

# Intraoperative Methadone and Short Stay Spine Surgery: Possible Barriers to Implementation and Future Opportunities

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**Abstract:** The frequency of shorter stay spine surgery is increasing. Acute pain is a common barrier to discharge following spine surgery. Long-acting opioid medications like methadone have the potential to provide sustained analgesia when given intraoperatively. Methadone has been effectively used in complex spine surgery, cardiac surgery, and more recently applied to ambulatory procedures. In this article, we summarize the pertinent available literature on the use of intraoperative methadone for spine surgery as well as the recent data on intraoperative methadone for ambulatory surgery. The aim of this perspectives article is to describe the potential opportunities for applying intraoperative methadone to shorter stay spine surgery as well as barriers to more widespread use. While there are currently no trials that have specifically studied methadone for shorter stay spine surgery specifically to date, it is a promising area for future research.

**Keywords:** acute pain, spine surgery, methadone

## Introduction

In the United States, the frequency of outpatient spine surgery is increasing.<sup>1</sup> In appropriate patients, outpatient surgery is cost efficient and has not been shown to compromise clinical outcomes. However, in order for patients to consistently achieve same day discharge, safe and reliable sustained post-operative analgesia is essential. Postoperative pain is common; in some reports, up to 80% of surgical patients experience significant post-operative pain.<sup>2</sup> Spine surgery patients are at high risk for significant post-operative pain given that preexisting pain is frequently an indication for surgery, the procedures require significant surgical tissue disruption and regional analgesia options (although emerging) are not widely available or fully validated at this time.<sup>3,4</sup>

The addition of intraoperative intravenous methadone doses has been shown to improve pain scores and decrease post-operative opioid requirements after cardiac surgery, major spine surgery, and abdominal procedures.<sup>5</sup> Methadone has several pharmacokinetic/pharmacodynamic properties that may make it useful for spine surgery. It has a rapid onset (approximately 4 minutes) and long elimination half-life (24–36 hours) with stable plasma concentrations after a single intraoperative dose.<sup>6</sup> Low dose methadone (5–10 mg) produces a short duration of analgesia (3–4 hours) whereas higher doses (20 mg) produce analgesia over a time course which approximates the drug's clinical effect (up to 35 hours). In addition to its strong  $\mu$ -opioid receptor agonist activity, methadone is a potent N-methyl-D-aspartate (NMDA) receptor antagonist, which may mediate the development of opioid tolerance, hyperalgesia, and the conversion of acute-to-chronic postsurgical pain. Finally, methadone inhibits brain serotonin and norepinephrine reuptake, which may positively affect mood and mood-related aspects of pain perception.

In this article, we will review the current evidence for intraoperative methadone use for spine surgery and discuss the potential advantages and perceived barriers to using intraoperative methadone for shorter stay spine surgery procedures.

## Study Selection

We elected not to perform a systematic review given the paucity of studies. We performed a search of the medical literature repositories including PubMed, EmBase, Cochrane Database and Google Scholar. The Search was performed in December of 2021. The first search terms included methadone AND laminectomy OR discectomy OR spine surgery. The second search terms included methadone AND ambulatory surgery OR perioperative OR surgery. We excluded trials that were not randomized controlled trials, not available in English or were published as abstracts. Our inclusion criteria were trials that investigated the use of a single intravenous dose of methadone intraoperatively. The population of interest were patients undergoing spine surgery as well as patients undergoing ambulatory or shorter stay surgery (defined as mean hospitalization less than 48 hours). All included studies were assessed with the Cochrane risk of bias tool ([Supplementary Figure 1](#)).

## Methadone for Major Spine Surgery

To date there are 3 randomized controlled trials that compare intraoperative methadone administration to shorter acting opioids alone ([Table 1](#)). The first was undertaken by Gottschalk et al who compared 0.2mg/kg of methadone prior to induction of anesthesia to sufentanil infusion in patients undergoing elective multilevel thoracolumbar spine surgery with instrumentation and fusion.<sup>7</sup> They reported sustained significant decreases in both pain scores and opioid utilization through 72 hours post-surgery. The study did not report any difference in respiratory or other adverse outcomes but was limited by a small sample size (13 patients in the methadone group and 16 patients in the control group).

Martin et al compared 0.1mg/kg of methadone plus a remifentanyl infusion to a remifentanyl infusion alone for adolescents undergoing posterior spinal fusion for scoliosis correction.<sup>8</sup> While they demonstrated a reduction in the intraoperative opioid requirements, they failed to show any difference in post-operative opioid consumption or pain scores.

Murphy et al compared 0.2mg/kg of methadone at the start of surgery to 2mg of intravenous hydromorphone at the end of surgery in patients undergoing elective posterior lumbar or thoracic spinal fusion.<sup>9</sup> In this trial, 62 patients received methadone and 57 patients received hydromorphone. The authors reported decreased intravenous and oral opioid requirements, improved pain scores, and improved patient satisfaction scores for the first three post-operative days following surgery. They did not observe any differences in respiratory depression or post-operative oxygen requirement between the groups. Murphy et al more recently compared intraoperative methadone to a combination of intraoperative methadone and ketamine for patients undergoing elective spine fusion surgeries.<sup>10</sup> Both groups had significant decreases in pain with movement compared to preoperative scores. Overall, they reported a very low incidence of post-operative complications with no differences between the groups. Only 3 patients in total had respiratory complications out of the 127 patients included in the study. The study defined respiratory complications as peripheral oxygen saturations less than 90% or respiratory rates less than 8 per minute and did not specify if the respiratory complications led to reintubation or transfers to intensive care units.

## Methadone for Short Stay Surgery

To our knowledge, there is one randomized controlled trial that investigated the use of intraoperative methadone for outpatient surgery. Komen et al performed a double blind dose escalation study for patients undergoing elective abdominal day surgeries. They compared a single dose of 0.1mg/kg methadone and 0.15mg/kg methadone to standard care with shorter acting opioids at the discretion of the anesthesiologist (fentanyl and hydromorphone).<sup>11</sup> The patients receiving 0.15mg/kg methadone required fewer opioids in the Post Anesthesia Care Unit (PACU) and at home. They reported no respiratory complications. There were no observed differences in sedation scores or time until readiness for discharge from PACU.

Pontes et al compared a single dose of 0.1mg/kg of methadone with 0.1mg/kg of morphine for patients undergoing bariatric surgery.<sup>12</sup> They reported a decrease in post-operative opioid requirement and lower pain scores at rest and with movement on the first post-operative day without an increase in post-operative complications. While these were not designated ambulatory or same day surgery cases, the mean length of stay in both groups was 32 hours.

**Table 1** Characteristics of Clinical Trials of Intraoperative Methadone in Complex Spine Surgery and Short Stay Surgeries

Author	Year	Type of Surgery	Experimental Group	# Experimental	Control Group	# Control Group	Declined to Participate
Gottschalk <sup>7</sup>	2011	Multilevel Spine	0.2mg/kg methadone	13	Fentanyl 0.25mcg/kg/h	16	NA
Murphy <sup>9</sup>	2017	Multilevel Spine	0.2mg/kg methadone	62	Hydromorphone	53	NA
Martin <sup>8</sup>	2018	Spinal fusion for Scoliosis	0.1mg/kg methadone	22	Remifentanyl infusion	19	NA
Murphy <sup>10</sup>	2021	Multilevel Spine	0.2mg/kg methadone + ketamine	61	0.2mg/kg methadone	66	47
Komen <sup>11</sup>	2019	Variable Ambulatory Surgeries	0.1 or 0.15 mg/kg methadone	39	Shorter acting opioids	21	42
Pontes <sup>12</sup>	2021	Bariatric Surgery	0.1 mg/kg methadone	69	0.1mg/kg morphine	68	23

## Barriers to Implementation

### Safety of Intraoperative Methadone

There are a number of barriers to the expansion of use of methadone for procedures with planned short length of stay. One of the most commonly cited is the concern for post-operative respiratory depression, which has greater consequences for patients who are discharged to home on the day of surgery. Indeed, in 2006, the Food and Drug Administration (FDA) issued a black box warning for methadone due to concerns for respiratory depression, though this advisory was targeted at titrating outpatient and long-term prescriptions of methadone. In the trials previously discussed, the incidence of respiratory depression was rare and not statistically significant when compared to the control groups. Respiratory depression has been observed at plasma concentrations of 100 ng/mL.<sup>6,13</sup> Methadone is a lipophilic drug with a large volume of distribution, which results in a biphasic course of elimination. With the doses that have been studied, in patients with normal liver and kidney function, the period of anticipated respiratory depression would be 30–45 minutes after administration due to methadone's rapid redistribution.<sup>6,13</sup>

An additional safety concern relates to methadone's association with significant cardiac arrhythmias.<sup>6</sup> Methadone prolongs the QTc interval by inhibiting voltage gated potassium channels and delaying repolarization of ventricular myocytes. The incidence of mild QT prolongation has been estimated to be between 41% and 49%. In rare cases, methadone has been implicated in precipitating arrhythmias including torsade de pointes. Preexisting long QT syndrome, larger doses (<100mg per day), liver and kidney disease and use of other QTc prolonging medications have been identified as risk factors for arrhythmias with methadone administration. In a retrospective clinical report, Dunn et al reported that 58.8% of patients who underwent complex spine surgery had QTc prolongation postoperatively. They reported that nearly 30% had a post-operative arrhythmia though this was most commonly sinus tachycardia. No patients experienced torsade de pointes. Their study was limited as it was not a randomized clinical trial, 33% of their patients remained intubated at the end of the procedures, and nearly all of the patients (98.7%) had an intravenous lidocaine infusion throughout the procedure.<sup>14</sup>

Methadone, while often used for chronic pain, is most known for its use as a therapy for opioid use disorder. As a result, patients and providers may have conscious or unconscious biases when deciding to use this medication. Methadone, more than other opioids, may carry a negative connotation by patients when used for opioid naïve patients during surgical procedures. In the previously discussed trials that included data on patient refusal,<sup>10–12</sup> a total of 112 patient refused to participate for a group of studies that eventually analyzed 324 patients. In a thematic analysis of online mentions, Chenworth et al found that methadone had generated more extreme negative opinions than positive opinions, and stigma was the second most common theme mentioned online.<sup>15</sup>

## Patient Selection

Appropriate patient selection is critical for both short stay spine surgery as well as intraoperative methadone. Patients with a history of significant cardiac or respiratory comorbidities, morbid obesity, or significant anticipated opioid requirements post operatively would likely be poor candidates for short stay surgery in general. In a review of a national database, younger patients, with better health status (ASA I or II), and shorter operative times were more likely to achieve successful outpatient laminectomy.<sup>1</sup>

Similar caution should be exercised when selecting patients for intraoperative methadone for short stay surgery. Patients with significant cardiac, pulmonary comorbidities, morbid obesity and known history of obstructive sleep apnea would be at higher risk for respiratory depression. Caution should be taken prior to considering intraoperative methadone for any patient with a known history of prolonged QT syndrome or history of cardiac arrhythmia or electrolyte disturbance. Additionally, given methadone's long half-life, patients and all care providers should be made aware of the potential duration of effect and counselled appropriately on risks, so that any additional analgesic medications are used appropriately.

## Opportunities

Despite the limitations aforementioned, intraoperative methadone is a promising tool in the armamentarium of anesthesiologists and acute pain physicians. Methadone was first formulated in 1938 and is inexpensive. One trial from the United States reported an acquisition cost of \$1.58 for a 5mg syringe of intravenous methadone.<sup>16</sup> Administering

methadone intraoperatively will not add to the anesthesia time and does not require specialized equipment or training. It could represent an ideal intervention for resource limited settings both in the United States or abroad. Further, methadone, as an intraoperative intravenous pain adjunct can be scaled rapidly and broadly to a variety of practice settings.

Unused opioid medications following surgery have been a significant public health concern and contributing factor to the ongoing opioid epidemic. In a recent review up to 92% of patients undergoing outpatient surgery and up to 90% of patients undergoing inpatient surgery reported outpatient opioid medications that they were prescribed but did not use.<sup>17</sup> To date, the use of intraoperative methadone has not reduced the incidence of leftover opioid prescriptions after surgery,<sup>11</sup> however, this has not been studied extensively. Intraoperative methadone has the potential for longer acting analgesia which, in theory, could reduce the need for outpatient opioid prescriptions for certain procedures. Consistent with these hypotheses, a secondary analysis of a randomized clinical trial comparing intraoperative methadone to hydromorphone found intraoperative methadone was associated with fewer episodes of pain in the first 3 months after spine surgery, and fewer patients who were still receiving opioids 3 months after surgery.<sup>18</sup>

## Future Directions

Overall, the evidence supporting intraoperative methadone for acute post-operative pain in spine surgery are limited to a few small-scale trials. Well designed, adequately powered studies which assess the safety and efficacy of methadone for shorter stay spine surgeries are needed. Allied to this, the procedure-specific risks and benefits of methadone should be clarified, including minimally invasive and endoscopic approaches to spine surgery. Risk stratification studies are additionally required to determine which patients could tolerate intraoperative methadone safely, and will be needed prior to methadone being recommend for more routine use. As perioperative providers are urged to improve post-operative pain management, increase the volume of shorter stay surgeries, and combat the opioid epidemic, novel uses of existing medications like methadone present a promising option that warrants further investigation and descriptions of clinical successes.

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