REVIEW ARTICLE

Intraoperative use of intrathecal methadone: Evaluation of perioperative analgesia, effectiveness and safety: A systematic review and analysis of the feasibility of its use

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ABSTRACT

Introduction: *Intravenous methadone has shown an opioid-sparing effect in high-risk surgeries. It was hypothesized that intrathecal methadone might provide better effects than intravenous administration due to a direct action on the spinal cord.*
Main objective: *To search the currently published literature on the intraoperative use of intrathecal methadone in humans, a systematic review was conducted.*
Design: *Studies from PubMed, Scopus, OVID, EMBASE, LILACS, Google Scholar, ELSERVIER, REDALYC, SciELO, Europe PubMed Central, and the Cochrane Library were searched from 1980 to June 2024. Search terms included "intrathecal methadone or spinal methadone," "methadone and spinal anesthesia," "spinal anesthesia," "intraoperative period," and "perioperative period." Randomized controlled trials (RCTs) published in English and Spanish involving human participants were considered.*
Main outcome: *The quality of post-operative analgesia measured by the Visual Analog Scale (VAS).*
Secondary outcomes: *Time to first opioid analgesic rescue, post-operative daily needs of morphine equivalents, and side effects.*
Results: *Forty-one articles were identified. Good agreement intra- and intergroup was found. Four full-text articles met the inclusion criteria. Quality assessment showed an overall low to "some concern" risk of bias. Intrathecal methadone 5-10 mg provided post-operative pain for about 6 hours (VAS average of 2.4/10) after knee and hip replacements, urological, and gynecological surgeries showing minimal side effects. Twenty milligram of intrathecal methadone can produce remarkable side effects. Intrathecal morphine at 0.5-1.0 mg showed significantly lower VAS levels during the 24 hours post-operatively ($p < 0.05$) but showed more side effects. Intrathecal anesthesia with methadone as adjuvant showed a longer analgesic effect than fentanyl, and better effect than placebo, without differences in side effects ($p < 0.05$).*
Conclusions: *Due to the limited sample size and the small number of selected RCTs showing significant methodological differences, a meta-analysis could not be completed. Therefore, overall statistical significance was not established between the four studies, and there is not enough evidence to give recommendations. Further research is needed to evaluate whether the doses found in this review retain comparable efficacy and safety profiles in a broader range of patient cohorts.*

In the reviewed literature, no objective or conclusive evidence of neurotoxicity was found from the use of a single dose of perioperative intrathecal methadone.

INTRODUCTION

Methadone, a synthetic opioid, has been widely used in detoxification treatments for opioid-dependent patients, opioid rotation in cases of tolerance, and in reducing opioid-induced hyperalgesia. It is also used in managing severe chronic pain, both oncologic and nononcologic, that is refractory to standard treatments.[1,2] Recent studies recommend the administration of intravenous methadone at the start of surgery due to its opioid-sparing effect during the perioperative period, resulting in significant reductions in post-operative pain. Its intraoperative use has been associated with a cumulative reduction in the need for rescue opioids post-operatively for up to 3-6 months. Intravenous methadone, particularly in highly painful surgeries, has yielded promising results in short- and medium-term post-operative satisfaction questionnaires.[3-5] Additionally, its use has shown both opioid-sparing effects and safety in outpatient surgeries, including gynecological laparoscopies.[6,7]

Intravenous methadone administered intraoperatively is a viable strategy and superior to intravenous morphine in reducing post-operative pain due to its mechanisms of action.[8] Methadone is a drug with unique pharmacodynamics since it has a potent agonist action on μ-opioid receptors, is an antagonist of N-methyl-D-aspartate (NMDA) receptors, and inhibits the reuptake of serotonin and norepinephrine. These various mechanisms of action of methadone confer it a potent antinociceptive and antihyperalgesic effect that distinguishes it from other opioids.[9-12] Additionally, its anti-NMDA effect synergistically enhances the analgesic and antiglutamatergic effects of ketamine used in the perioperative period.[13,14] All these mentioned effects of methadone as a nociception modulator converge in a considerable attenuation of peripheral and central sensitization phenomena, giving it advantages over other opioids.

However, publications on the use of intrathecal methadone as an analgesic for post-operative pain control are limited, whether administered as a sole agent or as an adjuvant to local anesthetics in spinal anesthesia. Some studies and case reports suggest potential benefits of its intrathecal use.[9-11] Randomized studies have compared the effectiveness of post-operative intrathecal methadone analgesia versus intrathecal morphine in patients undergoing knee replacement surgery, hip replacement surgery, and urologic surgery.[15,16] Other randomized controlled trials (RCTs) have compared the use of post-operative intrathecal methadone as an adjuvant to intrathecal anesthesia versus placebo or fentanyl in patients undergoing hip arthroplasty or vaginal hysterectomy.[17,18]

When evaluating different intrathecally administered opioids, it is important to consider their lipid solubility, and how different is the pharmacokinetics when the opioid administration is intravenous. The lipid solubility of an opioid is inversely proportional to its potency at the intrathecal level. More liposoluble opioids are less potent at the spinal level, while less liposoluble opioids show greater potency and a more prolonged effect when administered intrathecally [morphine = normorphine > pethidine > methadone].[19-22]

However, due to a direct action on the spinal cord, we hypothesize that an adequate dose of intrathecal methadone could be as effective as an equipotent intravenous dose. In the perioperative context, the evidence on the use of intrathecal methadone is scarce compared to other opioids such as fentanyl, sufentanil, and morphine. On the other hands, due to its antiglutamatergic and antihyperalgesic action, intrathecal methadone could provide better intraoperative and post-operative analgesia than intrathecal administration of fentanyl, or sufentanyl in patients undergoing surgeries related to severe acute pain, with risk of chronic pain development, or with a history of chronic pain with neuropathic component. The main objective of the present study was to search for existing information on the intraoperative use of intrathecal methadone in humans and evaluate its perioperative analgesic effectiveness through a systematic review of the literature.

DESIGN

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement.[23] The protocol was registered a priori in the International Prospective Register of Systematic Reviews with the registration number CRD42024549146, dated June 1, 2024. We adhered to the CONSORT 2010 checklist for reporting randomized trials and the PRISMA flowchart.

Search strategy

Studies from PubMed, Scopus, OVID, and the Cochrane Library were identified as primary sources

in the database from 1980 to June 2024. EMBASE, LILACS, Google Scholar, ELSERVIER, and specific search engines such as REDALYC, SciELO, Europe PubMed Central were also used to search the database. The search for publications was conducted up to June 2024. Nonpeer-reviewed publications were excluded from this search. Also, unpublished studies were not considered for the review. No contact was established with laboratories. Only articles published in English and Spanish were considered in the search. In English, the MeSH terms used were "methadone," "intrathecal methadone," "methadone and spinal anesthesia," "spinal methadone," "spinal anesthesia," "intraoperative period," "postoperative period," and "perioperative period." The search terms used in Spanish were "metadona," "metadona intratecal," "metadona subaracnoidea," "metadona y anestesia espinal," "anestesia espinal," "anestesia subaracnoidea," "periodo intraoperatorio," "periodo postoperatorio," and "período perioperatorio." Searches were carried out following the Peer Review of Electronic Search Strategies checklist, which included a peer review by another medical librarian.[24]

Study selection

The original studies included in the analysis were selected based on the PICOS criteria (Patients, Interventions, Control/Comparison, Outcome, Study Design):

P—human patients receiving intrathecal anesthesia to undergo surgery;

I—intrathecal methadone administration as adjuvant of spinal anesthesia or as a sole intrathecal medication;

C—comparison with placebo, morphine, fentanyl, or sufentanyl intrathecally;

O—duration and quality of post-operative analgesia measure by Visual Analog Scale (VAS), time to first analgesic rescue, post-operative daily rate of intravenous morphine milligram equivalents (MMEs), and side effects;

S—RCTs restricted to participants undergoing surgery that included adults more than 18 years old.

Inclusion criteria: RCTs that compared patients undergoing any surgery who received intraoperative single dose of intrathecal methadone as adjuvant of spinal anesthesia or as a sole intrathecal medication versus those who received another intrathecal opioid or placebo.

Exclusion criteria: Nonhuman trials, nonpeer-reviewed publications, case reports, case series, prospective observational studies, retrospective observational studies, review articles, letters to the editor. Also, studies about intraoperative methadone use by any other nonintrathecal route, studies of intrathecal methadone use for chronic pain management, or any intrathecal administration in a nonsurgical setting were excluded. The articles had to present a clear and detailed methodology, including a thorough description of intrathecal methadone administration, as well as a rigorous evaluation of perioperative analgesia and possible side effects associated with its intrathecal use. Only studies that guarantee the relevance and applicability of the results in clinical practice were considered.

Four authors distributed in two groups (V-RA, C-VYA and R-NE, R-OJ) independently selected abstracts as well as full-text article from the databases following the search strategies. For articles in which data were missing or unclear, the authors met the research team for clarification and any disagreement was resolved by a fifth reviewer (R-PC).

Data extraction

The following data were extracted[1]: demographic data of participants,[2] type of surgery, and outcomes of interest.[4]

Risk-of-bias assessment

The RCTs that met the inclusion criteria were analyzed with Cochrane's tool of risk-of-bias (RoB2).[25,26]

The quality of the RCTs was assessed based on the following criteria: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of reported results, and overall risk of bias. Evaluation of each domain was categorized as "High," "Low," or "Some concerns." A low risk of bias was identified when the items were analyzed reasonably. High risk was identified when the items were not performed or reported. "Some concerns" was identified when lack of information was provided to assess any item

as high or low risk, or due to an indetermined risk of bias.

Main variables to measure the outcomes

The primary objective was to evaluate the effectiveness of the intraoperative use of intrathecal methadone in humans for perioperative analgesia.

Primary outcome

Main variable:

- Post-operative VAS up to 12-48 hours.

Secondary outcomes

Secondary variables:

- Time to require the first opioid analgesic rescue in the post-operative period.
- Total post-operative opioids administered to control acute pain by calculating the daily rate of intravenous MMEs.
- The occurrence of side effects such as nauseas, vomiting, and pruritus. Signs or diagnosis of respiratory depression were also considered as variables to evaluate the safety.
- The presence of both transient and persistent neurological deficits in the post-operative period (sensory or motor) related to the use of intrathecal methadone.

RESULTS

After conducting the systematic search, which was performed independently by two groups of researchers of two members each, 41 articles were identified. Good intra- and intergroup agreement was found. A kappa coefficient of 0.80 was obtained. Figure 1 shows the PRISMA flowchart.[27] Each researcher separately analyzed the bibliographies of identified articles to ensure a comprehensive review. After excluding editorials, incomplete articles, animal studies, and those that did not discuss the use of intrathecal methadone, four full-text articles were selected that studied the perioperative use of intrathecal methadone (Table 1). For each trial that met the inclusion criteria, the methodological quality was evaluated using the Cochrane Collaboration's RoB2. Two RCTs had an overall low risk of bias, and two RCTs appeared to have "some concerns" of

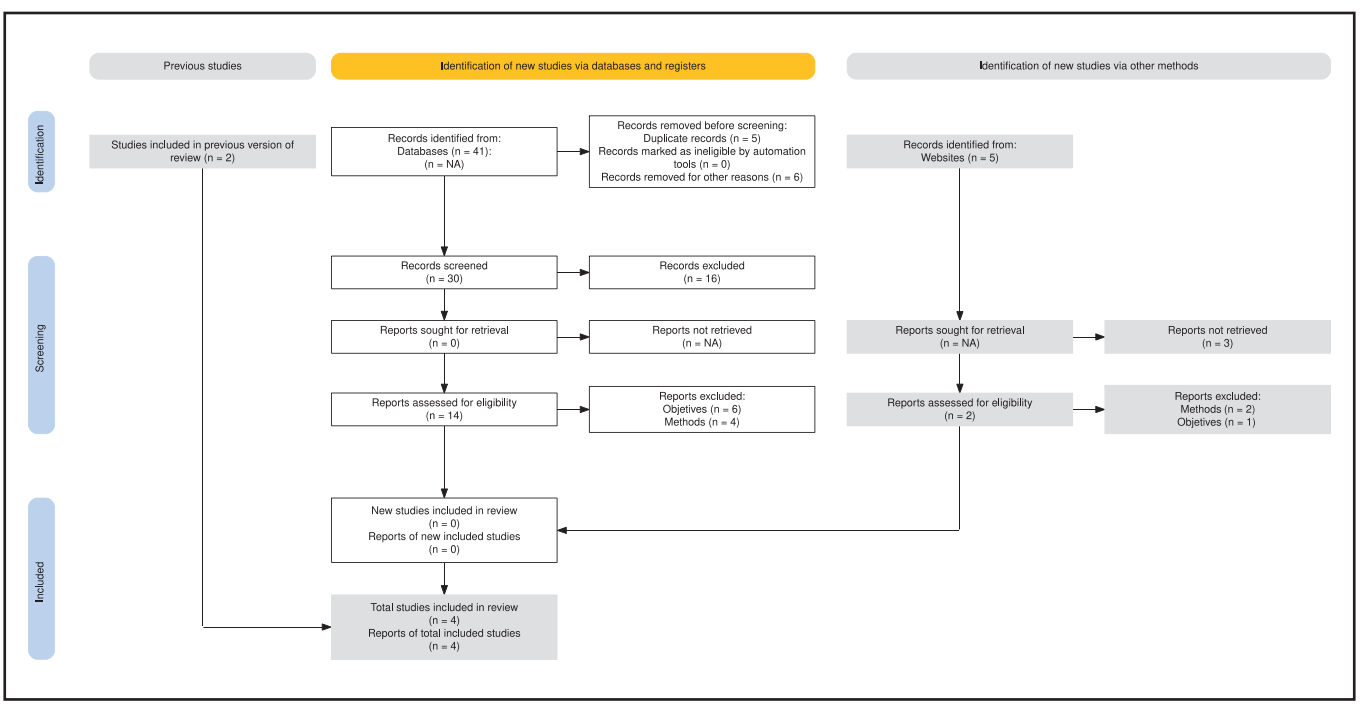

Figure 1. Flowchart according to PRISMA method.[21] *https://www.esbackathon.org/software/PRISMA2020.html*.

Table 1. Selected studies that met the inclusion criteria for intrathecal methadone use in the perioperative period

Author (year)	Study type Types of surgeries	Intrathecal methadone dosage	Comparison: Intrathecal morphine or fentanyl	Number of patients	Results/conclusions/limitations
Jacobson et al. (1989)[15]	*RCT* Orthopedic and urological surgery	Methadone *Group A*: 1.0 mg	Morphine: *Group B*: 0.5 mg Morphine: *Group C*: 1.0 mg	n = 30	The analgesia was more effective and prolonged in both groups with morphine ($p < 0.05$). The first rescue analgesic was 6.5 hours in the methadone group, and more than 24 hours in both morphine groups ($p < 0.05$). Respiratory depression occurred with 1 mg of morphine but was not observed with 1 mg of methadone or morphine at 0.5 mg. Morphine was associated with greater urinary retention in both groups. They conclude that the intrathecal dose of 1 mg methadone was inappropriately low.
Jacobson et al. (1990)[16]	*RCT* Knee and hip joint replacement surgery	Methadone: *Group 1:* 5 mg *Group 2*: 10 mg *Group 3:* 20 mg	Morphine: 0.5 mg	n = 38	Both medications provided excellent analgesia for 4 hours. After 4 hours, the quality of analgesia was better with morphine than methadone. Facial itching and drowsiness were less frequent with 5 mg of methadone. The authors considered unacceptable the incidence of side effects with 20 mg of methadone.
Fenandez-Liesa et al. (2000)[17]	*RCT* Total hip Arthroplasty Spinal anesthesia with 15 mg of hyperbaric 0.5 percent bupivacaine	Group M: Methadone 4 mg	Group C: (Saline)	n = 30	Groups were comparable regarding demographics. Group M: VAS significantly lower during first 6 hours (near VAS 0/10). After 6 hours, no differences in VAS were observed. Mean consumption of IV morphine was significantly lower in Group M between 4 and12 hours. Total morphine consumption for 72 hours was similar in both groups (27.2 mg vs 29.5 mg, $p = 0.69$). No statistical differences in nausea/vomiting, urinary retention ($p = 0.48$), and delayed oral intake. Pruritus more frequent in Group M ($p = 0.016$). No respiratory depression was observed in both groups. The authors did not report time required for first analgesic rescue.
Pérez et al. (2010)[18]	*RCT* Vaginal hysterectomy under spinal anesthesia with 13 mg of hyperbaric 0.5 percent bupivacaine	*Group BM:* Methadone 3 mg	*Group B*: Control (Saline) *Group BF*: Fentanyl 15 µg	n = 69	Methadone significantly prolonged the duration of analgesia in comparison with fentanyl. Methadone provided an analgesic effect 1.9 times longer than placebo and 1.5 times longer than fentanyl. Duration of the sensory motor block was significantly shorter in the methadone group (mean difference, 30 minutes). No differences in the incidences of side effects were observed between both opioid groups. No signs or symptoms suggestive of direct neurotoxicity were identified 1 month after its administration assessed by Tucker test.[25] The authors did not provide comparative tables displaying the VAS values.

RCTs: randomized controlled trials; VAS: Visual Analog Scale.

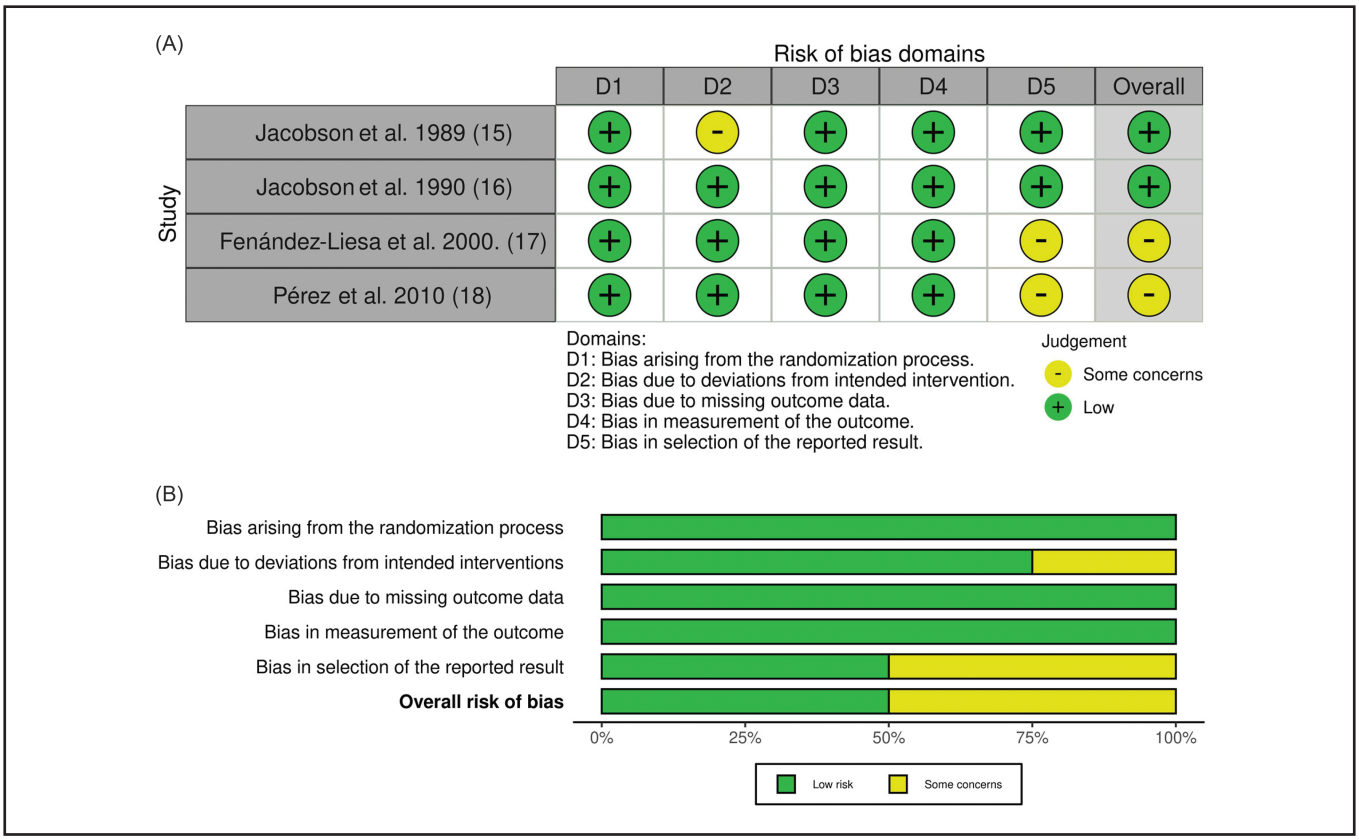

Figure 2. Cochrane collaboration summary of the risk-of-bias to each trail (RoB 2 tool). (A) Assessment of the risk-of-bias via the Cochrane RoB 2 tool displayed by means of a traffic light plot of the risk of bias of each included clinical study. Traffic light plot reports five risk of bias domains: D1, bias arising from the randomization process; D2, bias due to deviations from intended intervention; D3, bias due to missing outcome data; D4, bias in measurement of the outcome; D5, bias in selection of the reported result; yellow circle indicates some concerns on the risk of bias and green circle represents low risk of bias. Note: Figure image was created using *https://mcguinlu.shinyapps.io/robvis/*. RoB, risk of bias. (B) Weighted plot for the distribution of the overall risk of bias within each bias domain via the Cochrane RoB 2 tool (n = 4 clinical studies). Note: Figure image was created using *https://mcguinlu.shinyapps.io/robvis/*.

bias due to "bias in selection of the reported result" (Figure 2).

Description according to outcomes of the selected full-text articles that studied perioperative intrathecal methadone use (Table 1):

(A) Jacobson et al.[15,*] conducted a randomized, double-blind clinical trial comparing the analgesic effect and side effects of intrathecal methadone versus intrathecal morphine. The study included 30 patients assigned in three groups of patients undergoing orthopedic or urological surgery. Group A: 1.0 mg of intrathecal methadone, Group B: 0.5 mg of intrathecal morphine and Group C: 1.0 mg of intrathecal morphine. Intrathecal opioids were administered at the end of the surgery. Evaluation and follow-up began 1 hour after intrathecal opioid administration and continued for up to 20 hours post-operatively. Analgesic evaluation, analgesic rescue requirements, and adverse effects were recorded.

(A.1) Primary outcome:

- Pain scores (VAS) were significantly higher with methadone compared to both morphine groups (0.5 mg and 1.0 mg) ($p < 0.05$). During the first 6 post-operative hours, methadone group showed a mean

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VAS of 2.4/10 points. After 6 hours, the methadone group showed a mean VAS of 4.75/10 points. The mean VAS of morphine was zero in both groups during the 20 hours studied. Intrathecal morphine (0.5 mg and 1.0 mg) provided effective and prolonged analgesia. Methadone provided a lower level of analgesia compared to morphine.

(A.2) Secondary outcome:

- The time to require the first analgesic rescue was longer with morphine than with methadone (24 hours with 0.5 mg of morphine, 29 hours with 1.0 mg, and 6.5 hours with methadone; $p < 0.05$).

- The amounts of supplemental morphine (mg) administered systemically in the first 24 hours were significantly greater in the methadone group ($p < 0.05$). The methadone group used a median morphine of 26.0 mg (interquartile range [IQR]: 17-48 mg), the 0.5 mg intrathecal morphine group used a median of 3.0 mg (IQR: 0-12) and the 1.0 mg intrathecal morphine group used a median of 0 mg (IQR: 0-2).

- Respiratory depression was observed with 1.0 mg of intrathecal morphine ($p < 0.05$). Facial pruritus was only observed with intrathecal morphine. Urinary retention requiring catheterization was more frequently observed in patients with morphine than with methadone, but this was not statistically significant. There was a high incidence of nausea and vomiting in all groups.

The authors concluded that intrathecal morphine at doses of 0.5 mg and 1.0 mg provides significantly better analgesia than 1.0 mg of intrathecal methadone. They also explained that their results regarding analgesic effectiveness might be due to an inadequate dose of intrathecal methadone that was not equipotent to the doses of morphine used.

(B) Jacobson et al.[16,*] conducted a randomized, double-blind clinical trial to determine the effectiveness of various doses of intrathecal methadone for post-operative pain relief compared to intrathecal morphine. The study included 38 male patients undergoing knee or hip replacement surgery, who were assigned to one of three experimental groups to receive different doses of intrathecal methadone (5.0 mg, 10.0 mg, and 20.0 mg) and a control group with 0.5 mg of intrathecal morphine. The study was approved by the United States Food and Drug Administration (FDA), and written informed consent was obtained from each patient before anesthesia and surgery. There were no significant demographic differences between the groups, and they were comparable.

(B.1) Primary outcome:

- Both intrathecal morphine and different doses of methadone provided excellent pain relief during the first 4 hours after intrathecal anesthesia. However, all methadone groups had higher VAS scores than morphine ($p < 0.05$) with a half-life ($t_{1/2}$) of 4-6 hours.

(B.2) Secondary outcomes:

- Shorter times to requiring first analgesic rescue compared to morphine were found for all three doses of methadone ($p < 0.05$). Those times were 6.25 hours (IQR: 4-9), 6.5 hours (IQR: 5-10) and 6 hours (IQR: 4-10) for 5.0 mg, 10.0 mg, and 20.0 mg, respectively. The time to first analgesic request in the intrathecal morphine group was 15 hours (IQR: 14-27).

- The 0.5 mg intrathecal morphine group required an average of 5.5 mg of supplemental intravenous morphine (IQR: 0-24) in the first 24 hours compared with 23 mg,[9-33] 22 mg,[10-48] and 30 mg[20-45] with intrathecal methadone 5 mg, 10 mg and 20 mg, respectively.

- There were only three episodes of respiratory depression in the group with 20 mg of intrathecal methadone (n = 8). Greater degree of sedation and facial pruritus were found with the higher doses of methadone. The rest of the side effects were similar between the groups.

The authors concluded that doses of 10 mg and 20 mg of intrathecal methadone are not recommended for clinical application because of their greater incidence of supraspinal adverse effects due to probable rostral spread in the cerebrospinal fluid (CSF).

Unacceptable side effects were observed with a dose of 20 mg of intrathecal methadone. Intrathecal methadone at 5 mg provided effective analgesia for 4-6 hours in patients undergoing knee or hip replacement surgery with few side effects.

(C) Fernandez-Liesa et al.[17,*] evaluated the quality and duration of post-operative analgesia of 4 mg of intrathecal methadone as an adjunct to spinal anesthesia with 0.5 percent hyperbaric bupivacaine. A randomized, double-blind, placebo-controlled trial enrolled 29 patients undergoing total hip replacement was designed. According to the American Society of Anesthesiologists (ASA) Physical Status Classification System, the patients' health status before surgery was ASA I (healthy patient) or ASA II (patient with mild systemic disease). Patients were assigned in two groups: Group C (control, n = 14) with saline or Group M (methadone 4 mg, n = 15). Pain was assessed using VAS and morphine consuming during first 48 hours post-operatively. Post-operative analgesia was provided with intravenous morphine by a patient-controlled analgesia (PCA) device. There was no difference between groups with respect to demographics.

(C.1) Primary outcomes:

- VAS mean values were significantly lower during first 6 hours for Group M versus placebo (p = 0.04). From the 6 hours onwards, no significant differences in VAS mean values were observed.

(C.2) Secondary outcomes:

- The authors did not report the time to requiring the first analgesic rescue.
- The mean consumption of IV morphine was significantly lower between 4 and 12 hours in Group M. However, the total consumption of morphine during the 48 hours (period studied) was similar in both groups (27.2 mg vs 29.5 mg, p = 0.69).
- Regarding side effect no significative differences were observed. Two patients had urinary retention in the Group M but no statistical significance (p = 0.48). No respiratory depression was observed in either group. There was not oral intake delay in both groups (p = 0.32). Pruritus was more frequent in Group M (p = 0.016).

(D) Pérez et al.[18,*] compared the effect of fentanyl versus methadone as adjuvants of spinal anesthesia with bupivacaine. The main goal was to test the hypothesis that methadone would provide longer-lasting post-operative analgesia. A randomized, double-blind, placebo-controlled trial enrolled 69 women who underwent vaginal hysterectomy under spinal anesthesia (13 mg of 0.5 percent bupivacaine). The patients were randomized to three groups: Group B bupivacaine and saline (control), Group BF: bupivacaine and 15 μg of intrathecal fentanyl, and Group BM: bupivacaine and 3 mg of intrathecal methadone. The main outcome was duration of analgesic effect measured as the time to require the first rescue analgesic dose.

(D.1) Primary outcome:

- Intrathecal methadone as an adjuvant to bupivacaine spinal anesthesia improved patient comfort after surgery compared with fentanyl. However, a VAS comparison table between groups was not shown.
- Methadone significantly prolonged the duration of analgesia in comparison with fentanyl. With methadone, the analgesic effect was 1.9 times longer than in the placebo group and 1.5 times longer than in the fentanyl group.

(D.2) Secondary outcomes:

- The time until requesting the first dose of intravenous analgesia (established at VAS > 3) was 147.5 ± 32.4 minutes, 231.1 ± 109.9 minutes, and 289.3 ± 230.9 minutes for the bupivacaine and saline, bupivacaine and fentanyl (BF), and bupivacaine and methadone (BM) groups, respectively (p < 0.05).
- The authors did not report the mean 24-hour rescue intravenous morphine consumption.
- Duration of the sensory motor block was significantly shorter in the methadone group (mean difference, 30 minutes).
- No differences in the incidences of side effects were observed between the two opioid groups.

One patient in the BF group presented with generalized pruritus but did not require treatment.

- Oxygen saturation was recorded every 30 minutes with no significant differences observed between groups.
- Regarding the adverse effects of subarachnoid anesthesia such as bradycardia or hypotension, no significant differences were observed.
- No signs or symptoms suggestive of direct neurologic toxic effects were observed. Moreover, 1 month after hospital discharge, one of the researchers conducted telephone interviews with the patients to identify symptoms compatible with neurological toxicity. The test described by Tucker et al.[28] was used and no obvious signs of neurological toxicity were identified.

On the other hand, the authors carried out physicochemical studies of osmolarity and pH of the mixtures of bupivacaine with methadone or with fentanyl. The association of adjuvants with bupivacaine did not significantly change its density. However, there was a reduction in the pH of the mixture of isobaric bupivacaine with fentanyl and methadone. In theory, this could increase the onset time of anesthetic action.

The authors concluded that intrathecal methadone prolonged the post-operative analgesic effect of spinal anesthesia and shortened sensory motor block duration of 13 mg of isobaric bupivacaine. There were no clinical signs of toxicity from associating 4 mg of methadone to the anesthetic mixture with 13 mg of isobaric bupivacaine.

Additionally, 10 full-text articles analyzed were excluded from the review as they did not meet the inclusion criteria (Table 2). Some of these studies were conducted in animals, some studies described the use of neuraxial methadone via a different route than intrathecal, and others described the use of intrathecal methadone for the management of chronic oncologic pain. None of these described the use of intrathecal methadone in the perioperative setting. They are cited in Table 2 due to mentioning important pharmacological data.

DISCUSSION

Due to the limited sample size and the small number of selected RCTs showing significant methodological differences, a meta-analysis could not be completed. Therefore, overall statistical significance was not established between the four studies. The quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation approach is limited because the small sample size in each selected study and the limited research on the use of intrathecal methadone for the control of acute post-operative pain. There is not enough evidence to give recommendations, however, according to the few studies found in this review, a single dose of 5 mg of intrathecal methadone may offer good analgesia with fewer side effects in patients undergoing orthopedic and gynecological surgeries.* The duration of the analgesic effect of 5-10 mg of intrathecal methadone is on average 6 hours. On the other hand, in the literature reviewed, no conclusive evidence of neurotoxicity was found due to the use of single dose of intrathecal methadone[29,30] (Table 3).*

Neuraxial administration of opioids has proven to be an effective technique for pain management in cancer patients and perioperative settings. While morphine is the only opioid FDA-approved for intrathecal use, other opioids such as fentanyl, sufentanyl, hydromorphone, meperidine, and methadone are also utilized in clinical practice.[29]

Intrathecal opioids act by binding directly to opioid receptors in the brain and spinal cord, providing high-quality analgesia at significantly lower doses compared to oral, rectal, or parenteral administration, and with fewer side effects such as constipation, sedation, and respiratory depression.[20,21,29]

Although not FDA-approved for intrathecal use, methadone has been used off-label due to its effectiveness in patients with refractory pain to other opioids. However, its safety profile lacks robust documentation in clinical studies, underscoring the need for further research in this area.[30,*]

Methadone has intermediate lipid solubility relative to morphine and fentanyl (morphine:methadone:fentanyl ≈ 1:80:600), resulting in metameric distribution depending on the spinal puncture site. Rapid membrane diffusion due to its lipid solubility reduces its time in CSF and limits rostral ascent. Intrathecal methadone provides analgesia lasting 4-8 hours, which is an intermediate $t_{1/2}$

Table 2. Studies mentioning the use of intrathecal methadone but not meeting the inclusion criteria (listed in chronological order)

Authors Year	Type of study	Results/conclusions
Payne and Inturrisi (1985)[22]	Case–control study in experimental animals	Drugs are distributed rostrally into the CSF by mass flow. After subarachnoid spinal administration, morphine, but not methadone, is redistributed by mass flow to the cisternal CSF. These results provide a pharmacokinetic explanation for the therapeutic and side effects of spinal morphine.
Max et al. (1985)[34]	Patients with chronic cancer pain	Drug elimination from the CSF, as expressed by half-life ($t_{1/2}$), was faster for methadone and slower for Beta-endorphin.
McQuay et al. (1989)[19]	Case–control study in experimental animals	By extrapolation from animal data, it is suggested that intrathecal analgesic equipotency of morphine 0.5 mg is 8.5 mg of methadone. There was a significant inverse correlation between lipid solubility and intrathecal potency of opioids. The most lipid-soluble opioids are less potent, and the least lipid-soluble opioids were the most potent. The approximate order of potency was morphine = normorphine > pethidine > methadone.
Fernandez-Liesa et al. (2000)[11]	Case-reports (n = 2)	*Case 1:* A 69-year-old man underwent a right inferior lobectomy due to metastasis. He was administered 5 mg of hyperbaric intrathecal methadone by lumbar spinal puncture. After injection, the patient was placed in the Trendelenburg position for 10 minutes before starting general anesthesia. In UCI, 8 mg of IV morphine/24 hours was required. *Case 2:* A 61-year-old man underwent a right inferior lobectomy due to squamous cell cancer. He was also administered 5 mg of hyperbaric intrathecal methadone and put in Trendelenburg position. In UCI, 10 mg of IV morphine/24 hours was required. The patients had "acceptable" analgesia in both cases.
Mironer and Tollison (2001)[10]	Patients with chronic intractable noncancer pain	Intrathecal methadone may be an effective treatment option for patients with chronic nonmalignant pain resistant to other neuraxial agents.
Kedlaya et al. (2002)[29]	Review on treatment with intrathecal opioids for chronic cancer pain	The only FDA-approved medication for intrathecal use is morphine, however, intrathecal methadone is frequently used. Methadone has a low lipid solubility of 82 in CSF. It has a short duration of action (4-8 hours) with a rapid onset (10-20 minutes).
Mugabure et al. (2005)[40]	Narrative review	Morphine is the opioid with the highest medullary selectivity. Epidural methadone has moderate medullary selectivity. They are not an option for outpatients.
Allen et al. (2006)[39]	Case–control study in experimental animals	Opioid-induced intrathecal granulomas do not strictly depend on opioid receptor activation. Opioids at equianalgesic doses present different risks of granuloma formation. Racemic methadone and D-methadone also caused parenchymal necrosis in *continuous intrathecal infusion*. This effect is associated with the NMDA antagonist action of the D-isomer.
Newsome et al. (2008)[41]	Patients with chronic intractable cancer pain Evaluation of the efficacy of intrathecal morphine in continuous perfusion for patients with intolerable side effects	Evaluated intrathecal analgesia for refractory cancer pain. CSF samples taken from patients with effective analgesic response had higher concentrations of M6G than in patients with ineffective analgesia. The occurrence of side effects was associated with catheter tips infusing drugs near the lumbosacral roots resulting in a greater potential for lower extremity motor impairment and/or bladder/bowel dysfunction.
Hermanns et al. (2022)[30]	Review on the use of neuraxial opioids	Hydrophilic opioids such as morphine have slow onset of action, longer duration of action, and greater supraspinal action. Lipophilic opioids such as fentanyl and methadone produce rapid onset of action, but shorter duration, and lower incidence of respiratory depression and sedation.

FDA: US Food and Drug Administration; CSF: cerebrospinal fluid; NMDA: N-methyl-D-aspartate receptors; $t_{1/2}$: half-life.

Table 3. Key points to take home about perioperative use of intrathecal methadone as opioid-adjuvant in spinal anesthesia, and some comparative concepts regarding the use of intrathecal morphine and intrathecal fentanyl

Key points	
1.	Intravenous methadone has shown an opioid-sparing effect in high-risk surgeries prone to severe post-operative pain. This is attributed to its antiglutamatergic properties and its ability to mitigate central sensitization.
2.	Currently, there is limited evidence supporting the use of intrathecal methadone as an adjuvant to spinal anesthesia. As a result, further experimental and randomized controlled clinical studies are needed.
3.	A few RCTs in humans suggest that a single dose of 5 mg of intrathecal methadone, combined with spinal anesthesia, is both effective and safe dose for providing post-operative analgesia in knee replacement, hip replacement, and urological surgeries.
4.	A 5 mg dose of intrathecal methadone provides effective analgesia for 4-8 hours with minimal supraspinal side effects. However, its opioid-sparing effect in the short and medium term, as well as its impact on post-operative central sensitization, remains unclear.
5.	Research on the neurotoxicity of a single intrathecal dose of methadone is scarce and inconclusive. Existing studies are largely limited to animal models, intravenous methadone abuse, and continuous infusions, and focus primarily on other NMDA receptor inhibitors rather than methadone itself.
6.	Only one study was identified that assessed the clinical signs of neurotoxicity following a single intrathecal dose of 4 mg methadone combined with isobaric bupivacaine, 1 month after administration. The study found no clinical evidence of neurotoxicity.
7.	Methadone is not FDA-approved for intrathecal use, whether for acute post-operative pain or chronic pain management. However, intrathecal methadone has been successfully used in cases of chronic pain that are refractory to standard treatments.
8.	Morphine remains the gold-standard opioid for intrathecal administration in the management of acute perioperative pain. Its analgesic effect is at least twice as long as intrathecal methadone depending on the dose used.
9.	In patients undergoing vaginal hysterectomy with spinal anesthesia, a 3 mg dose of intrathecal methadone provides pain relief for 1.5 times longer than a 15 mcg dose of intrathecal fentanyl. Both medications show similar side effects after surgery.

RCTs: randomized controlled trials; FDA: US Food and Drug Administration; NMDA: N-methyl-D-aspartate receptors.

compared to morphine and fentanyl. Racemic methadone also acts as an antihyperalgesic and potent NMDA receptor inhibitor, particularly the D-isomer. These factors prompted our initial question for this review:

Is there evidence supporting the use of racemic methadone intrathecally in the perioperative period? Can intrathecal methadone offer potent spinal effects and attenuate central sensitization perioperatively? These queries motivated our systematic review, looking for evidence of opioid-sparing effects in short- and long-term post-operative pain reduction, like the benefits of intravenous methadone in various surgeries.[3,5,8,31,32]

However, literature on the use of intrathecal methadone in surgical and perioperative contexts has been surprisingly scarce. Only four publications met the inclusion criteria established for this review. These RCTs investigated the analgesic effect of intrathecal methadone at different doses compared to placebo, morphine, and fentanyl.[15-18]

Morphine, being hydrophilic, is 200-300:1 times more potent intrathecally than intravenously. The potency ratio of intrathecal fentanyl and sufentanyl versus intravenous administration is 10-20:1. In contrast, equianalgesic doses and potency ratios of methadone are complex and vary widely depending on the dose, interval, and route of administration. Due to methadone's relative lipid solubility, its intrathecal-to-intravenous potency ratio is approximately 4-10:1. Comparing the duration of analgesic action, a single intravenous dose of methadone (0.1-0.2 mg/kg) could exhibit a relatively similar duration to its equipotent intrathecal dose. However, some authors mention that intravenous methadone in a single dose has an effect of up to 8-12 hours

depending on the dose administered, and an opioid-sparing effect for months.[31] It should be noted that potency equivalences have not been extensively studied in the perioperative context, making it challenging to assign an equipotent dose. Therefore, further studies are needed to draw conclusions for its intrathecal use in the perioperative setting.

Then, another question arises: *Is there a pharmacological rationale for using intrathecal methadone?* At this point, the reasons remain largely hypothetical or theoretical. The advantage of using a lipid-soluble opioid intrathecally in combination with a local anesthetic lies in achieving increased intraoperative analgesic with rapid onset of action and reduced local anesthetic dosage. Once motor block recovery occurs, residual fentanyl analgesia lasts between 1 and 4 hours, a shorter duration than methadone and much less prolonged than morphine analgesia. Due to its lipid solubility, the duration of intrathecal methadone analgesia is 4-8 hours.[29] Depending on the type of surgery and the administered dose of intrathecal methadone, effective residual analgesia has been documented for approximately 8 up to 20 hours.[16]

Does it make sense to design RCTs to scientifically support the use of intrathecal methadone as an adjuvant opioid in spinal anesthesia? Perhaps intrathecal methadone (5 mg) could offer advantages over the use of fentanyl or sufentanyl as adjuvants in spinal anesthesia. Now, we can only affirm that 4 mg of intrathecal methadone as an adjuvant in spinal anesthesia with 13 mg of isobaric bupivacaine has a longer analgesic effect than 15 µg of intrathecal fentanyl.[18,*] Methadone, due to its rapid onset of analgesic action and relatively prolonged post-operative effect, and its antiglutaminergic effect, could be considered as an adjuvant with a broader multimodal antinociceptive effect during intrathecal anesthesia when mixed with a local anesthetic.[1,9] It would be interesting to elucidate the impact of intrathecal methadone as an NMDA receptor inhibitor and rescue opioid-sparing agent in the immediate and late post-operative periods. Of course, this proposal contrasts with all the scientific evidence from studies of fentanyl or sufentanyl, in addition to concerns about the neurotoxicity of certain anti-NMDA drugs administered into the CSF. According to our review, until now only one study assessed the possible clinical signs of neurotoxicity 1 month after the use of 4 mg of intrathecal methadone associated with spinal anesthesia. In this study, no clinical signs suggestive of neurotoxicity of single dose of intrathecal methadone mixed with isobaric bupivacaine were identified.[18]

On the other hand, studies using intrathecal methadone for chronic pain treatment have documented medium-term benefits. In the treatment of nonmalignant chronic pain, improved analgesia has been described up to 6 months after treatment with intrathecal methadone. Additionally, notable improvement in quality of life and less development of tolerance has been achieved with the use of intrathecal methadone. These results are like those obtained with intravenous methadone used in complex surgeries.[29-32]

This systematic review also aimed to find some evidence of similarity of the effects of intrathecal methadone in the treatment of chronic pain and in the treatment of acute post-operative pain. However, we found no evidence to support this.

According to the literature reviewed, a 5 mg dose of intrathecal methadone may provide adequate post-operative analgesia with few side effects.[16,*] For over three decades, an approximate equianalgesic dose relationship has been mentioned between intrathecal morphine and methadone. This relationship is morphine 0.5 mg: methadone 8.5 mg intrathecally.[19] Simplistically, we can infer that an intrathecal dose of 5 mg of methadone could be equivalent in analgesic effect to an intrathecal dose of morphine of 0.1 mg (100 µg). This analgesic effect would be located following a metameric distribution depending on the level of lumbar puncture, resulting in fewer supraspinal effects. However, these concepts are extrapolated from animal studies and merit pharmacokinetic and clinical trials.

Due to its metameric action, intrathecal methadone may be particularly useful in abdominal and lower limb surgeries. According to studies by Jacobson et al., 5 mg of intrathecal methadone appears to be the safest amount as a single dose when applied with the anesthetic mixture, particularly in relation to the onset of side effects such as respiratory depression. Beyond 5 mg, the post-operative analgesic effect of methadone is much more significant and prolonged, but also side effects may increase. Sedation and signs of respiratory depression may increase with intrathecal methadone doses exceeding 10 mg.[16]

For us, it has been interesting to find in the literature that the doses of methadone used are similar for the epidural and intrathecal routes, and range between 5 mg and 10 mg. In the case of epidural

administration of methadone, it is not entirely clear whether part of the effect is due in part to a systemic effect resulting from the absorption of the drug through the epidural venous vessels. To illustrate the variability in dosing and the erratic epidural-to-intrathecal potency relationship of methadone, it is interesting to reference the article by Perez et al.,[33] who used epidural methadone boluses ranging from 4 mg to 6 mg every 8 hours for post-thoracotomy pain control, achieving safe and adequate analgesia comparable to the control group receiving epidural PCA of ropivacaine/fentanyl. Additionally, Beeby et al.[34] and Haybes et al.[35] used 5 mg of epidural methadone for post-cesarean analgesia, with good analgesic outcomes reported in both studies. On the other hand, it is important to highlight that none of these articles documented neurotoxic effects or significant side effects of epidural methadone.[33-35]

The epidural route was not included in the inclusion criteria for this review. Published evidence on epidural use is also limited. Similarly, to intrathecal administration, the analgesic action of epidural methadone is also shorter than epidural morphine or diamorphine analgesia but longer than fentanyl.[31-35] Finally, its opioid-sparing effect in the short and long term when administered epidurally has not been sufficiently studied.

There are few publications on the side effects of intrathecal methadone at different doses. Experimental studies on histopathological safety, neurotoxicity, spinal blood flow, and behavioral changes in animals or humans are limited. Regarding neuro-cyto-safety, studies published by Hodgson et al.[36] and Yaksh et al.[37] mention a potential neurotoxic effect of NMDA receptor inhibitors administered intrathecally but are inconclusive regarding methadone. Most of these articles present data from animal studies. In humans, neurotoxicity data are related to prolonged intrathecal infusions and not to single doses. They also do not report anything about the use of methadone in single intrathecal doses or in prolonged or continuous infusions by this route. Thus, it is important to highlight that the study by Yaksh et al.[37] did not specifically investigate intrathecal methadone use, and Hodgson et al.[36] did not discuss the use of intrathecal methadone.*

Intrathecal methadone has been used more frequently for severe chronic oncological and neuropathic pain treatment, especially in cases resistant to treatment with other opioids. However, literature on this topic is also limited. Some publications are related to intrathecal use of methadone with continuous infusion pumps, many of which are anecdotal. None of these publications have reported clinical or histopathological signs of neurotoxicity.[10,30]

A study based on the use of intrathecal methadone for the treatment of nonmalignant chronic pain resistant to other neuraxial agents showed that intrathecal methadone is an effective treatment for nonmalignant chronic pain. More than a third of these patients maintained adequate pain relief for up to 6 months after intrathecal methadone treatment. Additionally, there was a significant improvement in quality of life and a lower development of tolerance. This outcome was likely related to methadone's mechanisms not mediated by opioid receptors and its antiglutaminergic modulatory effects, among others.[10]

The same author, Y. Eugene Mironer, has demonstrated that a nonracemic mixture of D-methadone and L-methadone at proportions of 3:1 by weight of D-methadone to L-methadone, in combination with another opioid other than methadone, can offer excellent benefit in the treatment of mixed pain.[10,*] Intrathecal methadone has been described as a potentially effective option in the management of refractory chronic pain, particularly in patients with inadequate responses to conventional analgesic therapies. Its ability to provide prolonged relief in this type of pain could also be attributed to its multiple antinociceptive mechanisms of action. Based on these examples, *does it make any pharmacological sense to look for adequate doses to combine methadone with morphine intrathecally?* It could be hypothesized that appropriate intrathecal doses of racemic methadone, or even nonracemic methadone, with intrathecal morphine could be useful in providing potent intraoperative analgesia and prolonged post-operative analgesia in patients undergoing surgeries related to severe acute post-surgical pain and at risk of becoming chronic.

A balanced combination of opioids with different lipid solubility and diverse antinociceptive mechanisms, eg, 50-100 µg of intrathecal morphine plus 5.0-8.0 mg of intrathecal methadone, could hypothetically allow for lower doses of each drug intrathecally, reducing their side effects, presenting a synergistic and additive analgesic effect with short- and long-term benefits. Additionally, intrathecal methadone use could be considered in patients with a history of chronic pain with neuropathic components, chronic opioid use, opioid tolerance,

hyperalgesia, and central sensitization phenomena undergoing surgeries susceptible to difficult analgesic management.

It is essential to consider the lipid solubility of an opioid to determine the appropriate doses for intrathecal use and, consequently, to make efficacy and safety comparisons with other opioids by the same route of administration. The lipid solubility of an opioid is inversely proportional to its potency at the spinal level. Those opioids that are less lipophilic show greater potency and a more prolonged effect when administered intrathecally [morphine = normorphine > pethidine > methadone].[19-22] Also, the different physical properties of opioids are important in determining their rostral distribution when administered intrathecally. Morphine redistributes rostrally via bulk flow in the CSF, providing a pharmacokinetic explanation for spinal morphine's therapeutic effects. Understanding the distribution of drugs in the CSF is critical for effective pain management.[22] Studies in rats have shown an inverse correlation between lipid solubility and analgesic potency.[19] In humans, peak concentrations of opioids such as morphine, methadone, and Beta-endorphin in the CSF after neuraxial administration are significantly higher than in plasma, and the duration of analgesia is related to the lipo-solubility of the opioid.[38] Morphine, with low lipid solubility (relative lipid solubility of 1 compared to methadone with relative lipid solubility of 80), offers longer-lasting analgesia compared to more lipophilic opioids such as methadone, which is rapidly eliminated.[22]

Methadone has advantages in terms of lower incidence of side effects such as nausea and vomiting.[16] Additionally, methadone exhibits less rostral spread in the CSF, limiting its effects on the brainstem and reducing the risk of supra-spinal adverse effects.[10,22]

A prospective study evaluated intrathecal methadone in patients who had already been treated with multiple intrathecal agents and the only reported adverse effect was transient blurred vision (one patient). The authors mentioned that methadone may be considered for neuraxial treatment of severe chronic pain due to its effectiveness in controlling pain refractory to other opioids such as morphine, oxycodone, and hydromorphone. No cases of neurotoxicity have been reported in humans during continuous infusions for refractory chronic pain control despite previous opioid treatments.[10]

On the other hand, chronic intrathecal opioid administration may be associated with granuloma formation. Apparently, the formation of these granulomas is not exclusively the result of the drug's chemical action but is more related to the presence of the catheter as a foreign body at the neuraxial level. Methadone has been shown to be effective in controlling intractable chronic pain, showing a lower risk of granuloma formation compared to other opioids in experimental studies.[39,40]

It is worth noting that methadone is a racemic mixture of D and L isomers. The D-isomer has minimal activity as a μ agonist but acts as a noncompetitive antagonist of NMDA receptors, blocking tolerance to intrathecal morphine. The L-isomer is a potent μ agonist and also an NMDA receptor antagonist, inhibiting serotonin and norepinephrine reuptake. These properties make methadone an attractive option for the intrathecal treatment of chronic intractable pain, but also for patients with chronic pain and central sensitization undergoing surgery. Further clinical trials are recommended to demonstrate any opioid-sparing effect of its perioperative use intrathecally, as has been demonstrated intravenously.[28]

Intrathecal opioid administration remains a valuable strategy for pain management.[10,42] The literature presents limited evidence for the use of intrathecal methadone in cancer patients, but it is even scarcer for the perioperative setting (Table 3). The choice of opioid should be based on its pharmacokinetic and pharmacodynamic properties, as well as the individual patient's response and the need to minimize side effects. Further studies are crucial to evaluate the pharmacokinetics and pharmacodynamics of intrathecal methadone for the management of acute post-operative pain.

Given how controversial the topic of intrathecal methadone neurotoxicity can be among experts, what can we take from this review on this issue? (Table 3).

There is a lack of data in the scientific literature and limited information on neurotoxicity in both animals and humans using an intraoperative single dose of intrathecal methadone.[40-42] Therefore, there is no definitive nor objective evidence to demonstrate that a single dose of intrathecal methadone is neurotoxic. Most concerns about methadone neurotoxicity come from studies involving continuous infusion in animals, with high doses, or nonintrathecal administration, such as intravenous methadone abuse.[42-44]

What great message does this review leave for future researchers? Or what will they need to help clarify our initial hypothesis?

To determine whether intrathecal methadone is safe and effective, more research needs to be done, such as the following:

- Preclinical studies specifically focused on single dose and histopathological changes
- Phase I/II trials in humans to evaluate safety and pharmacodynamics
- Comparative studies against standard intrathecal opioids, eg, morphine and fentanyl

Current evidence does not justify ruling out intrathecal methadone, but gradual and cautious clinical investigation is necessary before its widespread use.

What are the ongoing clinical trials comparing the use of methadone with the intrathecal use of hydromorphone or morphine intrathecally?

1. *Methadone versus intrathecal hydromorphone for post-operative analgesia in gynecologic oncology surgery.* ClinicalTrials.gov NCT06525740. However, this is a phase IV trial that uses intravenous methadone versus intrathecal hydromorphone.

2. *Intrathecal morphine versus intravenous methadone for post-operative analgesia following retroperitoneal lymph node dissection.* ClinicalStudyID NCT0659366522103. *https://centerwatch.com*. This is a phase III trial that uses intravenous methadone versus intrathecal morphine.

To ensure this article reaches current and future researchers interested in conducting RCTs on this topic, we must address the following question: *What are the current regulatory policies on intrathecal methadone?*

Regulatory agencies worldwide, such as the *FDA*, European Medicines Agency (*EMA*), UK Medicines and Healthcare Products Regulatory Agency (*MHRA*), and Spanish Agency of Medicines and Medical Devices (*AEMPS*), establish their own approval processes. However, many follow harmonized international standards, such as those set by the *International Council for Harmonisation* and the *World Health Organization*.[45-48]

Although *intrathecal methadone* has been studied for post-operative pain relief and chronic oncologic or neuropathic pain, none of these agencies have approved its use via this route.*

- The *FDA* considers intrathecal methadone *off-label*, advising extreme caution due to its long $t_{1/2}$ and risk of delayed respiratory depression.
- The *EMA* does not routinely recommend its intrathecal use, though some countries allow it in palliative care or experimental protocols.
- *The MHRA considers intrathecal methadone off-label.*
- The *AEMPS* has no specific approvals for this indication in Spain.

Off-label use refers to the prescription of a drug for an indication, route of administration, or patient group not included in the approved labeling. While off-label use is legal and can be based on sound medical judgment, it may carry additional risks and considerations. Healthcare providers should be aware of these factors when considering intrathecal administration of methadone. Table 4 shows some websites around the world with regulatory policies on methadone use.*

In summary, intrathecal methadone lacks broad regulatory approval but has been used in select cases of refractory chronic pain, particularly in cancer patients. Due to its complex pharmacokinetics and potential risks, its use may require careful monitoring in the perioperatory.

CONCLUSIONS

Further controlled clinical trials are needed to determine the role of intrathecal methadone in the perioperative setting. The pharmacokinetics, pharmacodynamics, and assessment of neurotoxicity risk with a single dose of intrathecal methadone as an adjunct to spinal anesthesia remain unknown and require elucidation. Additional research is necessary to evaluate the perioperative effects of intrathecal methadone, both racemic and nonracemic forms, and to compare its effectiveness with short- and long-term intravenous administration.

According to the few studies found in this review, a single dose of 4-5 mg of intrathecal methadone

Table 4. Some websites around the world with regulatory policies on methadone use

America:
• USA—Food and Drug Administration: *https://www.fda.gov*
• Canada—CHealth Canada: *https://www.canada.ca/en/health-canada.html*
• Argentina—Administración Nacional de Medicamentos, Alimentos y Tecnología Médica: *https://www.argentina.gob.ar/anmat*
• Brazil—Agência Nacional de Vigilância Sanitária: *https://www.gov.br/anvisa/pt-br*
• Colombia—Instituto Nacional de Vigilancia de Medicamentos y Alimentos: *https://www.invima.gov.co*
• Mexico—Comisión Federal para la Protección contra Riesgos Sanitarios: *https://www.gob.mx/cofepris*
Europe:
• EU—European Medicines Agency: *https://www.ema.europa.eu*
• UK—Medicines and Healthcare Products Regulatory Agency: *https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency*
• Germany—Bundesinstitut für Arzneimittel und Medizinprodukte: *https://www.bfarm.de/EN/Home/_node.html*
• Italia—Agenzia Italiana del Farmaco: *https://www.aifa.gov.it/en/*
• France—Agence Nationale de Sécurité du Médicament et des Produits de Santé: *https://ansm.sante.fr*
• Spain—Agencia Española de Medicamentos y Productos Sanitarios: *https://www.aemps.gob.es*
Asia-Oceania:
• Japan—Pharmaceuticals and Medical Devices Agency: *https://www.pmda.go.jp/english/*
• China—National Medical Products Administration: *https://english.nmpa.gov.cn*
• Australia—Therapeutic Goods Administration: *https://www.tga.gov.au*
• Singapore—Health Sciences Authority: *https://www.hsa.gov.sg*
• India—Central Drugs Standard Control Organization: *https://cdsco.gov.in*
• South Korea—Ministry of Food and Drug Safety: *https://www.mfds.go.kr/eng/*
Africa-Middle East:
• South Africa—South African Health Products Regulatory Authority: *https://www.sahpra.org.za*
• Saudi Arabia—Saudi Food and Drug Authority: *https://www.sfda.gov.sa*
• Egypt—Egyptian Drug Authority: *https://www.edaegypt.gov.eg*

might offer adequate analgesia with few side effects. The duration of the analgesic effect of intrathecal methadone is on average 6 hours. Nevertheless, it is important to note that these doses were specifically studied in orthopedic patients and patients undergoing gynecological/urological surgeries. Therefore, its applicability to other patient populations is uncertain. Since the studies involved few participants, the ability to generalize these findings to other surgical groups is limited. Further research is necessary to assess whether the doses found in this review retain comparable efficacy and safety profiles across a broader range of patient cohorts.

Neuraxial opioid administration is an effective strategy for pain management in cancer patients. Despite not being FDA-approved for intrathecal use, methadone has demonstrated efficacy in controlling intractable chronic pain. The choice of opioid should be based on its pharmacokinetic and pharmacodynamic properties, as well as individual patient response (Table 3).

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