Multimodal Postcesarean Delivery Analgesia

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KEYWORDS
- Acute pain • Cesarean delivery • Chronic pain • Multimodal analgesia
- Neuraxial analgesia • Nonsteroidal antiinflammatory drugs • Opioid analgesia
- Chronic pain

KEY POINTS
- Acute pain after cesarean delivery is common, and some patients may develop chronic postcesarean delivery pain.
- There are multiple options for postcesarean delivery analgesia, including neuraxial anesthesia, peripheral nerve blockade, and various combinations of oral, parenteral, and rectally administered medications.
- Long-acting neuraxial opioid medications provide the best postcesarean delivery analgesia and should be considered as part of a multimodal analgesic regimen.

INTRODUCTION

Avoidance of postoperative pain is a priority for both physicians and patients. A prospective observational study that used priority rankings to evaluate obstetric patient preferences found that the 2 most important concerns for parturients were avoidance of intraoperative and postoperative pain. Therefore, the goals of anesthetic care during labor and delivery should include:

- Optimization of peripartum pain management
- Maximizing patient satisfaction
- Minimizing medication-related side effects to the mother and her infant
- Allowing for early return to baseline function
- Preventing a prolonged hospital length of stay.

Cesarean deliveries are known to be associated with acute postoperative pain. However, there is also evidence to suggest that there may be an association with...
the development of chronic postoperative pain as well. Pain is multifactorial, and the experience of pain is subjective, with significant interindividual variability. Patient demographics and emotional states are known to influence the experience of pain. In addition, select genetic polymorphisms, such as those found on the G118 allele, may be associated with increased postoperative pain, although the results of genetic studies have been conflicting. It would be overly simplistic to reduce postcesarean delivery analgesia to a single form of treatment, especially in the context of the emotional surge associated with delivery. Thus, the use of a multimodal analgesic regimen, which uses a combination of drugs with different mechanisms of action, aims to achieve optimal analgesia through additive or synergistic drug actions and minimize associated side effects. Several studies in the postcesarean delivery setting have shown the superiority of multimodal analgesia compared with single-drug therapy alone.

Postcesarean delivery analgesia can be achieved through multiple routes: neuraxial anesthesia and analgesia, peripheral nerve blockade, and various combinations of oral, parenteral, and rectally administered medications (Box 1). The most common multimodal analgesic regimen includes a combination of neuraxial and systemic opioids and nonsteroidal antiinflammatory medications. In addition to standard pharmacologic treatment options, there are also nonpharmacologic interventions available to practitioners. This article summarizes and reviews the epidemiology, physiology, and treatment options for the management of postcesarean delivery pain.

**POSTCESAREAN DELIVERY PAIN**

Pain comes from the Old French word peine, poena in Latin, which means punishment or penalty. Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage; or described in terms of such damage. In the United States, pain is one of the most common symptoms leading patients to seek medical attention, which can significantly interfere with both quality of life and general functioning. Furthermore, national estimates of the cost of pain, which includes lost productivity and treatment costs, range from $560 to $635 billion annually.

Approximately 18.5 million cesarean deliveries are performed annually worldwide. In the United States, cesarean deliveries account for 30.5% of all births; a rate that has doubled since the mid-1990s. In a prospective, longitudinal study of 1228 women, 96% of participants reported pain immediately after delivery. Several studies have attempted to estimate the incidence of chronic postcesarean delivery pain (Fig. 1).

In prospective studies, the prevalence of persistent pain 2 months post partum have been estimated to be approximately 10%. An analysis of pain at 6 months and 1 year after delivery from that cohort revealed low rates of persistent pain, with

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**Box 1**

**Analgesic options for the management of postcesarean delivery pain**

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<td>Neuraxial analgesia (spinal, epidural, combined spinal-epidural) with a long-acting opioid</td>
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rates of 1.8% and 0.3%, respectively. In contrast, higher rates of postpartum pain have been obtained through survey-based studies. A survey mailed to 245 women 1 year after delivery found that the incidence of incisional pain at 3 months was approximately 19%, which decreased to 12% at 10 months post partum. A slightly higher estimate of pain at 1 year after delivery was obtained in a Finnish survey (n = 600, response rate 78%), which found the incidence of persistent pain after cesarean delivery to be 18%. At 2 years post partum, the incidence of chronic pain was approximately 20% in women who had elective cesarean deliveries for breech presentation (n = 1,159, 79% response rate). Studies that have attempted to characterize the intensity of persistent postpartum pain have found that a few women have daily severe or excruciating pain. Although the differences in incidence rates can largely be attributed to differences in study methodology, including varying definitions of chronic pain and data acquisition, most of these studies suggest that pain after childbirth is a significant public health concern.

PHYSIOLOGY OF POSTCESAREAN DELIVERY PAIN

There are 2 primary types of pain: fast (sharp) and slow (throbbing) pain, the latter of which is associated with tissue destruction. Pain receptors are free-nerve endings that respond to 3 types of stimuli: mechanical, thermal, or chemical (inflammatory mediators). Pain impulses are transmitted to the dorsal horn of the spinal cord via the neospinothalamic and the paleospinothalamic tract through fast (Aδ fibers) and slow pain (C fibers). Pain stimulates the release of several neurotransmitters and cellular mediators, including prostaglandins, substance P, glutamate, and calcitonin gene-related peptide. These neurotransmitters bind to receptors on nociceptive fibers, causing
further release of neurotransmitters and signal transmission to the central nervous system.

Cesarean delivery pain has 2 primary components: somatic and visceral pain. Somatic pain arises from direct tissue trauma from the surgical incision, whereas visceral pain is caused by inflammation. Somatic pain is transmitted via the anterior division of spinal segmental nerves, whereas visceral uterine nociceptive stimuli return to the central nervous system via afferent nerve fibers that ascend through the inferior hypogastric plexus and enter the spinal cord via the T10-L1 spinal nerves.23

Most cesarean deliveries are performed using a Pfannenstiel incision, a technique associated with less blood loss, fewer infections, and less postoperative pain than other incision types.24 A Pfannenstiel incision usually involves the T11-T12 dermatomes, whereas a vertical incision may extend from the T10-L1 dermatomes. However, operative pain may extend beyond these dermatomes from stretching of the skin or intraperitoneal tissue manipulation.

PHARMACOLOGIC ANALGESIC STRATEGIES

Neuraxial Analgesia

Most cesarean deliveries in the United States are performed using neuraxial anesthetic techniques.25 The American Society of Anesthesiologist’s Practice Guidelines for Obstetric Anesthesia recommend the use of neuraxial opioids for postoperative analgesia.26 The mechanism of opioid action is dependent on both the route of administration (spinal vs epidural) and the lipid solubility of the drug. Intrathecal opioids act primarily at $\mu$ receptors located within the dorsal horn of the spinal cord. In contrast, opioids administered in the epidural space act via 3 mechanisms: (1) systemic absorption by the vascular system (ie, supraspinal effect); (2) diffusion into the intrathecal space with subsequent action at the dorsal horn; and (3) rostral spread within the cerebral spinal fluid to the brainstem. Highly lipid-soluble opioids such as fentanyl and sufentanil have a rapid onset of action; however, because they are rapidly absorbed into lipid membranes and epidural veins, they also have a short duration of action. In contrast, hydrophilic opioids such as morphine have a slower onset of action, with a longer duration of analgesia. As a result, combinations of both lipophilic and hydrophilic opioids are often used to decrease intraoperative local anesthetic requirements while providing extended postoperative analgesia.

The decision on which neuraxial technique to use (spinal anesthesia, epidural anesthesia, or combined spinal-epidural anesthesia) for a given patient depends on multiple patient factors (eg, airway examination, obesity, medical comorbidities), surgical factors (eg, anticipated duration of surgery), and fetal factors (eg, presence of fetal distress). Neuraxial opioids may be administered intrathecally, as well as epidurally. A Cochrane review (n = 751)27 found no differences in intraoperative analgesia, need for intraoperative conversion to general anesthesia, postoperative pain relief, or need for neonatal interventions between spinal and epidural anesthesia. A retrospective cohort study (n = 949),28 which directly compared the quality of postcesarean delivery analgesic outcomes for patients receiving intrathecal morphine versus epidural morphine versus intravenous patient-controlled analgesia (PCA) morphine, found that patients who received intrathecal or epidural morphine reported lower pain scores at rest and with movement. There were no differences in postoperative analgesia between the 2 neuraxial anesthetic modalities. Therefore, for elective and nonelective cesarean deliveries, the preferred anesthetic technique seems to be spinal anesthesia.25
Given its hydrophilic properties, intrathecal morphine provides the longest duration of postcesarean delivery analgesia. The duration of postoperative analgesia ranges from 14 to 36 hours, with a median duration of 27 hours to first request for supplemental analgesia.29 In contrast, lipophilic opioids such as fentanyl do not confer significant postoperative analgesia with a median time to first request for supplemental analgesia after an intrathecal local anesthetic plus fentanyl mixture of only 4 hours (range 2–13 hours).29 Therefore, in the absence of contraindications, intrathecal morphine should be considered the gold standard for providing prolonged postoperative analgesia.

The optimal dose of morphine for postcesarean delivery analgesia has also been extensively studied. In a randomized controlled study (n = 108) in which parturients undergoing elective cesarean delivery under spinal anesthesia were randomized to escalating doses of intrathecal morphine ranging from 0 to 0.5 mg,30 the investigators found no differences in postoperative intravenous PCA morphine use between groups that received greater than 0.075 mg of intrathecal morphine. However, with escalating intrathecal morphine doses there was a dose-dependent increase in pruritus and the need for opioid-related side effect treatment. The investigators concluded that doses of intrathecal morphine greater than 0.1 mg did not significantly improve analgesia; but did increase opioid-related side effects.

If epidural anesthesia is selected for cesarean delivery, epidural morphine also provides excellent postoperative analgesia. It is well established that epidural morphine provides superior postoperative analgesia to intravenous or intramuscularly delivered morphine.28,31 A prospective dose-finding study (n = 60)32 randomized patients undergoing cesarean delivery under epidural anesthesia to escalating doses of epidural morphine (0–5 mg) and evaluated the quality of postoperative analgesia and opioid-related side effects. With escalating doses of morphine, there was a linear decrease in intravenous PCA morphine use. However, there also appeared to be a ceiling effect above 3.75 mg epidural morphine. In contrast to intrathecal morphine,30 opioid-related side effects were not dose dependent with escalating doses of epidural morphine.32 A systematic review (n = 431) found that the median duration of epidural morphine analgesia was 30 hours (95% confidence interval: 25–24 hours).33 The efficacy and duration of morphine analgesia are significantly reduced when morphine is administered after 2-chloroprocaine when compared with epidural lidocaine.34 Although the mechanism for this interaction is not clear, providers may choose to supplement epidural anesthesia with a longer-acting local anesthetic such as bupivacaine or increase the dose of epidural morphine to try to achieve optimal analgesia.

Other long-acting neuraxial opioid options include extended-release morphine and hydromorphone.35,36 The use of neuraxial meperidine has been described for postoperative analgesia. Although it has been shown to provide 2 to 4 hours of postoperative analgesia, it is associated with an increased incidence of intraoperative nausea and vomiting compared with local anesthetic alone.37 The use of adjuvant medications such as clonidine and neostigmine has been described to improve the quality of neuraxial anesthesia. However, their use is underexplored within cesarean delivery populations.23

Systemic Opioid Analgesic Techniques

There are several choices for opioid analgesia using multiple delivery routes (eg, intravenous bolus administration, intravenous PCA, intramuscular injection). Because there are large interindividual differences in pharmacokinetics with intramuscular injections, and because intramuscular injections are uncomfortable for patients, intravenous options are used more frequently for postoperative analgesia. In patients who
have received neuraxial morphine, supplemental opioid analgesia may not be neces-
sary during the first 24 hours, with as-needed medications being prescribed for break-
through pain. However, for patients who receive general anesthesia, or for those who
undergo neuraxial anesthesia without a long-acting neuraxial opioid, systemic opioids
are required during the postoperative period.

PCA has been shown to be superior to intermittent bolus injections or intramuscular
injections with regard to pain control, patient satisfaction, and adverse effects. The
choice of opioid should be made according to the speed of onset, duration of action,
efficacy, and side effect profile. The American College of Obstetricians and Gynecol-
ogists recommend against the use of meperidine, because it has been associated with
normeperidine neurotoxicity in the newborn. Regardless of the opioid chosen (ie, morphine, hydromorphone, fentanyl), it is important to adjust the dose and the interval
lockout time according to equivalent dosage and the duration of action, respectively.
Whether or not to incorporate a continuous basal infusion in addition to the PCA during
the first 24 hours postoperatively is controversial. As with neuraxial opioid administra-
tion, it is important to monitor for respiratory depression and sedation in patients
receiving parenteral opioid analgesia.

Tramadol is a weak \(\mu\)-opioid receptor agonist. It also induces serotonin release and
inhibits the reuptake of norepinephrine. Although there were high expectations for tra-
madol to confer analgesia with fewer side effects when compared with pure opioid
agonists, it has not been shown to be beneficial for postcesarean delivery analgesia.
In a randomized controlled trial (\(n = 204\)), Mitra and colleagues studied a combina-
tion of tramadol and diclofenac compared with acetaminophen and diclofenac for
postoperative analgesia after cesarean delivery. Although there were statistically sig-
nificant differences between the 2 drug regimens, there were no clinically significant
differences in pain scores during the first 24 hours after delivery. However, patients
in the tramadol/diclofenac group had a 7-fold higher incidence of nausea when
compared with control patients.

Codeine is a prodrug that needs to be metabolized to morphine for analgesic effi-
cacy. The enzyme responsible for this conversion is absent within nearly 10% of the
white population. These poor metabolizers are not likely to obtain analgesia; however,
they are likely to experience undesirable opioid-related side effects such as nausea
and vomiting. Furthermore, there are some ultrarapid CYP2D6 metabolizers who
are at risk of codeine intoxication. There has been a recent warning by the US Food
and Drug Administration on codeine use in nursing mothers after the death of a
breastfed 13-day-old neonate believed to have suffered a morphine overdose
because his mother was taking codeine. Subsequent investigation revealed that the
mother was a CYP2D6 ultrarapid metabolizer. Because of these concerns,
codeine is not recommended for use during the peripartum period. Tramadol is also
influenced by the CYP2D6 genotype, and interactions with any other coadministered
medication undergoing CYP2D6 metabolism should be anticipated.

Nonopioid Analgesic Techniques

Nonsteroidal antiinflammatory drugs (NSAIDs) provide inflammation suppression and
inhibition of the cyclooxygenase (COX) enzyme, which converts arachidonic acid to
prostaglandins and thromboxane. NSAIDs also inhibit a variety of chemical mediators
(eg, bradykinin) that are involved in the inflammatory and nociceptive response of
acute pain physiology. NSAIDs have been shown to be effective in reducing postce-
sarean delivery pain, particularly the visceral component of pain. NSAIDs have also
been shown to enhance opioid analgesia and decrease opioid-related side effects
through their opioid-sparing effect.\textsuperscript{44} NSAIDs are known to have undesirable side effects, such as gastrointestinal and postoperative bleeding caused by nonselective COX-1 inhibition. However, most multimodal analgesic regimens do not require high-dose or prolonged use of these medications for effective analgesia. There has been concern about drug transfer to breast milk and associated neonatal complications in patients receiving NSAIDs; however, the American Academy of Pediatrics regards this class of drugs to be safe for use in breastfeeding women.\textsuperscript{45}

Ketorolac is an NSAID that is available for intravenous administration. After transition to oral intake, patients may be moved to oral NSAIDs. The addition of acetaminophen to NSAID medications has been extensively studied as well. Although most studies have failed to show additional analgesic benefit when acetaminophen was added to an NSAID regimen after cesarean delivery,\textsuperscript{11} Munishankar and colleagues\textsuperscript{46} reported a reduction in morphine consumption using a combined NSAID-acetaminophen regimen when compared with acetaminophen alone (33.8 mg vs 54.5 mg morphine). These conflicting results may be explained by increased acetaminophen clearance during the third trimester of pregnancy and during the postpartum period.\textsuperscript{47} Therefore, most experts agree that NSAIDs, unless contraindicated, should be an important component of any multimodal regimen after cesarean delivery.

\textbf{Anxiolytics}

Anxiety has been associated with increased morphine consumption, obstetric complications, and postpartum depression.\textsuperscript{48} High State Trait and Anxiety Inventory scores, reflecting preoperative anxiety, are known predictors of increased analgesic requirements after cesarean delivery.\textsuperscript{49} However, unless a patient complains of anxiety, it is unlikely that including an anxiolytic medication as part of a multimodal analgesic regimen confers significant analgesic benefit.

\textbf{Ketamine}

Ketamine is an \textit{N}-methyl-\textit{D}-aspartate antagonist that has been used for postcesarean delivery analgesia. Heterogeneity exists among the studies that have evaluated the use of ketamine for postcesarean delivery analgesia, including the type of anesthesia used (ie, general vs neuraxial) as well as the dosing regimens (ie, single fixed dose vs weight-based dosing).\textsuperscript{50–52} Ketamine has an opioid-sparing effect when used in combination with general anesthesia but has not been shown to have such an effect when neuraxial anesthesia is used.\textsuperscript{52} Because high-dose ketamine is associated with many undesirable side effects, further work is necessary to better define its role during the postpartum period.

\textbf{Peripheral Nerve Blockade}

Transversus abdominis plane (TAP) blockade, ilioinguinal nerve blockade, and local anesthetic infiltration have all been described as adjuvant analgesic techniques for postcesarean delivery analgesia. However, the TAP block seems to be the most commonly used regional block when comparing these 3 techniques.\textsuperscript{53–56} The TAP block is a regional anesthesia block in which local anesthetic is deposited within the facial plane between the internal oblique and transversus abdominis muscles in the lumbar triangle of Petit.\textsuperscript{57} Nerves located in this fascial plane include the 9th to 11th thoracic intercostal nerves, the subcostal nerve, and the 2 branches of L1, the ilioinguinal nerve, and iliohypogastric nerves.\textsuperscript{23,57}

McDonnell and colleagues\textsuperscript{53} evaluated the analgesic efficacy of bilateral TAP blocks using 1.5 mL/kg of 0.75\% ropivacaine versus an equal volume saline in patients undergoing elective cesarean delivery with a bupivacaine/fentanyl spinal anesthetic
technique (n = 50). All patients received a multimodal analgesic regimen during the postoperative period, which included scheduled oral acetaminophen, rectal diclofenac, and patient-controlled intravenous morphine. Patients within the TAP block group had significantly reduced morphine requirements and lower postoperative visual analogue pain scores when compared with placebo controls. These differences persisted for 48 hours into the postoperative period. Subsequent studies, which used TAP blocks in combination with neuraxial morphine, failed to show any incremental benefit in postoperative analgesia.\textsuperscript{58}

A randomized controlled study (n = 80) recently compared postoperative analgesia with a 2-mg/kg bilateral bupivacaine TAP block to intrathecal morphine.\textsuperscript{59} Patients were randomized to 1 of 4 groups: saline TAP block/intrathecal morphine, saline TAP/intrathecal saline, bupivacaine TAP block/intrathecal morphine, or bupivacaine TAP block/intrathecal saline. All patients received a standardized postoperative analgesic regimen. The patients who received intrathecal morphine had the lowest pain scores with movement and the least morphine consumption. The TAP block did not improve pain with movement or reduce morphine consumption when given in combination with intrathecal morphine. Two recently published meta-analyses have similarly concluded that TAP blocks do not confer incremental analgesic benefit when given in combination with intrathecal morphine. However, TAP blocks are believed to be beneficial in the absence of intrathecal opioids.\textsuperscript{60,61} TAP blockade has also been described as a rescue analgesic technique for breakthrough pain after spinal anesthesia with intrathecal morphine.\textsuperscript{62} Box 2 summarizes patients who are candidates for TAP blocks. Because of the large volumes of local anesthetic injected during the regional technique, providers should be aware of the potential for local anesthetic toxicity, because several studies have documented high serum local anesthetic concentrations within 15 minutes after the procedure.\textsuperscript{63,64}

### NONPHARMACOLOGIC ANALGESIC STRATEGIES

**Music**

Music can alter emotions by mediating the endorphin system. In the nonobstetric setting, a meta-analysis of 8 randomized controlled trials (n = 712) found that listening to music reduces anxiety and pain during colonoscopies.\textsuperscript{65} One randomized controlled study\textsuperscript{66} evaluated the effect of music in patients undergoing cesarean delivery under general anesthesia (n = 100). Patients were randomized to listen to either Spanish guitar music from induction to skin incision versus white noise. There were no differences in postoperative pain scores, morphine consumption, or postoperative anxiety scores. In contrast, in another randomized controlled study (n = 60), patients undergoing cesarean delivery who listened to their favorite music for 40 minutes before surgery had less anxiety and lower systolic and diastolic blood pressures than those patients who did not listen to any music before surgery.\textsuperscript{67} In a similar randomized controlled trial (n = 60),\textsuperscript{68} listening to music for 30 minutes before cesarean delivery was associated with lower anxiety scores and pain scores postoperatively.

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<th>Box 2</th>
<th>Patients who are candidates for TAP blockade</th>
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<td>Patients who do not receive neuraxial opioids</td>
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<tr>
<td>Patients who undergo general anesthesia for cesarean delivery</td>
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<td>Patients with breakthrough pain after neuraxial analgesia</td>
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**Massage Therapy**

Massage therapy may induce excitation of the central analgesia system and trigger the release of endorphins. A recent study randomized patients to receive either 20 minutes of massage (5 minutes on each hand and foot), or no massage after cesarean delivery (n = 40) and evaluated postoperative pain. There was a significant decrease in pain scores, as well as a delay to the first request for rescue analgesia, within the massage therapy group.

**Aromatherapy**

A limited number of studies have evaluated the effect of aromatherapy, using lavender essence, on postcesarean delivery pain. Lavender is known to have antinociceptive properties. Lavender essence, in addition to a standard analgesic regimen, has been shown to be successful in reducing pain scores after elective cesarean delivery after spinal anesthesia.

**Breastfeeding and Skin-to-Skin Contact**

In animal studies, oxytocin has been shown to play a role in attachment behaviors, as well as in reducing pain thresholds. It is possible that breastfeeding and skin-to-skin contact with the newborn, which are known to release neurotransmitters, endorphins, and oxytocin, may modulate postcesarean delivery analgesia. However, it is possible that the increased oxytocin levels from breastfeeding or skin-to-skin contact may be counteracted by systemic and neuraxial opioids. In animal studies, opioids have been shown to inhibit oxytocin release. No prospective study has evaluated the role of breastfeeding or skin-to-skin contact on postcesarean delivery pain.

**DISCUSSION**

Pain after cesarean delivery is a multifactorial phenomenon. Because pain is considered the fifth vital sign, adequate pain control is regarded as a basic human right. The Joint Commission recommends that pain be evaluated and treated, as would any other abnormal vital sign. Appropriate treatment of pain allows for an earlier return to baseline function and greater patient satisfaction in addition to several other maternal and infant benefits, including early maternal-infant bonding. There are several options for providing effective analgesia after cesarean delivery. However, a multimodal analgesic approach that includes neuraxial opioids seems to be the gold standard for providing optimal patient outcomes. Future study is needed to refine available and developing analgesic techniques, as well as to explore the possibility of patient-specific therapy that is based on risk-stratification and patient pharmacogenetic profiles to optimize postoperative analgesia.

**REFERENCES**


