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Efficacy and Safety of Intrathecal Morphine for Cesarean Delivery: A Narrative Review

Alan D. Kaye[1] · Anne M. Lindberg[2] · Shivam S. Shah[3] · Rebecca J. Maitski[2] · Emily B. Pendarvis[3] · Jada F. Cooley[3] · Sam Amarasinghe[4] · Sagar Patel[4] · Zachary Palowsky[4] · Charles J. Fox[4] · Shahab Ahmadzadeh[4] · Sahar Shekoohi[4] · Christopher L. Robinson[5]

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Abstract

Purpose of Review Pain management is a critical aspect of care during and following a cesarean delivery. Without proper control of pain, individuals can experience poor mobility, increased thromboembolic events, and difficulty caring for the neonate in the postpartum period. There have been multiple methods for pain management for cesarean delivery and intrathecal morphine (ITM) has emerged as a prominent option for post-operative analgesia due to its efficacy, safety, and potential benefits over other treatments. This review analyzes data on efficacy, side effects, and safety of ITM and the pain control alternatives.

Recent Findings A comprehensive literature review was conducted to compare ITM with other analgesic techniques in post-cesarean patients. ITM was found to be as effective or better than other analgesic options, including bilateral quadratus lumborum block (QLB), opioid-free epidural analgesia (CSEA-EDA), and intravenous fentanyl. One study found that both ITM and oral analgesia were effective in pain control and that ITM caused fewer breakthrough pain events but had a longer duration and a greater rate of side effects than oral opioid analgesia. Commonly observed side effects of intrathecal opioids include nausea, vomiting, pruritus, and urinary retention, and it is thought that the adverse effects from intrathecal administration of opioids are short-lived.

Summary ITM may provide a decreased risk of DVT and coagulation by decreasing lower extremity weakness and numbness, thereby decreasing recovery time and increasing mobility. ITM is a safe and effective option for post-cesarean analgesia, with comparable pain relief to alternative forms of pain control, and side effects that are generally manageable. Further research is warranted to explore beneficial combinations with other methods of pain management and optimal dosing strategies.

Keywords Intrathecal morphine · Cesarean · Analgesia · Pain management · Efficacy · Safety

Introduction

Cesarean delivery is a surgical procedure typically provided when it is not indicated for a pregnant patient to deliver vaginally. Notably, higher cesarean delivery rates have been associated with lower maternal and neonatal mortality [1]. Globally, it is estimated that about 21.1% of all births occur through cesarean delivery [2]. Proper pain control post-cesarean delivery is vital as it can lead to poor mobility, increased thromboembolic events, and an decreased ability to care for the neonate during the postpartum period [3, 4]. The type of anesthesia used during the cesarean delivery can affect the pain intensity and analgesic requirements [5]. General anesthesia is only used in an estimated 6% of births in the United States, due to its maternal complications, such as increased risk of infection and thromboembolic events [6].

Currently, a multimodal analgesic approach is considered the gold standard for post-cesarean care [7]. This approach typically involves a combination of neuraxial morphine, non-steroidal anti-inflammatory drugs, and acetaminophen while minimizing opioid use [8]. Neuraxial morphine has been traditionally used, as it is cost-effective, easy to administer, and has greater analgesic effects [8]. Neuraxial morphine can be administered into either the intrathecal or epidural space to provide analgesia [9]. The aim of this review is to review the efficacy and safety of the use of intrathecal morphine (ITM) for cesarean delivery including the risks

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and side effects and the additional use of ITM in other surgical procedures.

Methods

Inclusion and Exclusion Criteria

Inclusion criteria were the following 1. Peer-reviewed studies in English with partcipants ≥ 18 years of age 2. Studies evaluating the use of ITM and other analgesic forms during cesarean delivery and other surgical procedures. Exclusion criteria were the following: 1. Non-peer reviewed studies 2. Studies not in English 3. Studies with participant < 18 years of age 4. Case reports or case series with < 10 participants. A total of 8 studies were reviewed in this narrative review.

Efficacy

Currently, ITM is the most common form of post-cesarean delivery analgesia. Our literature search found 7 studies that directly compare the effectiveness of ITM to alternative forms of pain management. Generally, ITM was found to be as effective or better than other analgesic options (Table 1). A study by Pangthipampai et al. found that ITM had a significantly higher pain-free period, compared to a bilateral quadratus lumborum block (QLB) [10]. QLB also had an increased morphine usage in the first 24 h compared to ITM alone. QLB had an initial, beneficial impact, but this was limited to the first 6–12 h post-cesarean delivery. When patients were provided intrathecal fentanyl post-cesarean section, patients experienced significantly higher visual analog scale (VAS) pain scores and required more intravenous morphine during the first 24 h compared to ITM [11]. Additionally, these patients had a higher rate of nausea and vomiting compared to ITM. ITM also provided better analgesia compared to opioid-free epidural analgesia (CSEA-EDA) [12]. Patients using ITM experienced a significantly lower frequency of rescue analgesic use in the first 24 h after the cesarean delivery. However, analgesia effects were found in both pain management options. Pruritus only occurred in patients using ITM, and patients using CSEA-EDA had more adverse effects that impact early ambulation, such as lower extremity numbness and weakness.

Several pain management options should be considered if ITM is contraindicated. One study found that a transversus abdominis plane (TAP) block used a significantly greater morphine equivalent dose between 10 and 24 h post-delivery and caused significantly greater pain at rest and on movement at 10 h post-delivery compared to ITM [13]. However, the TAP block had a significantly lower rate of side effects, such as nausea and vomiting, compared to ITM. ITM had a significant decrease in pain scores at 18 h compared to intrathecal hydromorphone (ITH), but there was not a significant difference between the two pain management options 24 h after the delivery [14]. There was also no significant difference in opioid use within the first 24 h, median opioid consumption, and side effects between the two options. ITH was a suitable alternative to ITM. ITM and oral analgesia were effective options for post-cesarean section pain [15]. ITM caused significantly fewer breakthrough pain events compared to oral analgesia, but ITM did have a longer duration and a greater rate of side effects.

Since ITM has previously been shown to be an effective pain management option after a cesarean delivery, several studies have studied the effect of a combination of ITM and another pain management option on post-cesarean delivery analgesia. Our literature review found 3 studies (one described in the aforementioned section, Pangthipampai et al. [10]) that directly compare the effectiveness of ITM alone to a combination of ITM with other forms of pain management (Table 2). Overall, these studies found that a combination of analgesic options provided better analgesia than ITM alone. A combination of ITM with continuous patient-controlled epidural anesthesia (PCEA) provided better analgesia than ITM alone during the first 24 h with mobilization and at rest during the first 12 hours [16]. The number of patients requiring rescue analgesics and the number of requests per patient was also significantly higher for patients being treated with ITM compared to patients using PCEA with ITM. ITM with PCEA was also found to have a significantly higher interval time before the first request for rescue analgesics. The efficacy of ITM alone compared to TAP with ITM in patients with pre-eclampsia was evaluated [17]. VAS scores in patients at rest and with movement were significantly lower in patients with the combination of TAP and ITM compared to ITM alone in the first 12 h and 8 h, respectively. Although there were no significant differences in opioid consumption or side effects between the two groups, patient satisfaction was significantly greater in patients with TAP and ITM compared to those with only ITM.

Safety

A common concern is the safety profile of ITM compared to other standards of care. In general, common side effects of oral opioids include sedation, dizziness, nausea, vomiting, constipation, physical dependence and tolerance, and respiratory depression [18]. However, it is thought that intrathecal administration of opioids has adverse effects that are more short-lived [19]. Commonly observed side effects of intrathecal opioids includes nausea, vomiting, pruritus, and urinary retention [20].

Table 1 Efficacy of intrathecal morphine compared to alternative forms of pain management

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Pangthipampai et al. (2021) [10]	In a randomized control trial, 60 women undergoing a cesarean delivery were split into three groups. 20 participants received 0.2 mg of intrathecal morphine (ITM). 18 participants received 0.2 mg of ITM with a bilateral quadratus lumborum block (QLB), and. 20 participants received only QLB	The pain-free period differed significantly among the groups: ITM only group had a median of 2.50 h, QLB with ITM group had a median of 7.75 h, and QLB only had a median of 1.75 h ($p=0.002$). Pairwise analysis showed significant differences between QLB with ITM and QLB only ($p<0.001$). The QLB only group also required significantly more morphine during the initial 24-h period ($p<0.001$). In the final analysis, the median pain-free period differed significantly between the ITM only group (2.50 h) and QLB with ITM group (8.02 h) (Gehan-Breslow $p=0.027$, Tarone-Ware $p=0.076$, log-rank $p=0.238$)	QLB with ITM improved early postoperative pain control after cesarean delivery compared to ITM alone, however, QLB alone resulted in shorter pain relief and increased morphine use within 24 h compared to ITM alone
Siti Salmah and Choy (2009) [11]	In a randomized, controlled, single-blind study 60 women, who were scheduled to undergo a cesarean delivery, were split into two groups, with 33 participants in the first group and 27 participants in the second group. The first group was given 0.1 mg morphine intrathecally via spinal, and the second group was given 25 µg fentanyl intrathecally	The results showed that patients who were given 0.1 mg morphine had significantly lower visual analogue scores for pain and required less cumulative patient-controlled analgesia (PCA) morphine compared to patients who were given 25 µg fentanyl over the 24-h study period ($p<0.05$). Additionally, patients with 0.1 mg morphine had a longer time to first demand for PCA morphine ($p<0.05$)	The use of 0.1 mg morphine provided better and longer postoperative analgesia after a cesarean section compared to patients with 25 microg of fentanyl
Suzuki et al. (2015) [12]	In a retrospective study, 59 women who underwent cesarean delivery were split into 2 groups, the intrathecal morphine hydrochloride (ITM) group and the combined spinal-epidural anesthesia followed by opioid-free epidural analgesia (CSEA-EDA) group	Within 24 h of cesarean delivery, the frequency of rescue analgesic use was significantly lower in the ITM group (0 times, range 0–3) compared to the CSEA-EDA group (1 time, range 0–6, $p=0.0497$). Lower extremity numbness and weakness were observed only in the CSEA-EDA group. Pruritus occurred only in the ITM group	ITM provides better anesthesia after a cesarean delivery compared to CSEA-EDA. ITM showed fewer adverse effects that impede early ambulation, such as lower extremity numbness and weakness, compared to CSEA-EDA
Loane et al. (2012) [13]	In a randomized control trial, 66 women, who were scheduled to undergo an elective cesarean delivery, were split into two groups comparing a transversus abdominis plane (TAP) block with a 0.5% ropivacaine 1.5 mg/kg versus intrathecal morphine (ITM) 100 µg with a sham TAP block	A significant difference was found between the two groups for morphine equivalents dose consumed between 10 and 24 h post-delivery, with the TAP group requiring more morphine compared to the ITM group (7.5 mg > 2.7 mg, $p=0.003$). Postoperative pain scores were consistently higher in the TAP group, with significant differences observed at 10 h post-delivery for pain at rest ($p<0.001$) and on movement ($p=0.001$). The TAP block group experienced a significant reduction in both nausea and vomiting ($p=0.002$) as well as pruritis ($p=0.007$) compared to the ITM group	Because of its higher analgesic consumption between 10 and 24 h post-delivery, the TAP block was not as effective as ITM. Pain scores were also higher after 10 h post-delivery in the TAP group. However, the TAP block did have a lower rate of side effects, so it may be a suitable alternative when ITM is contraindicated

Table 1 (continued)

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Sharpe et al. (2020) [14]	In a randomized clinical trial, 134 women undergoing cesarean delivery were split into 2 groups to compare the effectiveness of intrathecal morphine (ITM) versus intrathecal hydromorphone (ITH)	The ITM group showed a significant decrease in pain scores at rest at 18 h ($p=0.035$), but not at 24 h. There was no significant difference in opioid use between the two groups within the first 24 h. Median opioid consumption (oral morphine equivalents) and time to first request for postoperative opioids were not significantly different between groups	There were no significant differences in pain relief or side effects when ITM was compared to ITH. Considering global drug shortages, ITH could be an effective alternative to ITM
Yefet et al. (2021) [15]	In a randomized controlled trial, 187 women undergoing a cesarean delivery were split into two groups to compare the efficacy of spinal morphine to the efficacy of oral analgesia	The spinal morphine group had fewer events of moderate to severe breakthrough pain (numeric rating scale (NRS) pain ≥ 4) compared to the oral analgesia group (3.8 ± 1.7 vs. 4.8 ± 2.0, $p=0.0002$). Fewer women who received spinal morphine reported NRS ≥ 4 for pain between 6 and 18 h post-arrival to the maternity ward compared to the oral analgesia group ($p<0.05$). Compared to the oral analgesia group, the spinal morphine group had a longer duration and higher rate of nausea, pruritus, and vomiting	Both spinal morphine and oral analgesia were shown to be effective options for preventing and alleviating post-cesarean section pain. Although spinal morphine was slightly better than oral analgesics for preventing breakthrough pain, it had a higher rate of adverse effects

Low dose intrathecal morphine at 60 μg had a lower incidence of pruritus compared to high dose intrathecal morphine at 100 micrograms [21]. There was no difference between low and high dose morphine in regards to nausea, vomiting, and respiratory distress [21]. No chills or agitation were seen in either group.

ITM was compared with ITH in terms of the side effect profile [14]. One hundred and fifty micrograms of ITM were used compared to 75 μg of ITH. Overall, nausea significant enough to call for medication intervention was not statistically significant between the two groups, with 33% need for intervention in the ITH group and 32% in the ITM group ($p>0.99$). Additionally, there was no statistically significant difference in reported pruritus requiring medication intervention, 11% in hydromorphone group and 19% in morphine group required medications ($p=0.226$). In both groups, there was no observed respiratory depression with respiratory rate below 8 and no oxygen saturation below 92%.

With regard to urinary retention and delay in micturition post-spinal anesthesia, by Gautier et al. compared the addition of ITM to spinal anesthesia with prilocaine and sufentanil versus no ITM [22]. The study indicated a statistically significant effect in delay time to micturition with addition of intrathecal morphine to spinal anesthesia ($p<0.001$), with 8 h to micturition in the ITM group versus 6 h in the control group. Lastly, the recovery time of spinal-epidural anesthesia with ITM was compared to those who received opioid-free epidural anesthesia (CSEA-EDA). A common precaution post-cesarean delivery is development of deep vein thrombosis and coagulation. ITM may reduce the risk of thromboembolic disease and facilitate ambulation as it has been shown to decrease lower extremity weakness and numbness. This allows for patients to ambulate sooner and decrease risk of stagnant blood flow [12]. Reduced rescue analgesia use was also shown in the ITM group, which will ultimately decrease side effects associated with these additional medications. Postoperative nausea and vomiting were similar between ITM and CSEA-EDA groups.

Conclusion

Our narrative review examined the efficacy of ITM both alone and in combination with other forms of pain management and the safety of using ITM in the post-partum period. Consistent with our findings, studies revealed ITM to be the superior analgesic in the post-cesarean delivery period when compared to QLB alone, 25 μg of fentanyl, CSEA-EDA, TAP alone, and oral analgesics [10–13, 15]. There was no superiority of ITM when compared to ITH or epidural though it is important to note that both of these studies found no difference in pain relief or side effects between the two pain relief modalities, indicating that either may be

Table 2 Efficacy of intrathecal morphine alone compared to a combination of intrathecal morphine and an alternative form of pain management

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Sato et al. (2020) [16]	In a randomized controlled trial, 46 healthy women who were scheduled to undergo a cesarean delivery were split into two groups comparing intrathecal morphine (ITM) with continuous patient-controlled epidural anesthesia (PCEA)	The mean numeric rating scale (NRS) at rest was significantly higher in the ITM group than the PCEA with ITM group at 4 h (2.7 vs 0.6), 8 h (2.2 vs 0.6), and 12 h (2.5 vs 0.7). Additionally, mean NRS during mobilization was significantly higher in the ITM group than the PCEA with ITM group at 4 h (4.9 vs 1.5), 8 h (4.8 vs 1.9), 12 h (4.9 vs 2), and 24 h (5.7 vs 3.5). Significant differences were observed in the number of patients requiring rescue analgesics (78.3% vs 30.4%) and the number of requests per patient (1.22 ± 0.80 vs 0.3 ± 0.47) between the ITM group and the PCEA with ITM group, respectively, during the first 24 h postoperatively. Compared to the ITM group, the PCEA with ITM group also had a significantly higher interval time before the first request for rescue analgesics	The use of PCEA with ITM provides better post-cesarean section analgesia than ITM alone during the first 12 h at rest and the first 24 h with mobilization
Yan et al. (2023) [17]	In a randomized controlled trial, 119 women with severe pre-eclampsia who underwent a cesarean section were split into two groups comparing the efficacy ITM alone versus transversus abdominis plane (TAP) with ITM	Visual analog scale (VAS) pain scores at rest differed significantly between the TAP with ITM and ITM alone groups at 4, 8, and 12 h postoperatively ($P < 0.001$, $P < 0.001$, $P = 0.001$, respectively), but not at 24 h ($P = 0.498$). Similarly, VAS pain scores with movement showed significant differences at 4 and 8 h ($P = 0.062$, $P = 0.060$), but not at 12 or 24 h ($P = 0.364$, $P = 0.324$). A significantly higher proportion of patients in the TAP with ITM group reported high satisfaction with pain control compared to the ITM alone group (61.0% vs. 10.0%, $P < 0.05$). Overall maternal satisfaction was significantly higher in the TAP with ITM group (89.8% vs. 75.0%, $P < 0.05$)	Although TAP with ITM did not reduce opioid consumption, it effectively reduced postoperative pain scores at 4, 8, and 12 h in severe pre-eclampsia cesarean sections and had higher maternal satisfaction compared to ITM alone

used depending on the circumstances relative to individual patients [14, 15]. Additionally, there were three studies supporting the benefit of ITM in combination with PCEA, QLB, or TAP [10, 16, 17]. It is important to note that ITM with TAP did not reduce opioid consumption but did reduce pain at certain time markers post-operatively and led to a higher maternal satisfaction when compared to ITM alone [17]. A prospective cohort study has also shown that ITM might be effective and safe in the treatment of refractory pain for patients with cancer at or above the middle thoracic vertebrae. The study compares two delivery sites of ITM: the cisterna magna or the lower thoracic region, and details an improvement in pain relief, depression, as well as quality of life in patients who received ITM delivered to the cisterna magna [25].

Our narrative review found one article comparing the side effect profile of ITM at different doses and three articles comparing the side effect profile of ITM to other analgesic control modalities including intrathecal hydromorphone, spinal-epidural anesthesia, and CSEA-EDA. There were no differences in side effect profile between 60 µg and 100 µg of ITM with regards to nausea, vomiting, or respiratory distress but there was a decreased incidence of pruritus is in the group receiving 60 µg of ITM [24]. This indicates that the side effect of pruritus may be dose dependent. ITM and intrathecal hydromorphone preformed

similarly concerning side effects, with no clinical or statistical significance difference in nausea requiring antiemetics, pruritus, or respiratory depression [14]. There was a statically significant increase in urinary retention when ITM was added to spinal anesthesia of 2 h as opposed to the control group [23]. When ITM was compared to CSEA-EDA, ITM was found to require fewer opioids for breakthrough pain and have a similar side effect profile in regards to post-operative nausea and vomiting. Additionally, it was suggested that ITM use leads to earlier ambulation by reducing the lower extremity weakness in women due to the local anesthetic decreasing the risk of thromboembolic events in the post-partum period. These studies consistently report that ITM has a similar side effect profile as other commonly accepted and practiced analgesic control methods, further supporting the safety of ITM in cesarean delivery cases. Another factor to consider in the use of ITM for cesarean delivery is the racial disparities in anesthetic techniques and obstetric outcomes. According to a retrospective cohort study that includes 8 years of data, Black women face a much higher rate of severe maternal morbidity with significant short- and long-term health consequences postpartum than white women, and are also 44% more likely to receive general anesthesia than regional anesthesia during a cesarean delivery. The increasing evidence of the safety and efficacy of the use of ITM during cesarean delivery may aid in improving these racial disparities if this anesthetic technique is offered to Black women as often as it is offered to White women [26].

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Compliance with Ethical Standards

Competing Interests CLR and ADK are section editors for current pain and headache reports.

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Authors and Affiliations

Alan D. Kaye[1] · Anne M. Lindberg[2] · Shivam S. Shah[3] · Rebecca J. Maitski[2] · Emily B. Pendarvis[3] · Jada F. Cooley[3] · Sam Amarasinghe[4] · Sagar Patel[4] · Zachary Palowsky[4] · Charles J. Fox[4] · Shahab Ahmadzadeh[4] · Sahar Shekoohi[4] · Christopher L. Robinson[5]

✉ Sahar Shekoohi
sahar.shekoohi@lsuhs.edu

Alan D. Kaye
alan.kaye@lsuhs.edu

Anne M. Lindberg
alind3@lsuhsc.edu

Shivam S. Shah
sss002@lsuhs.edu

Rebecca J. Maitski
rmaits@lsuhsc.edu

Emily B. Pendarvis
ejb002@lsuhs.edu

Jada F. Cooley
jrf002@lsuhs.edu

Sam Amarasinghe
sam.amarasinghe@lsuhs.edu

Sagar Patel
sagar.patel@lsuhs.edu

Zachary Palowsky
zachary.palowsky@lsuhs.edu

Charles J. Fox
Charles.fox@lsuhs.edu

Shahab Ahmadzadeh
Shahab.ahmadzadeh@lsuhs.edu

Christopher L. Robinson
drrobinsondr@gmail.com

[1] Departments of Anesthesiology and Pharmacology, Toxicology, and Neurosciences, Louisiana State University Health Sciences Center Shreveport, Shreveport, LA 71103, USA

[2] School of Medicine, Louisiana State University Health Sciences Center at New Orleans, New Orleans, LA 70112, USA

[3] School of Medicine, Louisiana State University Health Sciences Center at Shreveport, Shreveport, LA 71103, USA

[4] Department of Anesthesiology, Louisiana State University Health Sciences Center at Shreveport, Shreveport, LA 71103, USA

[5] Department of Anesthesiology, Critical Care, and Pain Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA