Limitations:** none stated **Conclusion:** Analgesic benefits of a single dose of intraoperative methadone were observed during the first 3 months after spinal surgery (but not at 6 and 12 months)
2. Ye, et al. (2020), Pediatric Quality and Safety 5(4), 1-8	**Retrospective Matched Cohort Design (quality improvement [QI] project)** **Purpose:** methadone-based multimodal analgesia protocol, aiming to decrease the length of hospital stay (LOS), improve	n = 122 Control group (n=61, intrathecal morphine, gabapentin, intravenous opioids, and adjuncts) Protocol group (n-61, scheduled methadone,	InV: Methadone DV1: LOS DV2: pain scores DV3: total opioid use DV4: time to a first bowel movement DV5: post- discharge phone calls	Primary outcome: time to hospital discharge (days) Secondary outcomes: -opioid consumption (MME) on each postoperative day and in total -pain scores (scale 0–10 Numerical Rating Scale for pain and averaged over each postoperative	QI Macros to statistically analyze LOS and total Morphine Categorical variables compared using the Chi-square test Wilcoxon rank-sum test for comparison of medians.	New protocol patients were discharged earlier (median LOS, 2 days) compared with control patients (3 days; $P < 0.001$). Morphine consumption was lower in the protocol group ($P < 0.001$). Pain scores were higher in the protocol group on the day of surgery, similar on	**Limitations:** -This study was conducted on children, where our focus is on adults **Conclusion:** Methadone-based multimodal analgesia resulted in significantly lower LOS compared with the conventional regimen. It also provided improved pain control, reduced total opioid consumption, and early bowel movement compared with the control group

Author (Year)	Design/Method	Sample/Setting	Major Variables Studied	Measurement	Data Analysis	Findings	Appraisal: Worth to Practice
	pain control, and decrease the need for additional opioids	methocarbamol, ketorolac/ ibuprofen, acetaminophen, and oxycodone with intravenous opioids as needed		day), -opioid-related side effects (measured by time to first bowel movement) -post-discharge pain-related phone calls		postoperative day (POD) 1, and lower by POD 2 ($P = 0.01$). Reduced the median time to first bowel movement ($P < 0.001$), and the number of post-discharge pain-related phone calls ($P < 0.006$)	
3. Murphy & Szokol (2018), APSF 32(3), 81-82	Not a study	N/A	This was not a clinical trial, although mechanism of action and safety concerns were addressed.		N/A	SAFETY: **QT INTERVAL:** Patients receiving large doses of oral methadone for longer periods of time are at risk for QT prolongation, torsades de pointes, and cardiac death. The effect of a single dose of methadone on the risk of QT lengthening and torsades de pointes has not been examined, although no adverse cardiac events related to methadone administration have been described in clinical trials or case reports **RESP DEPRESSION:** At the present time, no adverse respiratory events related to methadone use have been described in the clinical trials. However, the studies are limited by small sample sizes and a lack of close postoperative respiratory monitoring to assess the incidence of hypoxemic events and airway obstruction. Further studies are needed	**Limitations:** Further studies are needed to define the optimal dose of this agent and which surgical patients may derive the greatest benefit from its administration in the operating room. **Conclusion:** methadone is a long-acting opioid with promising applications in the perioperative setting

Author (Year)	Design/Method	Sample/Setting	Major Variables Studied	Measurement	Data Analysis	Findings	Appraisal: Worth to Practice
						to assess this important outcome measure.	
4. Bolton et al. (2019), Canadian Journal of Pain 3(1), 49-57	**Randomized, Double-Blind Pilot Study** **Purpose**: Investigate the effect of preoperative oral methadone on pain scores, analgesia requirements, and opioid-induced side effects	N=21 Placebo: n=12 Methadone: n=9	InV1: Oral Methadone 0.3mg/kg InV2: Placebo (sweet syrup) DV1: Pain Scores DV2: -Morphine Requirements using PCA -Time to extubation -Level of Sedation -Side effects (N/V, pruritis, hypoventilation, hypoxia	Postoperative pain scores were measured and reported for 72 h postoperatively using a validated 0- to 10-point Verbal Rating Scale Secondary Outcomes: 24h postoperative morphine requirements, time to extubation, level of sedation, and opioid-related side effects, specifically nausea, vomiting, pruritus, hypoventilation, and hypoxia during a 72-h monitoring period	Kolmogorov-Smirnov test used and compared between groups with a t test if normally distributed and with a Mann-Whitney rank sum test if nonnormally distributed. The secondary outcomes with continuous data were similarly dealt with; secondary outcomes with categorical data were analyzed by chi-square test	Oral methadone did not reduce pain scores in the methadone group (P = 0.08). postoperative morphine requirement during the first 24 h was reduced by a mean of 23 mg in the methadone group (P < 0.005). No reduction in pain scores or PCA morphine was observed beyond 24 h postoperatively. There was no difference in incidence of opioid-related side effects between groups throughout the postoperative period.	**Limitations:** This study focused on the effect of Methadone on cardiac patients rather than spinal patients Also, this study examined the use of oral Methadone rather than IV Methadone Small sample size High-risk patients and opioid-tolerant patients were excluded from enrollment. It is unclear what effect pre-operative oral methadone would have in this group **Conclusions:** Though preoperative oral methadone did not reduce pain scores, morphine requirements were reduced in the first 24 h post-CABG.
5. D'Souza, et al. (2019), Pain, *161*(2), 237-243	**Meta-Analysis** Purpose: To compare postoperative opioid consumption and pain scores in surgical patients who received methadone by any route vs those who received another opioid by any route	10 studies (617 patients)	InV1: Methadone (any route) InV2: Other opioid (any route) DV1: Post-operative opioid consumption DV2: Pain Scores	Pooled odds ratios were calculated for a primary outcome of postoperative opioid consumption and secondary outcomes of time-to-extubation, time-to-first postoperative analgesia request, satisfaction, hospital length-of-stay, and complications. Postoperative pain scores were assessed qualitatively	N/A	Postoperative opioid consumption at 24 hours was lower in the methadone group vs control (P =0.01). Patients in the methadone group generally reported lower postoperative pain scores in 7 of 10 studies. Meta-analysis revealed g↑ satisfaction with analgesia in the methadone group vs control (0-100 visual analog scale; P= 0.004). No difference in time-to-extubation, time-to-first analgesia request, hospital LOS, or	**Conclusion:** Surgical patients who received intraoperative methadone had lower postoperative opioid consumption, generally reported lower pain scores and experienced better satisfaction with analgesia. **Recommendation:** the advantages need to be weighed carefully against dangerous risks with perioperative methadone, specifically respiratory depression and arrhythmia. Future studies should explore logistics, safety, and cost effectiveness

Author (Year)	Design/Method	Sample/Setting	Major Variables Studied	Measurement	Data Analysis	Findings	Appraisal: Worth to Practice
						complications (nausea, sedation, respiratory depression, and hypoxemia)	
6. Dunn, et al. (2018), Journal of Opioid Management, 14(2), 83-87	**Observational Study: Retrospective Review of perioperative records** **Purpose:** To investigate the incidence of perioperative adverse events in patients receiving intravenous methadone for major spine surgery.	N= 1,478 records of adult patients who underwent elective spinal fusion of 2 or more levels	InV: IV Methadone (mean intraoperative dose was 0.14 ± .07 mg/kg DV1: Respiratory Depression DV2: Time to Extubation DV3: Hypotension DV4: Hypoxemia DV5: Reintubation DV 6: Cardiac Complications DV7: Death	1°outcome: incidence of postoperative respiratory depression (respiratory rate < 8 breaths per minute [bpm]). 2°outcomes: time to extubation,hypoTN (systolic blood pressure < 90 or mean arterial pressure [MAP] < 60 based on the noninvasive blood pressure cuff or arterial line tracing), hypoxemia (oxygen saturation < 90 percent or need for supplemental oxygen > 2 L nasal cannula to maintain oxygen saturation > 96 percent), reintubation, cardiac complications including new cardiac arrhythmia, postoperative myocardial infarction (MI) (for patients with a troponin I level > 0.02 ng/mL and presence of electrocardiographic [ECG] changes from baseline), and QTc interval prolongation (>440 ms for men or >460 ms for women); postoperative nausea and vomiting	Chi-squared tests and Fisher's exact tests (for naloxone intraoperatively, MI postoperatively, in-hospital death, and 30-d mortality) were used to test for the differences in incidences of adverse events between opioid naive patients and chronic preoperative opioid users	1,142 patients (77.4%) were extubated in the operating room 543 (36.8%) experienced respiratory depression 1,180 (79.8%) hypoxemia 22 (1.5%) required reintubation. Cardiac complications included arrhythmias (289 patients, 29.9%), QTc prolongation (568 patients, 58.8%), and myocardial infarction (16 patients, 1.1%). Two in hospital deaths occurred (0.14 percent)	**Limitations:** only patients who received intraoperative methadone were assessed. Propensity matching to a control group that received a different intraoperative opioid would allow for comparison of adverse events between groups. The dose of intraoperative methadone was not standardized **Conclusion:** results demonstrate that the incidence of respiratory depression and hypoxemia were common (36.8 and 79.8 percent, respectively) but easily managed Mild-moderate respiratory depression is observed following a onetime dose of intraoperative methadone, and monitoring in an appropriate postoperative setting is recommended

Author (Year)	Design/Method	Sample/Setting	Major Variables Studied	Measurement	Data Analysis	Findings	Appraisal: Worth to Practice
				(PONV); Confusion Assessment Method (CAM) delirium score and in hospital and 30-day mortality.			
7. Friesgaard, et al. (2019), *Acta Anaesthesiologica Scandinavica, 63*(9), 1257-1261	**Randomized, double-blind study** **Purpose:** Investigate the role of a single-dose of intraoperative Methadone in reducing acute post-operative pain and opioid consumption	N=250 (anticipated)	InV1: Single-dose intraoperative methadone0.2mg/kg 60-minutes prior to extubation InV2: Single-dose intraoperative morphine 0.2mg/kg 60-minutes prior to extubation DV1: Opioid Consumption within first 6 hours DV2: Opioid Consumption within first 24 hours DV3: Pain intensity at 1, 6, 24, and 48 hours DV4: Patient Satisfaction with pain management at 3 and 24 hours DV5: PONV at 6, 24, and 72 hours DV6: Sedation at 0.5, 1, and 3 hours DV7: Adverse events in PACU DV8: Discharge from PACU	Primary Outcomes: Opioid consumption within first 6 hours and opioid consumption within first 24 hours Secondary Outcomes: -Pain intensity (0-10 scale) at 1, 6, 24, and 48 hours -Patient Satisfaction (0-10 scale) with pain management at 3 and 24 hours -PONV (none/mild/moderate) -Sedation (Ramsay Sedation Scale) -Adverse Events in PACU (hypoventilation, RR <10/minute; hypoxemia SaO2 <94%) -Discharge from PACU (minutes)	For the primary outcomes, all opioids during the first six and 24 post-operative hours will be converted to oral morphine equivalents. Categorical data (# of pts with moderate or severe PONV, # of pts with Ramsay Sedation Scale level 2 and any adverse effects in PACU) are to be compared using a chi-squared test. Medians with interquartile ranges are given for continuous data (pain intensity, time until readiness for discharge from PACU, pt satisfaction) compared with Mann-Whitney test. Means for normally distributed data (cumulative opioid consumption) compared with students t-test All p-values are two-sided and those <0.05 are considered significant	N/A; this study has not been conducted as of this article being published	**Limitations:** Patients are followed by telephone after discharge which may make information less accurate This study has not yet been performed, and therefore we can only use this article as a guide and compare it to other trial designs. This article focuses on a patient population undergoing hysterectomies, and therefore the results may be altered from that of a complex spinal surgery. Also, the patient population for this study would be limited to females, whereas our project is inclusive of both males and females.

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8. Gottschalk et al. (2011), Anesthesia & Analgesia, *112*, 218-223	**Prospective, RCT single-blinded study** **Purpose:** Explore the efficacy and examine the side effects of a single intraoperative dose of methadone compared with continuous sufentanil infusion in patients undergoing major lumbar spinal surgery	N=29, age 18-75 years undergoing multilevel thoracolumbar spine surgery with instrumentation and fusion Methadone group, n = 13 Sufentanil group, n = 16	InV1: Methadone (0.2mg/kg) before surgical incision InV2: Sufentanil continuous infusion (0.25 mcg/kg/hr) after a loading dose of 0.75 mcg/kg DV1: Pain score DV2: Cumulative opioid requirement DV3: Side effects at 24, 48, and 72 hours post-operatively	Pain score (visual analog scale 0-10) The cumulative opioid requirement at 24, 48, and 72 hours after surgery and the time of the first dose of pain medication were recorded. Complications such as the incidence of hypotension (defined as mean arterial blood pressure <50 mm Hg), the need for vasopressors, the incidence of respiratory depression (defined as a respiratory rate <8 breaths per minute, respiratory arrest, or the need for naloxone), the incidence of hypoxemia or desaturation (Sao2 <90% or the need for a supplemental oxygen to maintain Sao2 >96%), the incidence of cardiac arrhythmias, myocardial infarction, and the incidence of nausea and vomiting including the treatment were also recorded	Differences between groups were compared using the unpaired Student *t* test or Mann-Whitney *U* test. Incidences of side effects were compared using the chi-square test or Fisher exact test. P </= 0.05 was considered to be statistically significant. Computerized statistical analysis was performed using Sigma- Stat	Methadone reduced postoperative opioid requirement by approximately 50% at 48 hours, (P = 0.023); and 72 hours, (*P* = 0.024) after surgery. In addition, pain scores were lower by approximately 50% in the methadone group at 48 hours after surgery, (*P* = 0.026) The incidence of side effects was comparable in both groups.	**Limitations:** One weakness of this study is that the patients, but not the anesthesiologists, were blinded to the study medication; hence, the study was only single blinded. Blinding the surgeons, who were responsible for postoperative pain management, and the postoperative team, which did the pain assessments, to the study medication mitigates this weakness **Conclusion:** Perioperative administration of a single bolus of methadone before surgical incision resulted in a significant reduction of pain scores and reduced requirement of opioids in patients presenting for multilevel complex thoracolumbar spine surgery with instrumentation There was no difference in postoperative opioid consumption during the first 24 hours; patients who received methadone seemed to derive the greatest benefit between 48 and 72 hours Methadone requires no special preparation and can be given IV in the operating room immediately after the induction of general anesthesia

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9. Gourlay et al, (1984). *Anesthesiology*, *61*(1), 19-26	**Randomized Control Trial** **Purpose:** Establish whether there exists a relationship between blood methadone concentration and analgesic response and the inter-subject/intrasubject variability	N= 16 (mixed upper abdominal and spinal fusion)	InV: Methadone 20mg IV intraoperatively + supplemental 5mg doses (per pre-defined criteria) DV1: Duration of analgesia DV2: Pain Score DV3: Resp Rate	Serial blood samples collected following each methadone dose Duration of analgesia (hours) Pain score: Visual analog scale (0-10)	SPSS software; descriptive statistics including unpaired student's t-test and scattergram A level of significance of at least $p < 0.05$ was required to reject the null hypothesis	Duration of analgesia ranged from 7.4 hours to prolonged (= entire hospital stay) Mean total methadone dose was 42mg ± 10mg Mean pain scores were 1.3 ± 1.2 RR was reduced form 16-18 to 12-14 breaths/min (lasted only 30-45 mins)	**Conclusion:** Prolonged and safe postoperative analgesia can be obtained from methadone following methadone administration (Note: Much higher methadone doses administered in this study)
10. Kendall, et al., (2020), Anesthesiology Research and Practice*, 2020*, 1-9	**Meta-Analysis of RCT's** **Purpose:** Compare the analgesic efficacy of intraoperative methadone to morphine in patients undergoing surgical procedures	7 RCT's evaluating 337 patients	InV1: Intraoperative Methadone InV2: Intraoperative Morphine DV1: Post-op opioid consumption (MME) DV2: Postoperative pain (scale 0-10)	A systematic and quantitative meta-analysis following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The study was registered with the PROSPERO database	Meta-analysis was performed using the random effects model, WMD, standard deviation, 95% confidence intervals, and sample size Methodological quality was evaluated using Cochrane Collaboration's tool	Effect of intraoperative methadone on postoperative opioid consumption did not reveal a significant effect ($P = 0.43$. Effect of methadone on postoperative pain demonstrated a significant effect in the postanesthesia care unit, $P = 0.005$, and at 24 hours, $P < 0.001$.	**Conclusions:** The use of intraoperative methadone reduces postoperative pain when compared to morphine. In addition, the beneficial effect of methadone on postoperative pain is not attributable to an increase in postsurgical opioid consumption. Intraoperative methadone may be a viable strategy to reduce acute pain in surgical patients. **Recommendation:** Future studies with larger sample sizes and longer follow-up periods with more comprehensive reporting are warranted to draw

Author (Year)	Design/Method	Sample/Setting	Major Variables Studied	Measurement	Data Analysis	Findings	Appraisal: Worth to Practice
11. Karasch, E.D., (2011), *Anesthesia and analgesia*, *112*(1), 13–16	**Meta-Analysis**	N = 2 studies (Gottschalk and Gourlay studies above)	N/A	N/A	**Misconceptions of Methadone:** 1. The onset of methadone analgesia is slow, and therefore it is unsuitable for perioperative use; actually, the central nervous system effect site methadone concentrations rapidly equilibrate with plasma concentrations, evidenced by the short lag time between plasma concentrations and effects. Comparable to Fentanyl and Sufentanil (5-6 minutes). Morphine takes 4 hours. 2. The duration of methadone analgesia is shorter than its elimination half-life.	(continued) The relationship between elimination half-life and duration of effect depends also on the dose administered (as with any opioid). The clinical effect of small doses will be terminated by redistribution, whereas the effect of larger will be terminated by systemic elimination Thus, targeting doses and concentrations as high as possible above the minimal analgesic concentration, but below the threshold for respiratory depression, will achieve the longest-lasting analgesia. At concentrations approximately >/=20 mg, the duration of methadone analgesia approximates its elimination half-life. →	(continued) 3. Deals with metabolism of methadone. Methadone is considered to have a highly variable clearance and significance which has been attributed in the past to different cytochrome P450s. Actually, methadone metabolism may be less susceptible to inhibitory drug interactions than has been previously thought, and accumulated evidence demonstrates that is metabolized solely by CYP2B6

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12 Koman, et al. (2019), *Anesthesia and analgesia*, *128*(4), 802–810	**Randomized, Double-Blind Pilot Study** Purpose: To evaluate patients in same-day ambulatory surgery to see if intraoperative methadone, compared with short-duration opioids, reduces opioid consumption and pain Also to determine an effective intraoperative induction dose of methadone for same-day ambulatory surgery	N = 60 Methadone group, n= 40 Other opioid group, n = 20	InV1: Intraoperative methadone (0.1mg/kg) InV2: Intraoperative methadone (0.15mg/kg) InV3: Short-Duration Opioids prn DV1: Opioid Consumption DV2: Post-operative pain DV3: Effective methadone dose	Patient home diaries recorded pain, opioid use, and opioid side effects daily for 30 days postoperatively. Primary outcome was in-hospital (intraoperative and postoperative) opioid use. Secondary outcomes were 30 days opioid consumption, pain intensity, and opioid side effects. pain intensity (at rest, with coughing, and with activity) using a 0–10 Numeric Rating Scale. Observed sedation (Modified Observer 's Assessment of Alertness/ Sedation: MOAA/S, 0–5) recorded concurrently with pain assessments Adverse events Resp depression (<8/min), reintubation, ↓ oxygen saturation (<90% for >1 minute; <85% for >30 seconds), excessive sedation (MOAA/S, 0–2), pain/sedation mismatch (defined as	categorical outcomes comparing groups: x2 or Fisher exact test as appropriate, Continuous variables: Kruskal-Wallis test was used to compare groups For all analyses, *P* values <.05 were considered statistically significant	Median methadone doses were 6 and 9 mg in the 0.1 and 0.15 mg/kg methadone groups, respectively. Total opioid consumption (MME) in the PACU was significantly less compared with controls in subjects receiving 0.15 mg/kg methadone (*P* < .001) but not 0.1 mg/kg methadone (*P* = .60). Total in-hospital non-methadone opioid use after short-duration opioid, 0.1 mg/kg methadone, and 0.15 mg/kg methadone was 35.3 (25.0–44.0), 7.1 (3.7–10.0), and 3.3 (0.1–5.8) mg morphine equivalents, respectively (*P* < .001 for both versus control). In-hospital pain scores and side effects were not different between groups. In the 30 days after discharge, patients who received methadone 0.15 mg/kg had less pain at rest (*P* = .02) and used fewer opioid pills than controls (*P* < .0001) Patients who received 0.1 mg/kg had no difference in pain at rest (*P* = .69) and opioid use compared to controls (*P* = .08).	A single intraoperative dose of methadone (0.15 mg/kg ideal body weight) decreased intraoperative and post- operative opioid requirements and postoperative pain compared with conventional intermittent short-duration opioids, with similar side effects Limitations: This was a pilot and feasibility study, with small sample size. There was an elevated chance of type I error due to multiple outcomes. Not all patients returned the 30-day diaries. There was a predominance of women.

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				MOAA/S, 0–2 and pain score >5). Drug administration for prophylaxis/treatment of side effects (e.g., anti-emetics) Opioid side effects ORSDS (4-point Likert scale) for nausea, vomiting, constipation, difficulty urinating/concentrating, drowsiness, dizziness, confusion, fatigue, itching, dry mouth, and headache			
13. Murphy et al. (2017). *Anesthesiology*, 126(5), pp.822-833	**Randomized, double-blinded controlled trial** Purpose: assess the effect of the long-duration opioid methadone on postoperative analgesic requirements, pain scores, and patient satisfaction after complex spine surgery.	N = 115 N = 62: Methadone group N= 53: Hydromorphone group	InV1: Methadone 0.2mg/kg at start of surgery InV2: Hydromorphone 2mg at surgical closure DV1: Hydromorphone consumption POD 1 DV2: Pain scores DV3: Satisfaction with pain management	Primary outcome was intravenous hydromorphone consumption on postoperative day 1 (mg) Secondary outcomes: Pain scores (VAS 0-10 scale) and satisfaction (VAS 0-100 scale) in PACU on admission, at 1 hour, and 2 hours, and mornings and afternoons of POD 1-3	primary outcome: hydromorphone (mg) reported as the median (interquartile range) for both the methadone group and the hydromorphone group, compared using the Mann–Whiney U test. Secondary variables w/ nominal data compared using Pearson chi-square test or Fisher exact probability test Secondary outcomes with ordinal and nonnormally distributed continuous data compared between the randomized groups using the Mann–Whitney U test	Median hydromorphone use was reduced in the methadone group on POD 1 (4.56 *vs.* 9.90 mg) and POD2 (0.60 *vs.* 3.15 mg) and 3 (0 *vs.* 0.4 mg; all $P < 0.001$). Pain scores at rest, with movement, and with coughing were less in the methadone group at 21 of 27 assessments (all $P = 0.001$ to < 0.0001). Overall satisfaction with pain management was higher in the methadone group than in the hydromorphone group until the morning of postoperative day 3 (all $P = 0.001$ to < 0.0001).	Intraoperative methadone administration reduced postoperative opioid requirements, decreased pain scores, and improved patient satisfaction with pain management In patients undergoing posterior spinal fusion surgery (averaging two levels), IV methadone (0.2mg/kg) given at induction compared w/ IV hydromorphone (2 mg at surgical closure) resulted in decreased postoperative IV and PO opioid requirements and also diminished pain scores and improved patient satisfaction There were no differences between the methadone and hydromorphone groups in opioid-related or other adverse events Limitations: methadone dose–response studies have not been performed in adults undergoing spinal fusion surgery; therefore, the optimal dose that produces sufficient analgesia without inducing respiratory depression has not been determined Also, the two study opioids were given at different times during the surgical procedure. The administration of hydromorphone and

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					Normally distributed data compared between the randomized groups using the unpaired Student's *t* test		methadone simultaneously (*i.e.*, at induction of anesthesia) would have removed the confounding variables of time of opioid administration and the possibility that the methadone group had a preemptive analgesic effect (opioid given at the start of surgery), whereas the hydromorphone group did not. High-risk pts were excluded from study
14. Murphy & Szokol (2019). *Anesthesiology, 131(3), 678-692*	**Meta-Analysis** Purpose: to provide an assessment of clinical investigations that have evaluated the effect of intraoperative methadone on postoperative outcomes. Also, to address unanswered questions relating to the efficacy and safety of methadone and optimal dosing	N/A	N/A	N/A	N/A	In RCT's, no differences in the incidence of respiratory depression (< 8 -12 breaths/min) or hypoxemic events (oxygen saturations <92 - 90%) were observed between methadone and control groups No patients given methadone required naloxone infusions for prolonged respiratory depression. Methadone does not appear to increase the risk of other opioid-related side effects The dose] that will result in prolonged analgesia without inducing respiratory depression has not been clearly defined in the literature Increased risk of QT prolongation, torsade de pointes, and cardiac death Single dose of methadone may have a preventive analgesic effect and decrease the risk of the	There are limitations to many of the clinical trials. The majority of prospective clinical studies enrolled only a small number of patients. Such small sample sizes can produce false positive results or overestimate the magnitude of an association. Only a few investigations examined the potential analgesic benefits of methadone in conjunction with other opioid-sparing agents. At the present time, there is a need for larger-scale, double blinded investigations to define the efficacy and safety of intraoperative methadone The safety of methadone in higher-risk patients (the elderly, those who are morbidly obese, or those with cardiovascular disease) has not been documented in the published literature. Methadone has additional central nervous system effects (NMDA receptor antagonism and inhibition of serotonin and norepinephrine uptake) that may enhance recovery by attenuating the development of hyperalgesia and tolerance and improve mood state. RCT's have documented that the use of methadone in room is associated with significant ↓ in postoperative analgesic requirements, compared to patients administered shorter-acting intraoperative opioids Clinical trials have not supported the belief that the long half-life of methadone may

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						development of chronic postsurgical pain	contribute to prolonged sedation and respiratory depression
15. Pacreu, et al. (2012). *Acta Anaesthesiologica Scandinavica, 56*(10), 1250-1256	**Randomized, double blind study** Purpose: to compare post-operative opioid requirements in patients undergoing multilevel lumbar arthrodesis after the administration combined methadone–ketamine (MK) or methadone alone	. N=22 N= 11 in each group (MK combined and methadone alone)	InV1: MK combined (Methadone 0.1mg/kg at closure and Ketamine 0.5mg/kg bolus after induction followed by infusion 2.5mcg/kg/min. Post-op pain control PCA bolus methadone 0.25 mg plus ketamine 0.5 mg) InV2: Methadone alone (Methadone 0.1mg/kg at closure and saline bolus/infusion after induction. Post op pain control PCA bolus methadone 0.5mg) DV1: Pain intensity DV2: Post-op opioid requirements	Pain intensity: NRS on PACU admission, 24 hours, 48 hours Post-op opioid requirements: Methadone by PCA (mg) Remifentanil (mg)	The distribution of continuous variables in the two groups was compared with the Mann–Whitney U-test. Categorical variables were compared with the chi-square. Statistical significance was set at $P < 0.05$.	Remifentanil requirements were higher in the MK group ($P = 0.004$) probably because it causes a significant increase in BIS values and a less degree in mean arterial pressure and heart rate Patients in the MK group received 70% less methadone by PCA at 24 h (MK vs. methadone group, median and interquartile range) – 3.43 mg vs. 15 mg ($P < 0.001$) and at 48 h – 2 mg vs. 9.5 mg ($P = 0.001$). Patients in the MK group also attempted less doses, at 24 h: 19.5 vs. 98 ($P = 0.043$). Both groups had similar NRS values and comparable side effects	Perioperative MK combination significantly decreased opioid consumption by PCA
16. Sharma et al. (2011). Anesthesiology, 115(6), 1153–1161.	**Randomized Control Trial** Purpose: to determine the pharmacokinetics of intravenous methadone in children undergoing surgery and assess perioperative opioid-sparing effects	N= 31 Three groups of 10-11 pts Ages ranged from 10-18yo	InV1: Methadone 0.1mg/kg InV2: Methadone 0.2mg/kg InV3: Methadone 0.3mg/kg (up to 20mg) DV1: Pain rating DV2: Perioperative opioid consumption	Pain intensity was assessed by patients using the Wong-Baker FACES scale and a laminated card, 0 (no hurt) to 5 (hurts worst) Also assessed using a Colored-Visual Analog Scale, which was then scored with a metric ruler from 0 (no pain relief) to 10	Dose groups compared using ANOVA. Differences in methadone and metabolite enantiomer pharmacokinetics parameters were compared using paired Student *t* test or Wilcoxon signed rank tests, as appropriate. Opioid use and pain scores were analyzed by 2-way repeated measures ANOVA. Statistical significance	Methadone administration did not dose-dependently affect postoperative pain scores, and did not dose-dependently decrease daily or total postoperative opioid consumption in spinal fusion patients	A single intraoperative dose of methadone did not decrease postoperative opioid consumption in adolescents undergoing major spine surgery Limitations: this study was conducted on adolescents, while the focus of our project is on adults, 18yo or older

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				(maximum pain relief). Third method of assessing was per current institutional practice, using a VAS (0-10 scale) Opioid requirements: opiate use by each patient in each 24-h period. Intraoperative op opioids, postoperative patient-controlled analgesia use, and oral opioids were quantified in MME	was assigned at $P<$ 0.05.		
17. Udelsmann, et al. (2011). *Revista brasileira de anestesiologia*, *61*(6), 695–701	**Randomized, double-blind study** Purpose: to compare the requirements of postoperative analgesia in patients who received methadone, morphine, or placebo during anesthetic induction, while evaluating the prevalence of postoperative N/V	N = 55 N= 18: Methadone group N= 19: Morphine group N= 18: Placebo group	InV1: Methadone 20mg with induction InV2: Morphine group with induction InV3: Placebo with induction DV1: Duration of anesthesia DV2: Time until extubation, DV3: Time until the need of the first analgesic DV4: # doses required in 24 hours DV5: Assessment of analgesia by the patient DV6: N/V	Duration of anesthesia: (minutes) Time until extubation: (minutes) Time until the need of first analgesic: (minutes) # doses required in 24 hours: (Number) Pt assessment of pain: (VAS) Prevalence of N/V: (Number of incidents)	A descriptive analysis of the quantitative and qualitative variables was performed; to determine the association among the different qualitative variables Fisher's exact test or the Chi-square test was used. Quantitative variables were compared among groups using the non-parametric Kruskal-Wallis test and Tukey test. A level of significance of 5% was adopted.	Differences in the duration of anesthesia and time until extubation were not observed. The first dose of analgesic in patients who received methadone was administered later than in patients in the other two groups. The need of analgesics in the methadone group was lower, quality of analgesia was better, and prevalence of N/V was also lower.	Methadone during anesthetic induction was effective for analgesia in large size surgeries. Lower incidence of N/V was observed in the methadone group and therefore it is a low cost option available that should be utilized. Limitations: This study focused on cardiac surgery, while our project has a focus on multi-level spine surgery. (However, it can be argued that these results can be also applicable to spine surgery, and both types are considered complex surgeries.) These results opposed those of Gottschalk et al., who observed lower postoperative opioid consumption only 48 hours after the administration of methadone, rather than immediately as this study found