Intrathecal Hydromorphone for Cesarean Delivery: In Search of Improved Postoperative Pain Management: A Case Report

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Currently, morphine and fentanyl are the most commonly used intrathecal opioids for the postoperative pain management of patients who underwent cesarean delivery. Unfortunately, the analgesic benefits of these 2 drugs tend to fall into different extremes based on lipid solubility. Intrathecal hydromorphone may provide more consistent analgesia because its lipid solubility falls between that of the other 2 opioids.

A 22-year-old woman with a 39-week intrauterine pregnancy, gravida 2, para 1, came in for a scheduled second-time cesarean delivery. Her preoperative history included a morphine allergy discovered when administered intrathecally during her first cesarean delivery. Thus, in this case, preservative-free hydromorphone, 100 μg, was administered intrathecally as the opioid replacement for the spinal anesthetic. Intrathecal hydromorphone was found to have provided superior pain relief with fewer side effects in this patient, who received intrathecal morphine for the same surgery 2 years earlier.

This case report supports an emerging hypothesis that intrathecal hydromorphone is not only safe but possibly more effective than other intrathecal opioids for pain management after cesarean delivery. The purpose of this case report is to encourage the development of more research regarding this use of intrathecal hydromorphone.

Keywords: Cesarean delivery, hydromorphone, intrathecal, pain management.

The percentage of cesarean births in the United States increased from 20.7% in 1996 to 31.1% in 2006.1 This continuing rise in cesarean delivery rates is thought to be driven by the increasing rate of primary cesarean delivery and a steep decline in the rate of vaginal birth after cesarean delivery.2 Cesarean deliveries are now the most commonly performed operating room procedure in US hospitals.3

In response to this growing surgical phenomenon, anesthesia providers must search for more effective ways to accommodate postoperative pain management in this population of new mothers. These new mothers present unique pain management challenges in finding the right form of pain management. Some of these challenges include the following: the mother’s immediate need to interact with the newborn postoperatively, the need to ambulate as soon as possible, and the anesthesia provider’s concern over the passing of opioids through the breast milk. With these kinds of challenges at hand, many anesthesia providers have preferred to use intrathecal opioids given in conjunction with a local anesthetic for spinal anesthesia before the cesarean delivery.

Disposition of intrathecal opioids is complex and compartmental. Simultaneously, intrathecal opioids travel cephalad within the cerebrospinal fluid; enter the spinal cord, where they may bind to nonspecific sites within the white matter or specific opioid receptors within the dorsal horn; and transverse the dura mater to enter the epidural space, where they bind to epidural fat.4 The dominant receptor in spinal analgesia is the μ-receptor. This is the same receptor that is responsible for certain side effects such as central opioid-invoked pruritus and respiratory depression. Eventually, all opioids are diffused into the plasma compartment through vascular uptake, where metabolism and ultimately excretion take place.

One of the most important factors in determining the individual properties of an opioid is the lipid solubility.5 This characteristic of an opioid is determined by octanol-water partitioning. Because octanol and water are immiscible, the distribution of a compound between octanol and water can be used to calculate the partition coefficient of that molecule. The more hydrophilic (lower octanol-water partition coefficient) an opioid is, the more it tends to remain in the cerebrospinal fluid and bind to opioid specific receptors (such as μ-receptors). This produces a delayed but longer duration of analgesia, along with a generally higher incidence of side effects because of the cephalic or supraspinal spread of these compounds.6 The more lipophilic (higher octanol-water partition coefficient) an opioid is, the more it tends to stay within the cerebrospinal fluid, which limits the cephalic spread and development of certain side effects such as pruritus and respiratory depression.5
Traditionally, only 2 opioids are commonly used for postoperative pain management after cesarean delivery nationwide. These opioids are morphine and fentanyl. Morphine, on one side of the spectrum, is extremely lipophilic (octanol-water partition coefficient of 1), and fentanyl, on the other side of the spectrum, is extremely hydrophilic (octanol-water partition coefficient of 955). As just described, these drugs have unique characteristics for analgesia based on their lipid solubility. For example, fentanyl has a very quick onset of action (5 to 10 minutes) but a short duration of action (2 to 4 hours), whereas morphine has a slow onset of action (30 to 60 minutes) but a long duration of action (6 to 24 hours). Therefore, an anesthesia provider could recognize the benefits of trying to find an opioid that includes some characteristics of both of these drugs. This drug would need to have a lipid solubility ratio between 1 and 955 on the octanol-water partition coefficient scale.

Fortunately, a very common opioid meets this criterion. Hydromorphone has an octanol-water partition coefficient of 525, meaning it is not as hydrophilic as morphine and not as lipophilic as fentanyl. In other words, hydromorphone has a quicker onset of action than morphine, but a longer duration of action than fentanyl. Yet it has not been studied specifically in the use of postoperative pain management after cesarean delivery. It has been recently studied extensively as a substitute for postoperative pain management after cesarean deliveries. Of the studies found, a wide range of dosing, including anything from 20 μg to 100 μg, of intrathecal hydromorphone was safely used without any serious adverse effects. After discussing the option with the patient, she agreed to the use of intrathecal hydromorphone (100 μg) for postoperative pain management. Preoperative medications included a scopolamine patch (1.5 mg) behind the right ear, famotidine (Pepcid, 20 mg) orally with a sip of water, and citric acid-sodium citrate (Bicitra, 30 mL) orally.

Intraoperatively the patient was sat upright for the spinal anesthesia. Monitors were in place according to American Association of Nurse Anesthetists (AANA) and ASA guidelines. Her vital signs at this point were as follows: blood pressure, 124/74 mm Hg; heart rate, 74/min; respiratory rate, 20/min; and pulse oximetry reading, 99% on room air. Intrathecal access with adequate clear cerebrospinal fluid flow at the L3-4 interspace was achieved on the first attempt using a 25-gauge Pencan spinal needle. No paresthesias were noted. The spinal anesthetic administered included 1.6 mL of 0.75% bupivacaine with dextrose and 100 μg of preservative-free hydromorphone. No adverse events were noted, and the spinal anesthetic administered included 1.6 mL of 0.75% bupivacaine with dextrose and 100 μg of preservative-free hydromorphone. No adverse events were noted, and the patient was then instructed to lie supine with left uterine displacement to avoid aortocaval compression for the cesarean delivery. As expected with 0.75% bupivacaine, a full motor and T4 sensory block set up within 5 to 10 minutes. A Pfannenstiel incision occurred at approximately 8 AM. The procedure included exposure of the uterus along with a low transverse uterine incision commonly performed during cesarean delivery. The uterus was sutured closed and then reintroduced into the abdominal cavity. Skin closure was performed with a subcutaneous stitching style. The surgical procedure was uneventful, with the patient not reporting any pain or discomfort throughout the entire procedure.

**Case Summary**

A 22-year-old woman with a 39-week intrauterine pregnancy, gravida 2, para 1, was admitted for a scheduled cesarean delivery at 7:30 AM. Her only reason for cesarean delivery was that she had a previous cesarean delivery 2 years earlier. Results of her physical assessment and her preoperative history were for the most part unremarkable. She presented as a healthy parturient (157.5 cm, 68.9 kg) whose only medications were prenatal vitamins and iron supplements for anemia. She was classified as an ASA physical status 2. Her preoperative complete blood cell count results included a hemoglobin level of 11.5 g/dL, a hematocrit of 34.2%, and a platelet count of 339 × 10³ μL. She had had nothing by mouth since midnight and complained of hunger and thirst the morning of surgery.

When the planned spinal anesthetic was explained to the patient, she mentioned an allergy to morphine that she discovered with her last cesarean delivery. The patient said morphine was added to her spinal anesthetic, and she later developed uncontrollable pruritus along with hives. The patient also complained of poor pain coverage amid these adverse reactions, creating an undesirable birthing experience that she did not want to revisit with this delivery. After discussing the situation with the anesthetic team, a consensus was made to find another long-acting opioid that could substitute for morphine while allowing the patient to more quickly recover, interact with her infant, and have a reduced potential for transmission via breast milk. Hydromorphone was suggested because it was the most commonly used longer acting opioid aside from morphine. However, after a quick online database search was initiated, it was discovered that there were less than a handful of studies regarding intrathecal use of hydromorphone for postoperative pain management, and none were specific to cesarean deliveries. These opioids are morphine and fentanyl. Yet it has not been studied specifically in the use of postoperative pain management after cesarean deliveries.

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No intravenous (IV) opioids were administered intraoperatively, only prophylactic ondansetron (Zofran), 4 mg IV, for possible postoperative nausea and vomiting, and oxytocin (Pitocin), 20 U diluted in a 1-L bag of lactated Ringer’s solution, for postpartum uterine contraction.

Postoperatively the patient remained without signs of discomfort and stated a pain score of 0 on a scale of 0 to 10, indicating no pain. Vitals signs were as follows: blood pressure, 102/63 mm Hg; heart rate, 78/min; respiratory rate, 18/min; and pulse oximetry reading, 98% on room air. She was observed in the postanesthesia care unit for 1 hour and then transferred to the mother-baby unit. Before her transfer to the mother-baby unit, the patient’s pain level remained at 0 of 10 despite resolution of the spinal motor block and partial resolution of the sensory block. No additional opioid analgesic was administered. The patient was not placed on an IV patient-controlled analgesia pump. The plan was to see how long the intrathecal hydromorphone supplied adequate analgesia and then, if possible, start the patient on oral pain medications similar to what she would be prescribed for use at home, thus eliminating the need for additional IV opioids.

An hour after being admitted to the mother-baby unit, the patient illustrated full resolution of the spinal sensory block in addition to full resolution of the motor block. At this point, it was assumed that pain management was dependent on the intrathecal hydromorphone. The patient did not request any additional pain medication until approximately 11 PM the day of surgery (about 15 hours after skin incision). Her pain score at that time was 2 of 10 and she was treated with oxycodone, 10 mg orally, which met her analgesic needs. In the interim between the cesarean delivery and her first treatment with an oral opioid, the patient was able to interact with her newborn without any sedation and breastfeed without worry of opioid transfer to the child. She was also able to ambulate effectively 8 hours postoperatively without reporting extreme discomfort at any time. The next request for pain medication did not occur until another 9 hours later at approximately 8 AM the following day. She reported a pain level of 4 on a scale of 0 to 10 and was treated effectively with another 10 mg of oxycodone orally.

On the 1-day postoperative visit from the anesthesia provider, the patient stated that this birthing experience was exponentially better than her last one, primarily because of the outstanding postoperative pain management. She highly recommended intrathecal hydromorphone for other patients. Her only complaint was that she reported having had slight itching after the procedure, which was relieved with diphenhydramine (Benadryl), 25 mg IV every 6 hours for 2 doses. No nausea or vomiting or additional adverse reactions were noted. The patient remained on oral opioid analgesia until discharge and did not require subsequent IV opioids throughout the entire admission.

Discussion

Cesarean delivery rates continue to increase in the United States at an alarming rate. In fact, the rate has climbed by more than 50% over the last decade. Given these statistics and the unique needs of the postoperative mother discussed earlier, obstetric anesthesia providers must identify potential optimal alternatives for postoperative pain management in this surgical population beyond the traditional use of intrathecal morphine and fentanyl.

Currently, morphine and fentanyl are the only commonly used intrathecal opioids for postoperative pain management after cesarean delivery. In fact, preservative-free morphine is the only drug approved by the US Food and Drug Administration for intrathecal use in the treatment of acute pain. Both of these opioids have beneficial characteristics due to their lipid solubility. Fentanyl (lipophilic with an octanol-water partition coefficient of 955) is known to have a quick onset of analgesic action, but it is short in duration. Morphine (lipophobic with an octanol-water partition coefficient of 1), represents the extreme opposite ratio. Morphine is recognized for its slow onset of analgesic action, but longer duration. To try to accommodate the beneficial properties of both drugs, many obstetric anesthesia providers have combined the 2 in their administration of spinal anesthetics for cesarean deliveries. Unfortunately, to combine these 2 opioids, you must reduce the dose of both, which also reduces their known analgesic potential.

Hydromorphone (octanol-water partition coefficient of 525) provides a faster and more potent onset of action than morphine, and a longer duration of action than fentanyl. In one study, 37 patients with chronic malignant pain were switched to intrathecal hydromorphone therapy after failure of pain control by intrathecal morphine. This study demonstrated that the pharmacologic complications, such as nausea and vomiting, pruritus, and sedation, were reduced by hydromorphone in most patients. Analgesic responses were also improved by at least 25% in many of the patients. In response, hydromorphone has begun to gain popularity and acceptance as an alternative to morphine for treatment of chronic pain using continuous intrathecal drug delivery systems. Theoretically, it should also be safe and effective for postoperative pain management in patients undergoing cesarean delivery. As presented in the Table, the onset and duration of analgesia of intrathecal hydromorphone correlates with that of intrathecal morphine. However, the range for these properties of the 2 drugs is broad. Knowing how lipid solubility factors into the pharmacodynamics of intrathecal opioids, it is fair to assume that intrathecal hydromorphone factors into the earlier side of the range and intrathecal morphine factors into the latter side of the range. Therefore, a conservative anesthetic approach to intrathecal hydromorphone use in the patient undergoing cesarean delivery would be to
take the same precautions and guidelines one would for the use of intrathecal morphine.

This case report describes the successful postoperative pain management of a patient undergoing cesarean delivery through the administration of intrathecal hydromorphone in conjunction with the spinal anesthetic. The unique needs of the patient, such as early ambulation, immediate interaction with the newborn, and avoidance of opioid transfer through the breast milk to the child, were met with this therapeutic choice. Furthermore, the pharmacodynamic properties of hydromorphone eliminated the need for additional IV opioids for adequate analgesia. The intrathecal hydromorphone provided analgesic properties early enough and long enough to avoid any IV opioids before oral pain medications could be implemented. Overall, the patient’s and clinician’s satisfaction were extremely high despite the fact that mild pruritus developed postoperatively. Inopportune, neuraxial opioid-induced pruritus seems to be induced via the same central μ-receptors that provide spinal analgesia. This has been confirmed through the clinical response of μ-opioid receptor antagonists in humans. According to the patient, however, the pruritus was significantly less compared with the pruritus she experienced with the intrathecal morphine administered during her first cesarean delivery.

This case report supports the developing hypothesis that intrathecal hydromorphone is not only safe, but possibly more effective than other intrathecal opioids in providing intraoperative and postoperative pain management for the patient undergoing cesarean delivery. However, because of the limited body of research and anesthesia literature on this topic, many obstetric anesthesia providers may be hesitant to try this intrathecal opioid option. Yet it was discovered that 100 μg of preservative-free intrathecal hydromorphone provided superior pain relief and fewer side effects in a patient undergoing cesarean delivery who received intrathecal morphine for the same surgery 2 years earlier. Therefore, hydromorphone appears to be a good choice for intrathecal analgesia.

The author suggests that the anesthetic guidelines instituted for intrathecal morphine can be safely transferred for the use of intrathecal hydromorphone. This includes 24-hour postoperative observation, which all patients who underwent cesarean delivery qualify for after having invasive abdominal surgery.

Since the occurrence of this case, Bayfront Anesthesia Services PA (the author’s employer) has adopted intrathecal hydromorphone as a primary choice to pain management in cesarean delivery. In February 2009, intrathecal hydromorphone was added to the standing orders for intrathecal morphine as a substitute equivalent (Figure). No adverse events, such as respiratory depression or apnea, have occurred using the same anesthetic guidelines for intrathecal hydromorphone as one would use for intrathecal morphine. In fact, because of the higher lipid solubility of hydromorphone, common side effects of intrathecal opioids (such as pruritus) are less intense and shorter in duration than those of morphine. The author was disappointed to find that there are no articles in the literature review regarding intrathecal administration of hydromorphone in cesarean deliveries. The purpose of this case report is to encourage the development of more research regarding this use of intrathecal hydromorphone.
Figure. Standing Orders for Epidural and Intrathecal Anesthesia

Abbreviations: CRNA, Certified Registered Nurse Anesthetist; q, every; hr, hour; RR, respiratory rate; IV, intravenous; Pt, patient; foley, Foley catheter; PRN, as needed; max, maximum; rev, revised.


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